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Complexes of Greatly Enhanced Thermodynamic Stability and Metal Ion Size-Based Selectivity, Formed by the Highly Preorganized Non-Macrocyclic Ligand 1,10-Phenanthroline-2,9-dicarboxylic Acid. A Thermodynamic and Crystallographic Study

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The metal ion-complexing properties of 1,10-phenanthroline-2,9-dicarboxylic acid (PDA) are reported. The protonation constants ($pK_1 = 4.75$, $pK_2 = 2.53$) and formation constants (log K_1) for PDA with Mg(II) (3.53), Ca(II) (7.3), Sr(II) (5.61), Ba(II) (5.43), La(III) (13.5), Gd(III) (16.1), Zn(II) (11.0), Cd(II) (12.8), Pb(II) (11.4), and Cu(II) (12.8) were determined by UV–vis spectroscopy in 0.1 M $NaClO_4$ at 25 °C. The log K_1 values for most of these metal ions were high enough that they were not displaced from their PDA complexes even at pH 2. The log K_1 values were determined using the UV spectra to monitor the competition with EDTA (or DTPA; EDTA = ethylendiamine tetraacetic acid, DTPA = diethylenetriamine pentaacetic acid) as a function of pH according to the equilibrium: M(EDTA) + PDA + nH$^+$ = M(PDA) + EDTAH$_n$. The log K_1 values indicate that the rigid extended aromatic backbone of PDA leads to high levels of ligand preorganization and selectivity toward large metal ions (e.g., Ca(II), Cd(II), Gd(III)) with an ionic radius of about 1.0 Å and greatly enhanced thermodynamic stability as compared to similar ligands without the reinforcing aromatic backbone. The structure of [Ca(PDA)(H$_2$O)$_2$]·2H$_2$O (**1**) is reported: orthorhombic, *Fdd*2, $a = 44.007(9)$ Å, $b = 18.945(4)$ Å, $c = 7.2446(14)$ Å, $V = 6040(2)$ Å^3, $Z = 16$, $R = 0.0882$. The Ca(II) ion has a coordination number of eight, lying in the plane of the tetradentate PDA, with Ca–N bonds averaging 2.55 Å and Ca–O bonds to the two acetate groups of PDA averaging 2.45 Å. These are very close to the normal Ca–L bonds of this type, supporting the idea that a metal ion the size of Ca(II) (ionic radius ≈ 1.0 Å) will fit into PDA in a low-strain manner. The remaining four coordination sites on Ca(II) in **1** come from two coordinated water molecules and a chelating carboxylate bridging from an adjacent [Ca(PDA)(H$_2$O)$_2$]·2H$_2$O complex. Potential applications of PDA as a ligand in biomedical applications such as Gd(III) contrast agents in MRI are discussed.

Introduction

The design of ligands for biomedical[1], biological[2], and environmental[3] applications and for metal ion separations,[4] is of considerable interest, in which ligand preorganization has been an important aspect. A ligand is more preorganized when it is more constrained, as the free ligand, to be in the conformation required for complexing the metal ion.[5] Examples of highly preorganized ligands are crown ethers,[6] cryptands,[7] and aza-macrocycles,[8] whose macrocyclic structure leads to considerable thermodynamic stabilization[7,8] compared to nonmacrocyclic analogues.

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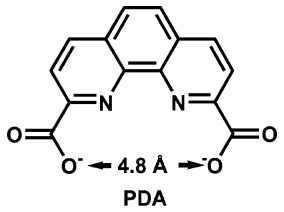


Figure 1. Ligand PDA showing the O···O separation in the MM-generated structure.

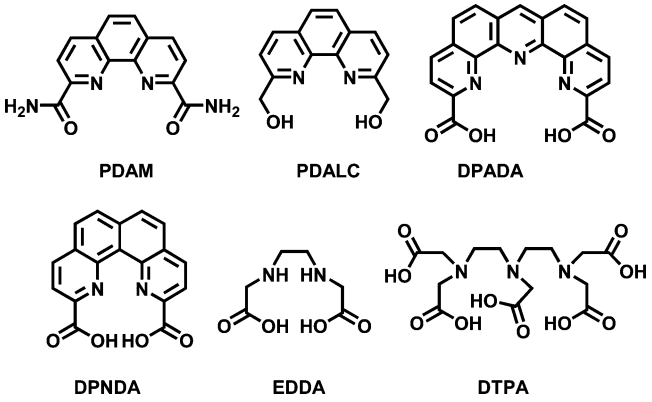
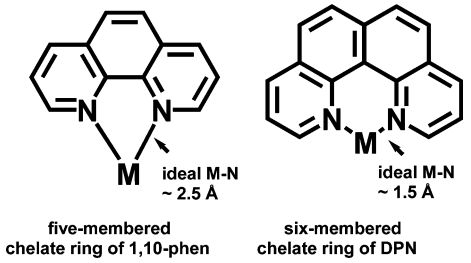


Figure 2. Some ligands discussed in this paper.

The rigidity of extensively delocalized systems suggests that a cyclic structure should not be necessary to obtain highly preorganized ligands. PDA (Figure 1) is based on 1,10-phenanthroline, which is extremely rigid, and molecular mechanics (MM) calculations using the MM2 force field[9] suggest that the two carboxylates at the 2 and 9 positions on PDA are constrained quite strongly to remain in the plane of the aromatic part of the ligand. PDA thus has a fairly fixed distance between the two potentially coordinating O-donors of the carboxylates. This O···O distance, which from MM should be 4.8 Å, requires a fairly large metal ion such as Ca(II) or Gd(III), of an ionic radius[10] (r^+) of about 1.00 Å, to fit into this gap. PDA should thus show strong selectivity for large metal ions ($r^+ \approx 1.0$ Å) relative to small metal ions ($r^+ < 0.8$ Å).

The structure of PDA should give its complexes high thermodynamic stability as compared to its less preorganized analogue EDDA (ethylenediamine-*N*,*N*′-diacetic acid, Figure 2). Admittedly, EDDA with its sp^3-hybridzed N-donors is not an ideal analogue for PDA, with its sp^2-hybridized pyridyl N-donors. However, the saturated N-donors of EDDA are stronger bases than the pyridyl N-donors of PDA, so that, if anything, the comparison should understate the effect of the high levels of preorganization of PDA on complex stability. A rule of ligand design[11,12] suggests that five-membered chelate rings, as formed by PDA, will for steric reasons complex with less strain with large metal ions; this effect should be enhanced by the rigidity of PDA. This is summarized for pyridyl-type N-donors in the graphic, where it is seen that for the five-membered chelate ring of the 1,10-phen complexes, large metal ions are coordinated with the least steric strain, while for the six-membered chelate ring of dipyridonaphthalene (DPN), a very small metal ion fits best.



