Macrocyclic Ligands with 18-Membered Rings Containing Pyridine or Furan Groups: Preparation, Protonation, and Complexation by Metal Ions

George L. Rothermel, Jr., Lan Miao, Anna L. Hill, and Susan C. Jackels*

Department of Chemistry, Wake Forest University, Winston-Salem, North Carolina 27109

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The synthesis of 18-membered macrocyclic ligands containing saturated amine and either pyridine or furan heterocyclic units is described. The protonation equilibria were studied by potentiometric titrations in which four protonation steps were observed for each ligand in the pH ranges 3–12. The protonation mechanism of these macrocyclic ligands was determined from potentiometric titrations followed by ^{1}H NMR and is consistent with protonation of only the saturated amine groups in the pH range studied. The formation constants for complexes of pyo$_2$[18]dieneN$_6$ with Ca(II), Mg(II), Mn(II), Cu(II), Zn(II), Cd(II), La(III), and Gd(III), determined potentiometrically, follow the order of the Irving–Williams series and are consistent with 1:1 metal ion binding. Furthermore, pyo$_2$[18]dieneN$_6$ binds as well or better than its saturated homolog, [18]aneN$_6$. In contrast, furo$_2$[18]aneN$_4$O$_2$ does not bind effectively in comparison to the saturated homolog, *trans*-[18]aneN$_4$O$_2$. The difference in binding may be due to a combination of enthalpic (polarity of ligating groups and steric strain of the ligand) and entropic (rigidity of the ligand) contributions.

Introduction

Polyaza macrocyclic ligands of the series [*X*]aneN$_y$, where *X* varies between 9 and 30 and *y* between 3 and 10, have been the subject of many investigations.[1,2] The smaller members of the series with $y = 3$ or 4 have become classics of coordination chemistry, and the larger members with $y = 7$ or greater have been of recent interest as hosts for inorganic and organic cations and for multiple metal ions. The members of intermediate size with $y = 5$ or 6 have received less attention as ion hosts[3] or metal chelating agents,[4,5] even though it was pointed out long ago that [18]aneN$_6$ is the smallest ligand theoretically capable of performing an octahedral wrap about a metal ion.[6] Richman and Atkins[7] synthesized [18]aneN$_6$, and Kimura et al.[4,5] have investigated its binding constants with a number of metal ions. The isomers of Co[18]aneN$_6^{3+}$ and their interconversions have been studied in detail by Searle.[8] It is of particular interest that [18]aneN$_6$ binds well to lanthanide ions; therefore, this ligand can serve as a model for the design of ligands for large ions. However, its binding to Ca(II) is quite modest with a log K^{CaL} of 2.5.

Linear polyaza ligands incorporating 2- and/or 2,6-substituted pyridine groups have higher metal ion binding constants than their saturated polyamine analogues.[9] This increased stability has been attributed to factors arising from both enthalpic and entropic components. Pyridine's higher dipole moment relative to alkyl amines increases its effective donor attraction, even in cases of non-π-bonding metals. In addition, pyridine-containing chelate rings have lower ring strain than analogous chelate rings formed from alkyl amines.[9] The entropic contributions of pyridine-containing ligands with Ni(II) have been attributed to preorganization or restricted rotation of pyridine-containing chelate rings.[10]

Pyridine has been incorporated into macrocyclic polyaza ligands to provide multiple-metal ion chelators,[11] large-cavity macrocycles,[12] cryptands,[13] and components of ion-selective electrodes.[14] In this work, we are interested in incorporating pyridine groups into [18]aneN$_6$ in order to produce a ligand with increased rigidity and potentially improved binding ability toward Ca(II) and the trivalent lanthanides. Similarly, the incorporatin of furan into the [18]aneN$_4$O$_2$ framework can potentially improve the binding ability of this ligand. The template syntheses, based on 2,6-pyridinedicarbaldehyde or 2,5-furandicarbaldehyde, pioneered by Nelson[15] and Fenton,[16] provide high-yield synthetic routes to furan- and pyridine-containing macrocycles.

In this paper we report the preparation, characterization, and metal binding properties of the ligands pyo$_2$[18]dieneN$_6$ and furo$_2$-[18]aneN$_4$O$_2$, shown in Chart I. The stability constants for complexes of these ligands will be compared with the saturated donor analogues, [18]aneN$_6$ and [18]aneN$_4$O$_2$.

Experimental Section

Preparations. Starting materials were obtained from Aldrich Chemical Co. or Fisher Scientific Co. and were used without further purification. 2,6-Pyridinedimethanol and $BaMnO_4$ were prepared by following literature procedures.[17-20] The preparation of 2,6-pyridinedicarbaldehyde[21] was improved by using $BaMnO_4$ and is therefore reported in detail.