Structures have been reported for the Co(II),[13] Ni(II),[14] Mg(II),[15] Cr(III),[16] and Cu(II)[17] complexes of PDA. These support the idea that PDA is best suited to complex large metal ions, in that, for example, in the PDA complex of the small ($r^+ = 0.67$ Å) Ni(II), one carboxylate is left uncoordinated. A UV−vis study of the Dy(III) complex has been reported,[18] as has the use of modified versions of PDA for docking the Dy(III) complex in grooves of DNA.[19] The Eu(III) complex of a sulfophenyl-substituted PDA has also been used[20] as a fluorescence marker for protein labeling. A study of the stability of the Eu(III) complex has also been reported.[21] The high stability of the UO_2^{2+} complexes of PDA, and their recognition by monoclonal antibodies has also been discussed.[22] We report here the formation constants (log K_1) of PDA with a variety of metal ions in 0.1 M $NaClO_4$ at 25.0 °C. Ca(II) is of about the right size to coordinate in a low-strain manner with PDA, unlike the previously reported structures,[13−17] which are all too small to complex effectively with PDA. The structure of $[Ca(PDA)(H_2O)_2]\cdot 2H_2O$ is thus reported here.

A particular challenge in ligand design is to design a ligand that will complex Gd(III) strongly enough to prevent its escape into the body but to do so with as few donor atoms as possible to leave as many sites on the Gd(III) as possible to be occupied by water molecules.[23−27] The effect of Gd(III) upon the MRI signal is transmitted through coordinated water molecules, and the more of these there are the more effective will the contrast agent be, all else being equal. Currently employed ligands, such as DTPA, occupy eight coordination sites, leaving only a single site for water. The Gd(III)/PDA complex might, by contrast, be expected to have

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five coordinated water molecules, which should greatly improve the contrast ability of Gd(III)-based MRI agents. We discuss here the possibility of using the ligand design principles embodied in PDA as a future approach to designing improved Gd(III) MRI imaging agents.

Experimental Section

Materials and Methods. PDA was synthesized by a literature method.[28] The metal perchlorates were obtained from VWR or Strem in 99% purity or better and used as received. All solutions were made up in deionized water (Milli-Q, Waters Corp.) of > 18 MΩ. cm^{-1} resistivity.

Synthesis of $[Ca(PDA)(H_2O)_2]\cdot 2H_2O$ (1). The synthesis of **1** was carried out by dissolving 0.0709 g of PDA (0.248 mmol) in *n*-butanol (20 mL) and 0.0765 g of $Ca(ClO_4)_2\cdot 4H_2O$ (0.246 mmol) in H_2O (20 mL). The $Ca(ClO_4)_2\cdot 4H_2O$ solution was placed in a 30 × 150 mm test tube in a hot water bath at approximately 80 °C. A layer of *n*-butanol was then added to the aqueous solution of $Ca(ClO_4)_2\cdot 4H_2O$ to allow an initial interface between *n*-butanol and H_2O to form. The *n*-butanol solution of PDA was added carefully to the test tube while hot. An effort was made to avoid disturbing the interface between the two solvents. The contents of the test tube were left in a slowly cooling hot-water bath. This technique leads to slow crystallization of the otherwise highly insoluble complex, which otherwise precipitates too rapidly. Crystals of $[Ca(PDA)(H_2O)_2]\cdot 2H_2O$ accumulated on the interface of the *n*-butanol/H_2O layers and were collected by vacuum filtration. Anal. Calcd for $C_{14}H_{10}N_2O_8Ca$: C, 44.92; H, 2.69; N, 7.48%. Found: C 45.34; H, 2.72, N, 7.58%.

Formation Constant Determination. These were determined by UV−vis spectroscopy following procedures similar to those of Choppin et al.[29] for studying 1,10-phen complexes. UV−vis spectra were recorded using a Varian 300 Cary 1E UV−vis spectrophotometer controlled by Cary Win UV Scan Application, version 02.00(5), software. A VWR sympHony SR60IC pH meter with a VWR sympHony gel epoxy semi-microcombination pH electrode was used for all pH readings, which were made in the external titration cell, with N_2 bubbled through the cell to exclude CO_2. The pH meter was calibrated prior to every titration and standardized using pH 4.00, 7.00, and 10.00 (±0.01) buffers (Fisher). The cell containing 50 mL of ligand/metal solution was placed in a bath thermostated to 25.0 ± 0.1 °C, and a peristaltic pump was used to circulate the solution through a 1 cm quartz flow cell situated in the spectrophotometer. The pH was altered in the range of 2−10 by additions to the external titration cell of small amounts of $HClO_4$ or NaOH as required using a micropipet. After each adjustment of pH, the system was allowed to mix by operation of the peristaltic pump for 15 min prior to recording the spectrum.

PDA is not very water soluble (~10^{-4} M), but it has intense bands in the UV that can be used to monitor complex formation[18] in solution. The variation of the spectra of PDA solutions as a function of pH in 0.1 M $NaClO_4$ at 25 °C is seen in Figure 3a. Two protonation constants of PDA were determined from the variation in absorbance as a function of pH at nine different wavelengths (Table 1). Fitting of the theoretical absorbance versus pH curves was accomplished using the SOLVER module of EXCEL.[30] For a set of spectra for any one metal ion with PDA, SOLVER was used to fit protonation constants and molar absorbtivities for the species in solution involving PDA. The standard deviations given for pH_{50} values in Table 1 were calculated using the SOLVSTAT macro provided with ref 30. The species involving competing ligands, such as EDTA or DTPA, do not absorb in the region of the spectrum studied. Log K_1 for Ba(II), Sr(II), and Mg(II) could be determined by monitoring absorbance of a solution of 2 × 10^{-5} M PDA and with 10^{-2} M M^{2+}, as a function of pH, while for the Ca(II) solutions, 2 × 10^{-5} M concentrations of each Ca^{2+} and PDA were employed. The method employed here is similar to that used by Choppin et al.[29] to determine log K_1 values for Th(IV) with 1,10-phen. Thus, from the pH at which the metal