2,6-Pyridinedicarbaldehyde. 2,6-Pyridinedimethanol (1.00 g, 7.19 mmol) was stirred with 100 mL of methylene chloride. Finely crushed,

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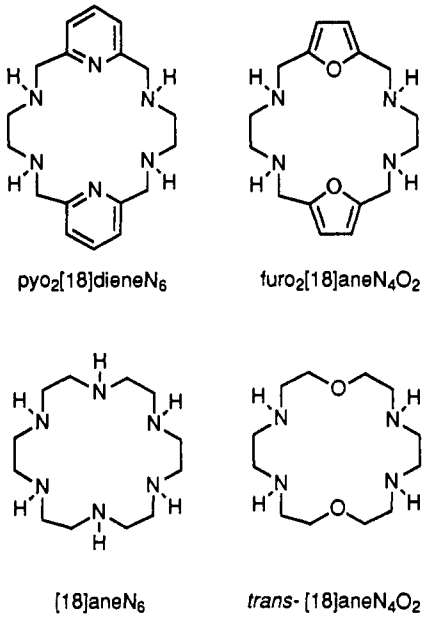
Chart I



dry $BaMnO_4$ (15.0 g, 58.5 mmol) was added with constant stirring. After being refluxed with constant stirring for 12 h, the dark blue mixture was then allowed to cool to room temperature and was diluted with 200 mL of methylene chloride. The mixture was filtered through microcrystalline cellulose, and the dark blue solid material was washed repeatedly with methylene chloride. The filtrates were combined and then evaporated to dryness under reduced pressure. The cream colored solid product was isolated and dried in a vacuum desiccator (yield 0.62 g, 64%). Mp = 122 °C, lit[21] mp = 122–123 °C. ^1H NMR ($CDCl_3$/TMS reference 0.00 ppm): δ = 8.20 (m, 3 H), 10.19 (s, 2 H). ^{13}C NMR ($CDCl_3$/TMS): δ = 125.4, 138.5, 152.9, 192.4.

3,6,14,17,23,24-Hexaazatricyclo[17.3.1.1^{8,12}]tetracosa-1(23),8,10,12-(24),19,21-hexaene Tetrahydrobromide Monohydrate (pyo$_2$[18]dieneN$_6$·4HBr·H$_2$O). A solution of ethylenediamine (2.00 mL, 30 mmol in 20 mL of methanol) was added dropwise over 15 min to a stirred solution of 2,6-pyridinedicarbaldehyde (4.05 g, 30 mmol) and $BaCl_2·2H_2O$ (3.66 g, 15 mmol) in 150 mL of anhydrous methanol. The mixture was refluxed for 4 h. After the yellow solution was allowed to cool to room temperature, solid $NaBH_4$ (3.0 g, 80 mmol) was added slowly and the flask was placed in an ice bath and was stirred for 30 min. A second addition of $NaBH_4$ (1.5 g, 40 mmol) was made, and the resulting yellow-white mixture was stirred at room temperature for 1.5 h. Evaporation of the solvent under reduced pressure yielded a yellow-white product that was extracted with chloroform (4 × 100 mL) and was filtered. Evaporation of the combined extracts to dryness under reduced pressure yielded an orange oil. This oil was dissolved in 80 mL of methanol, and 48% hydrobromic acid (about 12 mL) was added until pH paper tested strongly acidic. During the addition, an off-white solid precipitated (8.1 g, 83% yield, crude tetraprotonated macrocycle). The product was recrystallized by dissolving in a minimum amount of hot H_2O to which was added a small amount of activated carbon. After the mixture was filtered, absolute ethanol was added to incipient cloudiness while the heating and stirring were maintained. The solution was cooled to room temperature and placed in a refrigerator overnight. The white crystalline solid (59% recovery) was washed with ice cold ethanol and stored in a vacuum desiccator. Mp = 291 °C dec. ^1H NMR (D_2O, reference DSS at 0.00 ppm): δ = 3.79 (s, 4 H), 4.55 (s, 4 H), 7.46 (d, J = 7.8 Hz, 2 H), 7.90 (t, J = 7.8 Hz, 1 H). ^{13}C NMR (D_2O, dioxane reference at 66.5 ppm): δ = 44.8, 51.3, 122.4, 139.6, 150.2. Anal. Calcd for $C_{18}H_{32}N_6OBr_4$: C, 32.36; H, 4.83; N, 12.58; Br, 47.84. Found: C, 32.24; H, 4.79; N, 12.71; Br, 46.74. IR (cm^{-1}): ν_{O-H} 3460 (m), 3410 (m); ν_{C-H} 3020–3010 (s), 2980–2960 (s); ν_{N-H} 2800–2330 (m, br); $\nu_{C=C,C=N}$ 1595, 1580, 1550, 1465 (m), 1438 (s). MS (of fully deprotonated ligand) (m/z, ion, relative %): 326.3 (parent ion), $C_{18}H_{26}N_6^+$, 20.2; 163.2, $C_9H_{13}N_3^+$, 74.8; 133.2, $C_7H_7N_3^+$, 70.4; 105.2, $C_7H_7N^+$, 100.0; 77.2, $C_5H_3N^+$, 29.2.

2,5-Furandicarbaldehyde was prepared by $BaMnO_4$ oxidation of 2,5-furandimethanol analogous to the preparation of 2,6-pyridinedicarbaldehyde given above. Yield: 70%. Mp = 109–110 °C, lit[22] mp = 109–110 °C. ^1H NMR ($CDCl_3$/TMS): δ = 7.32 (s, 1 H), 9.83 (s, 1 H). ^{13}C NMR ($CDCl_3$/TMS): δ = 119.4, 154.2, 179.2.