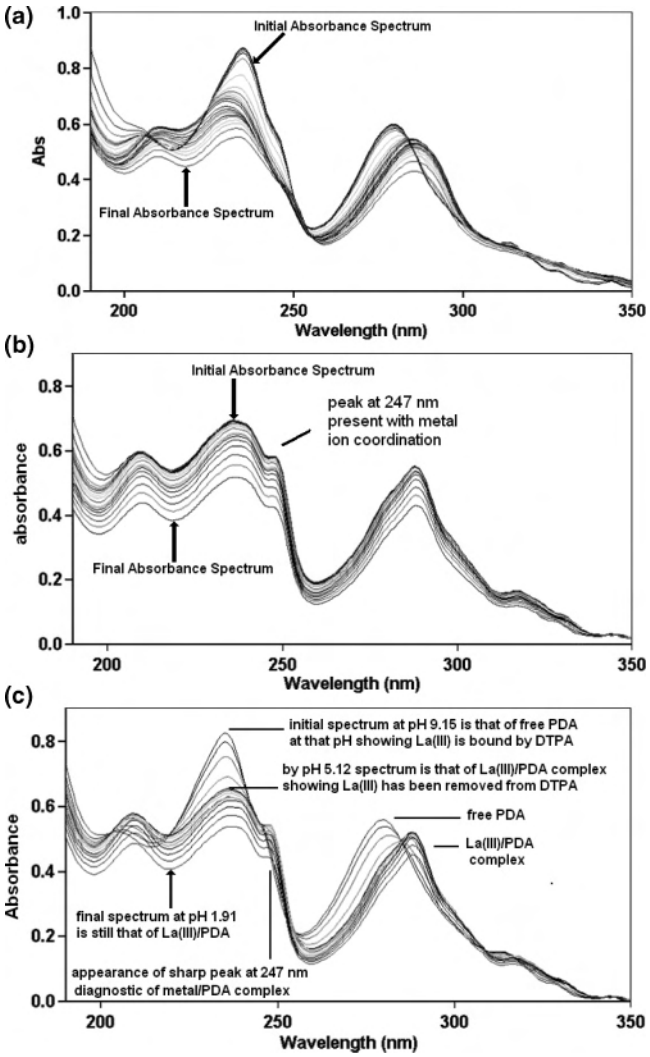

Figure 3. (a) Spectra of 2 × 10^{-5} M PDA in 0.1 M $NaClO_4$ as a function of pH. Initial spectrum is at pH 9.15, while the final spectrum is at pH 1.91. (b) Spectra of 2 × 10^{-5} M PDA with an equimolar amount of La(III) as a function of pH. The initial pH is 9.15, and the final pH is 1.91. The spectral changes are due only to dilution as acid was added. (c) Spectra of 2 × 10^{-5} M PDA with equimolar amounts of La(III) and DTPA, as a function of pH in the range from 9.15 (initial) to 1.91 (final).

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Table 1. pH_{50} Values[a] and Protonation and Formation Constants for a Selection of Metal Ions with PDA Determined Here (0.1 M $NaClO_4$, 25 °C)

Lewis acid	equilibrium[b]	pH_{50}	log K_1(PDA)[c]	log $K_1(PDA)_{(corr)}$[d]
H^+	$H^+ + L^{2-} \rightleftarrows HL^-$		4.75(2)	
	$H^+ + LH^- \rightleftarrows H_2L$		2.53(5)	
	$H^+ + OH^- \rightleftarrows H_2O$		13.78[e]	
Mg^{2+}	$Mg^{2+} + L^{2-} \rightleftarrows MgL$		3.53(5)[f]	3.53(5)
Ca^{2+}	$Ca^{2+} + L^{2-} \rightleftarrows CaL$	7.17(3)	8.2(1)[g]	7.3(1)
			7.4(1)[f]	
	$CaL + H^+ \rightleftarrows CaLH^+$		3.2(1)	3.2(1)
Sr^{2+}	$Sr^{2+} + L^{2-} \rightleftarrows SrL$		5.61(4)[f]	5.61(4)
Ba^{2+}	$Ba^{2+} + L^{2-} \rightleftarrows BaL$		5.43(5)[f]	5.43(5)
La^{3+}	$La^{3+} + L^{2-} \rightleftarrows LaL^+$	8.52(4)	14.4(1)[g]	13.5(1)
		6.45(3)[h]	15.1(1)[h]	
Gd^{3+}	$Gd^{3+} + L^{2-} \rightleftarrows GdL^+$	8.08(9)	17.0(1)[g]	16.1(1)
		7.3(1)[h]	17.6(1)[h]	
Zn^{2+}	$Zn^{2+} + L^{2-} \rightleftarrows ZnL$	5.49(4)	11.9(1)[g]	11.0(1)
Cd^{2+}	$Cd^{2+} + L^{2-} \rightleftarrows CdL$	6.67(2)	13.7(1)	12.8(1)
Pb^{2+}	$Pb^{2+} + L^{2-} \rightleftarrows PbL$	4.95(2)	12.3(1)[g]	11.4(1)
Cu^{2+}	$Cu^{2+} + L^{2-} \rightleftarrows CuL$	5.28(4)	13.7(1)[g]	12.8(1)

[a] The pH_{50} is the pH in the equilibrium M(EDTA) + PDA + nH^+ = M(PDA) + $EDTAH_n$ at which the concentrations of M(EDTA) and M(PDA) are equal. The standard deviations for the pH_{50} values were calculated using the SOLVSTAT macro available in ref 30. Note that the coefficient of determination (R^2) for the pK_a determination for PDA was 0.99944, while that for the metal ion competition equilibria was typically 0.99 or better. [b] In these equilibria, L = PDA. [c] Where no pH_{50} is given, these log K_1 values were calculated directly from the competition between the proton and the metal ion for coordination to the ligand. Where a pH_{50} is given, the log K_1(PDA) value was calculated from the pH_{50} and a literature value[31] for log K_1(EDTA). Note that a problem in doing this is that log K_1(EDTA) values have not been determined[31] in 0.1 M $NaClO_4$ for these ions (but in 0.1 M K^+ or $N(CH_3)_4^+$ salts), so that when such numbers become available, the log K_1(PDA) values calculated from the pH_{50} and log K_1(EDTA) might be altered slightly. [d] These are corrected, as described in the text, for the fact that the log K_1(EDTA) values used in calculating log K_1(PDA) are too high because they do not include competition from the Na^+ ion, which should lower log K_1(PDA) by about 0.9 log units. The log $K_1(PDA)_{(corr)}$ values thus have had this correction made. [e] From ref 25. [f] Calculated by using bands in spectrum between 200 and 350 nm to monitor the equilibrium M(PDA) + nH^+ = M + $PDAH_n$. [g] Calculated from pH_{50} and the reported[31] value for log K_1(EDTA) as described ion the text. [h] Because of the intrinsic interest in the comparison between DTPA and PDA as complexing agents for Gd(III) in MRI applications, a competition experiment between DTPA and PDA was carried out, which gave a pH_{50} for M(DTPA) + PDA + nH^+ = M(PDA) + $DTPAH_n$. The different log K_1(PDA) values given for La(III) and Gd(III) do not indicate error, but the fact that EDTA and DTPA should form complexes with Na^+ of some stability, which is not taken into account in these calculations.

ion was displaced by protons and knowledge of the pK values for PDA, the metal ion formation constants could be calculated.[29] However, for other metal ions, the log K_1 values were too high for this to be practical because the complexes persisted down to well below pH 2 without break up by the acid. Instead, a competition reaction with EDTA, and for some metal ions also DTPA, was used (the octadentate DTPA was used with metal ions of high coordination number, such as La(III), Gd(III), or Ca(II), to reduce the possibility of formation of mixed-ligand complexes)

$$M(EDTA) + PDA + nH^+ = M(PDA) + EDTAH_n \qquad (1)$$

EDTA complexes have log K_1 values[31] for the large metal ions that are not much higher than those of PDA, which is remarkable since EDTA is hexadentate while PDA is only tetradentate, with quite similar donor atoms. However, with a pK_1 and pK_2 (first and second protonation constants) of 9.52 and 6.13 for EDTA[31] at an ionic strength of 0.1 (Na^+ as cation), reaction 1 moves from left to right as the pH is lowered, since PDA has a pK_1 of 4.75. The reaction can be monitored in the UV as a function of pH, and the log K_1 values for the PDA complexes for each metal ion can be calculated from eq 1. The approach of monitoring the competition between EDTA (or DTPA) and PDA as a function of pH works remarkably well. Thus, Figure 3a shows the set of spectra for 2×10^{-5} M PDA ligand in the pH range of 9.1−1.9. Figure 3b shows a similar set for 2×10^{-5} M concentrations of each of PDA and La(III) as a function of pH, and Figure 3c shows the set of spectra for 2×10^{-5} M concentrations of each of PDA, La(III), and DTPA. DTPA (or EDTA) and La^{3+} do not absorb significantly in the range of 200−350 nm, so that the spectral changes reflect changes in the PDA ligand from one protonated form to another or in the formation of the La(III) complex. Figure 3a thus shows the changes in the spectra of the free ligand as a function of pH. Figure 3b shows the spectrum of the La(III)/PDA complex, and all the changes observed are caused by dilution only. In Figure 3c, where a 1:1:1 mixture of PDA, EDTA, and Gd(III) are present, it is seen that at high pH (the "initial" spectrum at pH 9.15) the spectrum is identical to that of the free ligand in Figure 3a at high pH. As the pH is lowered in Figure 3c, the spectrum switches over by pH 5.12 to be completely that of the La(III) complex, after which all the spectra are identical with those of the La(III)/PDA complex. One can fit a curve to the data which gives a pH at which the midpoint of this transition occurs, where the concentrations of the La(III), EDTA, and PDA complexes are equal, which is referred to here as the pH_{50}.

Where the pH_{50} occurs in the experiments here for any metal ion in eq 1, [M(PDA)] = [M(EDTA)] = [PDA] = $[EDTA_{total}]$ = 10^{-5} M, where $[EDTA_{total}]$ = [EDTA] + [EDTAH] + $[EDTAH_2]$ + ... + $[EDTAH_6]$. One can therefore calculate [EDTA] from eq 2 and the known[31] protonation constants (K_{a1}, K_{a2}, K_{a3}, ...) for EDTA (or DTPA for experiments involving DTPA)

$$([H^+] = pH_{50})\ [EDTA] = [EDTA_{total}]/\{1 + K_{a1}[H^+] + K_{a1}K_{a2}[H^+]^2 + K_{a1}K_{a2}K_{a3}[H^+]^3 + ...\} \qquad (2)$$

One therefore knows [EDTA] in eq 3, where all other species are 10^{-5} M

$$K_{exch} = [M(PDA)][EDTA]/[M(EDTA)][PDA] \qquad (3)$$

One can then calculate log K_1(PDA) for the metal ion from

$$\log K_1(PDA) = \log K_1(EDTA) + \log K_{exch} \qquad (4)$$

Figure 4a shows the spectra of 10^{-5} M Ca(II)/PDA solutions as a function of pH. The group 2 metal ions are different from other metal ions in that the complexes with PDA are of sufficiently low stability that they are broken up at low pH to yield the protonated ligand and free metal ions, as seen in Figure 4a. One can thus calculate log K_1 for Ca(II) in a straightforward manner using the UV spectra to monitor the breakdown of the PDA complexes at low pH. With other group 2 metal ions, the PDA complex is too weak to form strongly at the 2×10^{-5} M level, and higher free metal ion concentrations were used. For Ca(II), it was also possible to perform a competition experiment between EDTA and PDA for binding to Ca(II), as seen in Figure 4b. Figure 5a and b shows the variation in absorbance spectra for Gd(III)/PDA as a function of pH. In Figure 5a, there is no added EDTA, whereas in Figure 5b there is added EDTA. Figure 5 is important in that it shows that for Gd(III), EDTA is only a slightly stronger ligand than PDA. One obtains (Table 1) log K_1(PDA) values for Ca(II) by these two

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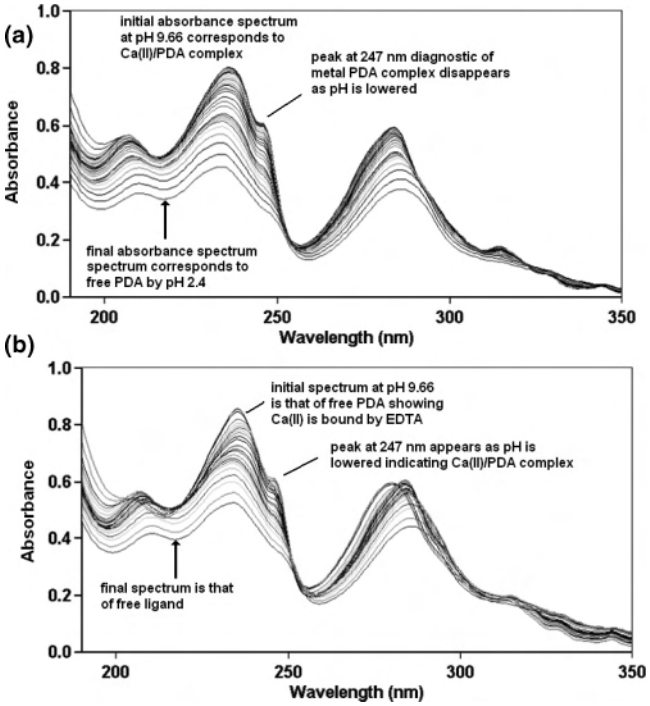

Figure 4. (a) 2×10^{-5} M Ca(II) and 2×10^{-5} M PDA as a function of pH from initial = 9.66 to final = 1.91. (b) 2×10^{-5} M Ca(II), 2×10^{-5} M PDA, and 2×10^{-5} M EDTA as a function of pH from initial = 9.66 to final = 1.91.

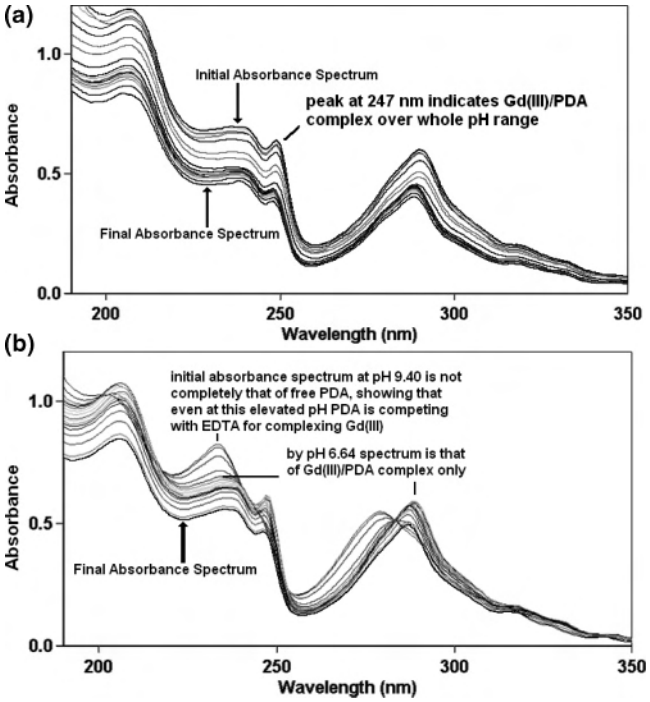

Figure 5. (a) 2×10^{-5} M Gd(III) and 2×10^{-5} M PDA as a function of pH from initial = 9.40 to final = 1.99. The changes in the spectra are due only to dilution as acid was added to lower the pH. (b) 2×10^{-5} M Gd(III), 2×10^{-5} M PDA, and 2×10^{-5} M EDTA as a function of pH from initial = 9.40 to final = 1.99. The initial spectrum is not that of free PDA ligand alone but shows presence of some Gd(III)/PDA complex.

methods that differ by some 0.8 log units. This does not represent the inaccuracy of the approaches employed. Rather, EDTA forms a complex of considerable stability with the Na^+ ion present in 0.1 M $NaClO_4$. Log K_1(EDTA) for Na^+ in 0.1 M $[(CH_3)_4N]^+$ as ionic background[31] is 1.86. Thus, one would expect log K_1(EDTA) for any metal ion to be about 0.86 log units lower in a 0.1 M Na^+ ionic background compared to a background cation such as K^+, which binds only weakly. Thus, the difference in log K_1 for Ca(II) with EDTA measured directly is not dependent on the value of log K_1(EDTA) for Ca(II) and so is lower than that measured by competition with EDTA by 0.8 log units, not too different from the expected difference of 0.9 log units. When log K_1(EDTA) values become available for metal ions in a 0.1 M Na^+ background, then better log K_1(PDA) values can be calculated from these using the pH_{50} values in Table 1. For the present, the log K_1(PDA) values for the group 2 metal ions determined without competition with EDTA can be regarded as final. As a reasonable adjustment, log K_1(PDA) values determined from pH_{50} by competition with EDTA would drop by about 0.9 log units once log K_1(EDTA) values in 0.1 M Na^+ become available, and so a list of "corrected" log K_1(PDA) values is given in Table 1 where log K_1(PDA)(corr) = log K_1(PDA) − 0.86, where log K_1(PDA) has been determined from pH_{50} and log K_1(EDTA) values not determined in a 0.1 M Na^+ ionic background.

Table 2. Crystal Data and Structure Refinement for the $[Ca(PDA)(H_2O)_2]\cdot 2H_2O$ Complex (**1**)

empirical formula	$C_{14}H_{10}N_2O_8$
fw	370.29
temp	183(2) K
wavelength	0.71073 Å
cryst syst	orthorhombic
space group	*Fdd*2
unit cell dimensions	a = 44.007(9) Å
	b = 18.945(4) Å
	c = 7.2446(14) Å
vol	6040(2) Å^3
Z	16
GOF on F^2	0.999
Final R indices [$I > 2\sigma(I)$]	R1 = 0.0882, wR2 = 0.1937
R indices (all data)	R1 = 0.1367, wR2 = 0.2193.

Crystallography. A Rigaku Mercury diffractometer, using the ω scan mode, was employed for crystal screening, unit cell determination, and data collection. The structure was solved by direct methods and refined to convergence.[32] No absorption corrections were made. Some details of the structure determination are given in Table 2, and the crystal coordinates and details of the structure determination of **1** have been deposited with the CSD (Cambridge Structural Database).[33] A selection of bond lengths and angles for **1** are given in Table 4.

Results and Discussion

Formation Constants. The formation constants (log K_1) determined here for PDA complexes are shown in Table 1. The UV−vis method for determining the log K_1 values appears to work well, and the competition between PDA and EDTA or DTPA appears to be a viable method for determining log K_1 values for complexes of very high stability. A minor problem at this time, as discussed in the Experimental Section, is that the log K_1 values for the EDTA and DTPA complexes have been determined[31] with cations other than Na^+ as ionic background, and Na^+ forms complexes of some stability with both EDTA and DTPA. Thus, the values that can be regarded as complete in Table 1 are the log K_1(PDA) values for the group 2 metal ions (Mg, Ca, Sr, Ba) that did

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(33) Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, United Kingdom.

not involve competition with EDTA for determination of log K_1. Correction for complexation of EDTA by Na^+ has been applied in Table 1 to give the log $K_1(PDA)_{(corr)}$ values. It is not anticipated that these values will change significantly should the log K_1(EDTA) values determined in 0.1 M $NaClO_4$ become available for calculating log K_1(PDA), but it should be kept in mind that these log K_1(PDA) values might be refined slightly. A reviewer has questioned whether metal ion hydrolysis might not be important in the competition experiments used here. Calculations show that EDTA and DTPA will, for the metal ions studied, completely suppress hydrolysis up to a pH of 9, which is the highest pH reached, so that consideration of hydrolysis reactions is not necessary. A reviewer has raised the possibility of a complex of PDA with Na^+, which has not been completely ruled out. The protonation constants of PDA have been determined in 0.1 M $LiClO_4$ and found to be the same as in 0.1 M $NaClO_4$. If Na^+ does form a complex with PDA, one would then have the unusual situation that it was of identical stability to the Li^+ complex. Perusal of ref 31 shows that Li^+ invariably forms more stable complexes than does Na^+ with aminocarboxylate ligands. Unfortunately, the spectroscopic study of PDA cannot be carried out in the weakly coordinating K^+ or $(CH_3)_4N^+$ cations as ionic background, since the ClO_4^- salts of these cations are largely insoluble, and their soluble nitrates are unsuitable since NO_3^- has a strong absorption band in the UV.

Two previous studies[18,34] that report a log K_1 value for PDA with lanthanides, one of which[34] was pointed out by a referee, should be mentioned here. Both involved monitoring absorbance as a function of pH and gave log K_1 values for the Dy(III)[18] and Eu(III)[34] complexes. Both of these studies report that the first pK of PDA is above 10, which is supported by reference to a very high value for the pK_a of picolinic acid given in ref 35. One should say at once that there is no reason to expect a first protonation constant of PDA much different from that of 1,10-phen (4.92[31]) or even pyridine itself (5.20). The critically selected[31] first protonation constant of the similar picolinic acid is reported as 5.39, based on 51 separate reports[31] of this value, none of which report an unusually high value for the first protonation constant. Inspection of the absorbance versus pH curves given in ref 34 in fact show no significant inflection apart from that at 4−5 found here, so it is hard to see how such a high pK value for PDA was obtained. Similarly, the absorbance versus pH curves for PDA in Figure 6c show no inflection in absorbance in the range of 5−10, showing no protonation constant in this range. One suggests that since the determinations of log K_1 for lanthanides[18,34] were based on an erroneous set of protonation constants for PDA, these log K_1 values must be regarded as doubtful. Figure 6c shows the variation in absorbance, corrected for dilution during the titration, of a 2×10^{-5} M solution of PDA in 0.1 M $NaClO_4$. The solid lines drawn in were calculated from protonation constants of 4.75 and 2.53 and the appropriate molar absorptivities for the PDA, PDAH, and $PDAH_2$ species at each wavelength. This model of the protonation scheme of PDA in the pH range of 2−10 fits the data extremely well,

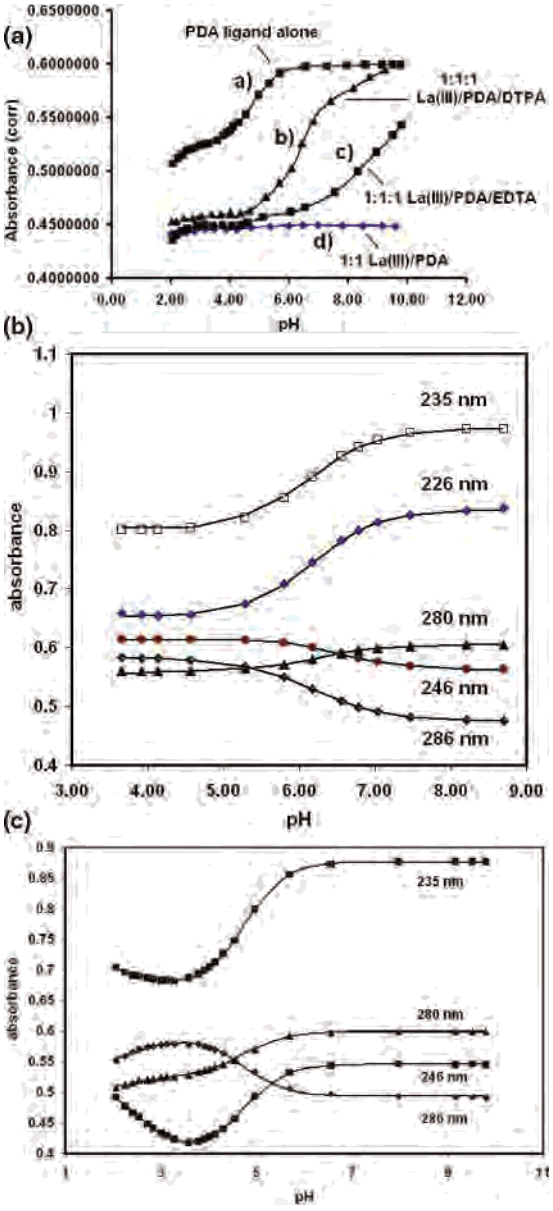

Figure 6. (a) Variation of absorbance at 280 nm as a function of pH for 2×10^{-5} M PDA solutions. Line a is 2×10^{-5} M PDA alone; line b is 1:1:1 of 2×10^{-5} M of each of PDA, La(III), and DTPA, and line c is 1:1:1 of 2×10^{-5} M of each of PDA, La(III), and EDTA. Line d is 1:1 PDA/La(III). All spectra were recorded in 0.1 M $NaClO_4$ at 25 °C. Absorbances are corrected for dilution. (b) Variation of absorbance (corrected for dilution during the titration) at the five different wavelengths shown, as a function of pH, for a 1:1:10 ratio of PDA (2×10^{-5} M), Ca-(II) (2×10^{-5} M), and EDTA (2×10^{-4} M). The solid lines are theoretical curves for a single protonation event (pH_{50}) all fitted simultaneously using SOLVER[30] with a pH_{50} of 6.20 and appropriate molar absorbtivities for the Ca(II)/PDA and PDA free ligand species at each wavelength. This titration was carried out with a 10-fold excess of EDTA compared to PDA, so pH_{50} is depressed by one log unit compared to pH_{50} for equal concentrations of PDA and EDTA ($pH_{50} = 7.17$ in Table 1). (c) Variation of absorbance (corrected for dilution during the titration) at four different wavelengths shown, as a function of pH, for 2×10^{-5} M PDA in 0.1 M $NaClO_4$. The solid lines are theoretical curves calculated[30] from pK values of 4.75 and 2.53 and appropriate molar absorbtivities for PDA, PDAH, and $PDAH_2$ at each wavelength.

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Table 3. Formation Constants (0.1 M $NaClO_4$, 25 °C) for a Selection of Metal Ions with PDA, Determined Here, and for EDDA,[31] and the Ionic Radii of the Metal Ion[a]

metal ion	ionic radius[b]	log K_1(PDA)[c]	log K_1(EDDA)[d]	Δ log K[e]
Ba^{2+}	1.36	5.4	3.3	2.1
Pb^{2+}	1.19	11.4	10.6	0.8
Sr^{2+}	1.18	5.6	3.6	2.0
Ca^{2+}	1.00	7.3	4.0	3.3
La^{3+}	1.03	13.5	7.0	6.5
Gd^{3+}	0.93	16.1	8.1	8.0
Cd^{2+}	0.95	12.8	9.1	3.7
Mg^{2+}	0.74	3.5	4.0	−0.5
Zn^{2+}	0.74	11.0	11.1	−0.1
Cu^{2+}	0.57	12.8	16.2	−3.4

[a] The protonation constants for PDA were determined to be 4.75(2), 3.71(2), and 2.09(2) in 0.1 M $NaClO_4$ at 25 °C [b] In angstroms, ref 11. [c] Uncertainty in log $K \approx 0.1$. [d] Ref 31, ionic strength = 0.1. [e] Δ log K is the log K value for M(EDDA) + PDA = M(PDA) + EDDA.

with a coefficient of determination (R^2) of 0.99944 provided by SOLVSTAT[30] over all wavelengths.

The metal ion-complexing properties of PDA are quite interesting. In Table 3, the log K_1(PDA) values for metal ions are compared with log K_1 for EDDA. (Note that the log K_1(PDA) values are those corrected for complex formation of EDTA with Na^+ as discussed above.) As mentioned above, EDDA is a less than perfect comparison with PDA, but it should be borne in mind that in aqueous solution saturated amines are stronger bases than pyridines,[31] so that basicity differences between PDA and EDDA should favor the latter. Thus, any stabilization resulting from the rigid backbone of PDA should be, if anything, understated. If one focuses first on the divalent metal ions, very large metal ions (i.e., those with an ionic radius[10] well above 1.0 Å), namely, Sr(II), Ba(II), and Pb(II), show a stabilization of the PDA complex relative to the EDDA complex of about 1−2 log units. For divalent metal ions with ionic radii close to 1.0 Å, namely, Ca(II) and Cd(II), the stabilization increases to 3.3−3.7 log units. For smaller metal ions with ionic radii less than 0.8 Å (Mg(II), Zn(II), Cu(II)), the PDA complexes are actually less stable than the EDDA complexes. This is a satisfying picture that fits with the MM calculations discussed below that show that the best-fit size of the metal ion for complexing with PDA has an ionic radius of about 1.0 Å. Very small metal ions such as Cu(II) appear quite unable to coordinate with all four donor atoms of PDA, and so they form complexes of comparatively low stability.

The log K_1(PDA) values for the trivalent metal ions La(III) and Gd(III) are quite remarkable. These show stabilizations of 6.5 (La(III)) and 8.0 (Gd(III)) log units compared to the EDDA complexes. These metal ions have ionic radii[10] very close to 1.0 Å, so that large stabilization would be expected, but this is very much greater than found for the similarly sized divalents Cd(II) and Ca(II). There is clearly something additional at work here. It seems reasonable to suggest that PDA helps trivalents overcome two possible problems[12] that these metal ions have with ligands such as 1,10-phen. First, ligands with pyridyl groups in them have serious steric problems caused by interaction between the *ortho*-H atoms on the pyridyl group and the other adjacent coordinated ligands, such as water molecules. Relevant to the discussion here is the structure[36] of the $[La(1,10\text{-phen})_2(H_2O)_5]^{3+}$ complex cation, where it is seen that *o*-hydrogens on the 1,10-phen come as close as 2.28 Å to the O atoms of adjacent coordinated waters, which can be compared to the sum of the van der Waals radii[37] of H and O of 2.7 Å. The presence of carboxylates at the ortho positions of the 1,10-phen moiety in PDA removes this problem, and it has been estimated[12] that each such replacement of an H atom by a carboxylate increases log K_1 by 1.4 log units. Clearly, the hydration spheres of the M^{3+} ions will be much more strongly held and more extensive than those for the M^{2+} ions, and so, adverse steric effects from *o*-H atoms on the 1,10-phen groups will be more of a problem for M^{3+} ions. A further problem for the pyridyl groups coordinated to M^{3+} ions is that these cannot hydrogen bond (H-bond) with the solvent.[38] Stabilization by H-bonding should be much more important for M^{3+} than M^{2+} ions, and so the inability of pyridyl groups to H-bond should be more serious for M^{3+} ions. Clearly, the presence of carboxylates will reduce the charge on the M^{3+} ion, and they will also H-bond better with the solvent.

The very large stabilization for the PDA complex of Gd^{3+} is particularly interesting. A major factor in the efficacy of Gd(III)-based MRI contrast agents is[23−27,39] the number of water molecules bound to the Gd^{3+}. Ligands such as PDA have high complexing power with Gd(III) but are only tetradentate. One might thus hope that five waters would be coordinated to Gd(III) in its PDA complex, which might give the Gd(III) unprecedented MRI contrasting activity. Another important aspect of PDA is the comparatively low affinity for the small metal ions Zn(II) and Cu(II). The ligand part of the Gd(III) MRI agent prevents displacement of the toxic Gd(III) by Zn(II)[23−27,39], also present in body fluids. The selectivity of PDA for Gd(III) relative to Zn(II) is 5.1 log units compared to 4.2 log units for DTPA and 0.9 for EDTA. The log K_1(PDA) value of 16.1 reported here for Gd(III) is quite low compared with[31] log K_1(DTPA) = 22.4. One might thus think that PDA binds Gd(III) too weakly to be a successful MRI agent. However, if one considers that at the biological pH of 7.3, PDA is not protonated, while DTPA has protonation constants (0.1 M Na^+) of 9.90 and 8.40, this will reduce the effective log K_1 of DTPA at biological pH to 22.4 − (9.9 − 7.3) − (8.4 − 7.3) = 18.7. A further reduction of some 2 log units might be expected if Na^+ forms a complex with DTPA that might have a log K_1 value of ∼3. Thus, as this simple calculation shows, the effectiveness of binding of PDA and DTPA at pH 7.3 is about the same, which corresponds with the pH_{50} of 7.3 determined here by UV spectroscopy for the competition between DTPA and PDA to bind with Gd(III). This result is further reinforced by tracer experiments[40] with ^{153}Gd, which show that in

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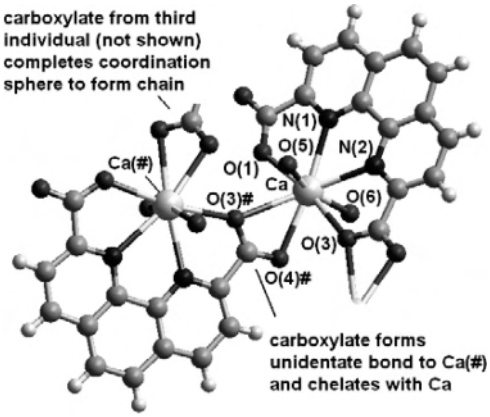

Figure 7. Structure of the complex in $[Ca(PDA)(H_2O)_2]\cdot 2H_2O$ (**1**) showing two individuals bridged by a shared carboxylate group. This bridging leads to a chain of such individuals. The numbering scheme for the donor atoms coordinated to one Ca is shown. The O(5) and O(6) oxygens are from water molecules coordinated to the Ca. There are two disordered water molecules in the lattice (not shown).

Table 4. Selected Bond Lengths (Å) and Angles (deg) for $[Ca(PDA)(H_2O)_2]\cdot 2H_2O$ (1)[a]

Ca(1)−O(6)	2.387(7)	Ca(1)−O(5)	2.420(8)
Ca(1)−O(1)	2.468(7)	Ca(1)−O(4)#	2.534(7)
Ca(1)−N(2)	2.555(7)	Ca(1)−O(3)#	2.638(7)
Ca(1)−O(3)	2.461(7)	Ca(1)−N(1)	2.550(8)
N(1)−Ca(1)−N(2)	62.8(2)	N(1)−Ca(1)−O(1)	63.1(2)
N(2)−Ca(1)−O(3)	63.2(2)	N(1)−Ca(1)−O(6)	89.0(2)
N(2)−Ca(1)−O(5)	78.1(3)	O(1)−Ca(1)−O(3)	170.7(2)
O(3)#−Ca(1)−O(4)#	50.9(2)	O(1)−Ca(1)−O(3)#	73.6(2)

[a] The # symbol indicates that the atom involved is from a neighboring $[Ca(PDA)(H_2O)_2]\cdot 2H_2O$ individual involved in forming a four-membered chelate ring via a bridging $-COO^-$ group.

competition experiments at biological pH, when analyzed by TLC, the Gd is almost exactly evenly distributed between the PDA and the DTPA. It may turn out that PDA does not satisfy all the requirements to be completely successful as an MRI agent, but the work reported here suggests that the principles embodied in the type of architecture present in PDA and its analogues could be used to design improved Gd(III)-based MRI agents.

Structure of $[Ca(PDA)(H_2O)_2]\cdot 2H_2O$ (1). The structure of the complex in **1** is shown in Figure 7, which shows that there is a chain of $[Ca(PDA)(H_2O)_2]$ individuals. These are held together by the carboxylates, which are shared between Ca atoms from two adjacent individuals, forming a unidentate bond to the Ca atom from the same complex, and chelating with the Ca from a neighbor. Each Ca(II) is 8-coordinate, including the four donors from the PDA ligand, two coordinated water molecules, and the bridging chelating carboxylate from a neighboring $[Ca(PDA)(H_2O)_2]$ individual. What is important is the extent to which PDA coordinates to Ca(II) in a low-strain manner in **1**. The Ca−N bond lengths (Table 4) involving the 1,10-phen moiety of PDA, at 2.550 and 2.556 Å are very similar to those found in 8 structures for Ca(II) with 1,10-phen itself in the CSD,[33] which average 2.57 ± 0.04 Å. The N−Ca−N angle in **1** is 62.8°, compared to an average of 64.2 ± 1.0° for the 1,10-phen structures of Ca(II) in the CSD. Similarly, the Ca−O bonds to the carboxylates of PDA in **1** average 2.46 Å for unidentate

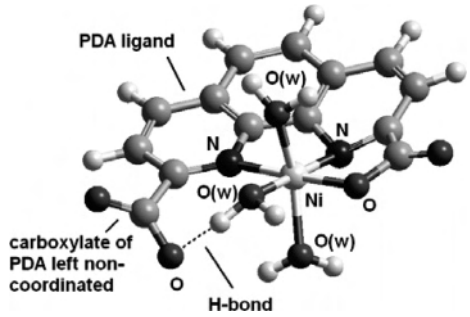

Figure 8. Structure of the complex $[Ni(PDA)(H_2O)_3]$ generated by semiempirical PM3 calculation.[41] The starting structure had the Ni(II) bonded to all four donor atoms of PDA, with three waters coordinated to the Ni(II). During refinement, the PDA became only 3-coordinating, and an H-bond formed between the noncoordinated carboxylate of PDA and one of the water molecules coordinated to the Ni(II). This structure generated by semiempirical calculation strongly resembles the reported[14] complex of Ni(II) with PDA.

bonding, with N−Ca−O angles of 63.1 and 63.2°, compared to the chelate rings of pyridine carboxylate complexes of Ca(II) in the CSD with Ca−O bonds averaging 2.46(2) Å and N−Ca−O angles averaging 63.7(1.4)°. In addition, the Ca(II) lies almost exactly in the plane of the very nearly planar PDA ligand. One can thus conclude that the structure of **1** suggests that the Ca(II) in the tetradentate PDA ligand has as near as possible the same geometry as Ca(II) in structures of much less sterically demanding ligands in the CSD which have the same donor groups, and therefore Ca(II) binds to PDA in a low-strain manner.

The structure of the Ni(II) complex[14] of PDA is quite revealing. Here, the Ni(II) with an ionic radius[10] of 0.74 Å is too small to span the donor atoms of PDA, which appears to require a metal ion with a radius of ∼1.0 Å. The structure shows that the Ni(II) in its PDA complex does not bond to all four donor atoms and is effectively only 3-coordinate from the PDA, with one carboxylate left noncoordinated and H-bonded to a water on the Ni(II). Interestingly, semiempirical[41] PM3 calculations on this same complex, with a starting structure with a Ni(II)/PDA complex with the Ni bonded to all four donor atoms of PDA, refined to a structure (Figure 8) with only 3-coordinating PDA, similar to the experimental structure.[14]

MM Calculations on PDA Complexes. MM can be used to determine best-fit sizes of metal ions[11] for complexing with any particular ligand by calculating the strain energy of the metal−ligand complex as a function of the M−L bond length. In such a calculation, all the force constants involving the metal ion are kept constant, and the ideal M−L bond length is varied over the desired range. A plot of U_{ML} (the strain energy of the complex) versus M−L length thus gives a curve with a minimum in it, which then corresponds to the best-fit M−L length. Such a calculation was carried out for $[M(PDA)(H_2O)_2]$ keeping all force constants at the default values in HyperChem[9] for high-spin Ni(II) and varying the ideal Ni−N and Ni−O lengths. The latter was kept at a constant 0.06 Å shorter than the M−N length, which is a typical difference in bond length caused by the smaller ionic

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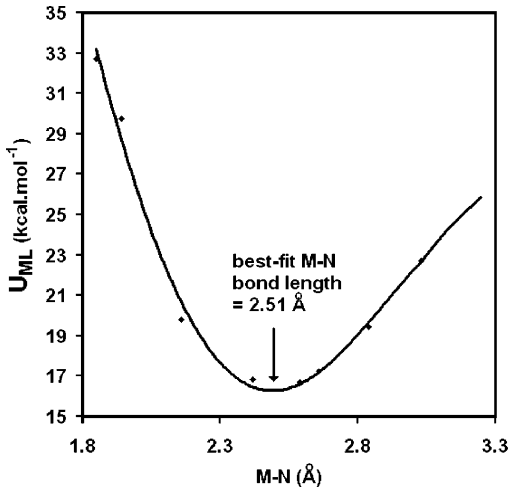

Figure 9. Plot of strain energy (U_{ML}) for the [M(PDA)(H_2O)$_2$] complex calculated by MM[11] as described in the text, as a function of ideal M−N bond length.

radius[10] of O than N. The plot of U_{ML} versus M−N length is shown in Figure 9. The best-fit M−N length is about 2.51 Å, which means that with an ionic radius[10] for N of 1.55 Å, the best-fit ionic radius should be 0.96 Å. This agrees quite well with metal ions with ionic radii in this vicinity (Cd(II), 0.95; Gd(III), 0.92, Ca(II), 1.00, La(III), 1.03 Å) forming complexes with PDA that show the greatest thermodynamic stabilization of their PDA complexes.

Studies on other derivatives of PDA are being carried out and indicate that ligands such as PDAM and PDALC (Figure 2) also show large thermodynamic stabilizations.[42] DPADA in Figure 2 should show an even stronger stabilization than PDA. The ligand DPNDA (Figure 2) should follow the ligand chelate ring-size rule[11,12] and be highly selective for small metal ions. The ligands described here have many potential applications, including selective removal of metal ions from radioactive wastes, and detection of Ca(II) in biological systems by fluorescence.[43] A distinct ligand design advantage that these ligands offer compared to macrocycles is the ability to include negative O-donors such as carboxylates and phenolates within the highly preorganized part of the ligand, which leads to much greater thermodynamic stability and sharper metal ion selectivity. Slow metalation and demetalation reactions are a drawback to the use of macrocycles in many situations. The presence of terminal donor atoms within the highly preorganized binding site of the ligands described here lead to rapid metalation/demetalation reactions, which preliminary work with PDA suggests is the case. Interestingly, transmetalation reactions, such as displacement of Gd(III) by Cd(II), are extremely slow, on the order of hours to days depending on the concentration of the entering metal ion, which could be useful in biomedical situations where loss of, for example, Gd(III) from a contrast agent by displacement by, for example, Zn(II) should be slow.

Conclusions. This study has shown for the first time the significant stabilization of complexes of metal ions of a tetradentate ligand such as PDA, which is derived by attachment of donor groups to the 2 and 9 positions of 1,10-phen and owes its high level of preorganization to the rigidity of its 1,10-phen-based backbone. Ligands of this type show sharp selectivity for metal ions with an ionic radius of about 1.0 Å. PDA is a member of an unrecognized class of ligands, which includes 1,10-phen itself, which show levels of preorganization higher than that of macrocycles, and show promise of being useful in a wide variety of applications.

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Supporting Information Available: Crystallographic data in CIF format. This material is available free of charge via the Internet at http://pubs.acs.org.

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