21,22-Dioxa-3,6,13,16-tetraazatricyclo[16.2.1.1^{8,11}]docosa-1(20),8,-10,18-tetraene Tetrahydrobromide Hydrate (furo$_2$[18]aneN$_4$O$_2$·4HBr·1.5H$_2$O). A solution of ethylenediamine (2.68 mL, 40 mmol) in 40 mL of methanol was added dropwise with stirring over a period of 15 min to a stirred solution of 2,5-furandicarbaldehyde (5.0 g, 40 mmol) and $Ba(SCN)_2·3H_2O$ (6.4 g, 20 mmol) in 360 mL of anhydrous methanol. The mixture was stirred for 3–4 h at room temperature. Then solid $NaBH_4$ (6.05 g, 160 mmol) was added slowly, and the flask was placed in an ice bath and was stirred for 30 min. Then the mixture was stirred for an additional 2 h at room temperature. Evaporation of the solvent under reduced pressure yielded a yellow-white solid that was extracted with chloroform (4 × 100 mL) and was filtered. Evaporation of the combined extracts to dryness under reduced pressure yielded an orange oil. The oil was dissolved in 60 mL of methanol, and 48% hydrobromic acid (about 15 mL) was added to produce a pale yellow precipitate in a strongly acidic solution. The yellow solid was isolated and dried under vacuum (8.8 g, 70% yield). The crude product was recrystallized by the same procedure given above for pyo$_2$[18]dieneN$_6$·4HBr (74% recovery). Mp = 273 °C dec. ^1H NMR (D_2O, reference DSS at 0.00 ppm): δ = 3.47 (s, 2 H), 4.49 (s, 2 H), 6.79 (s, 1 H). ^{13}C NMR (D_2O, reference dioxane at 66.5 ppm): δ = 40.8, 42.4, 115.9, 146.2. Anal. Calcd for $C_{16}H_{31}N_4O_{3.5}Br_4$: C, 29.33; H, 4.77; N, 8.55; Br, 48.79. Found: C, 29.24; H, 4.81; N, 8.56; Br, 48.00. IR (cm^{-1}): ν_{O-H} 3590 (w); ν_{C-H} 3015 (m), 2980 (s); ν_{N-H} 2780–2380 (m, br); $\nu_{C=C}$ 1570, 1540 (m). MS (of fully deprotonated ligand) (m/z, ion, relative %): 304.3 (parent ion), $C_{16}H_{24}N_4O_2^+$, 3.24; 152.2, $C_8H_{12}N_2O^+$, 85.3; 122.2, $C_6H_6N_2O^+$, 100.0; 94.2, $C_6H_6O^+$, 87.4; 66.2, $C_4H_2O^+$, 14.4.

Characterization Methods. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, TN. IR spectra were obtained on a Perkin-Elmer Model 1330 spectrophotometer using mineral oil mulls on KBr disks. ^1H and ^{13}C NMR spectra were obtained on a Varian VXR-200 spectrometer at 200 MHz. Mass spectra were obtained using a Hewlett Packard Model 5990A mass spectrometer and a Hewlett Packard Model 5890 Series 2 gas chromatograph with a column (12 m × 0.2 mm × 0.33 μm) comprised of methyl silicone gum. Samples were injected as solutions in methylene chloride, and the column was ramped between 150 and 300 °C over 12 min.

Potentiometric Titrations. Potentiometric titration data were obtained using a Mettler DL21 automatic titration in conjunction with Mettler TS^2 titration software operating on a Zenith 386-SX computer. The electrode employed during these titrations was a combination glass electrode (Mettler DG-111-SC) that was standardized at pH 4.00 and 7.00 before each titration. Titrations were carried out in a jacketed cell maintained at 25.0 ± 0.1 °C by a MGW Lauda Brinkman RM6 constant-temperature circulator. Ligand solutions for titrations were prepared by weight from analyzed samples in CO_2-free, deionized distilled water. KCl (0.1 or 0.2 M) was employed to maintain constant ionic strength, and nitrogen gas was bubbled through the solution for 15 min before the titration and then used to blanket the titration vessel. The solutions were titrated with 0.1 M NaOH that was previously standardized against potassium hydrogen phthalate. Metal chlorides and/or nitrates were purchased as 99.9+% purity, and their solutions were titrated to check for the presence of excess free acid. Since an insignificant amount of free acid was found in each case, no correction was included for excess free acid. Solutions of metal salts were standardized complexometrically with EDTA using an appropriate indicator.[23] To prepare solutions containing equimolar metal and ligand, an aliquot of standardized metal solution was added to the ligand solution prepared as above. The protonation and formation constants were determined from three separate potentiometric titrations by fitting titration data using a model for the equilibria present in the system and the program BEST.[24] The standard deviations reported in Tables I and II are from the three data sets. The titration curves had 50–100 points taken with up to 2 min between points for equilibration. Species distribution curves were generated[24] with the program SPE, which calculates the percent species versus pH using the experimentally determined log K_a's.

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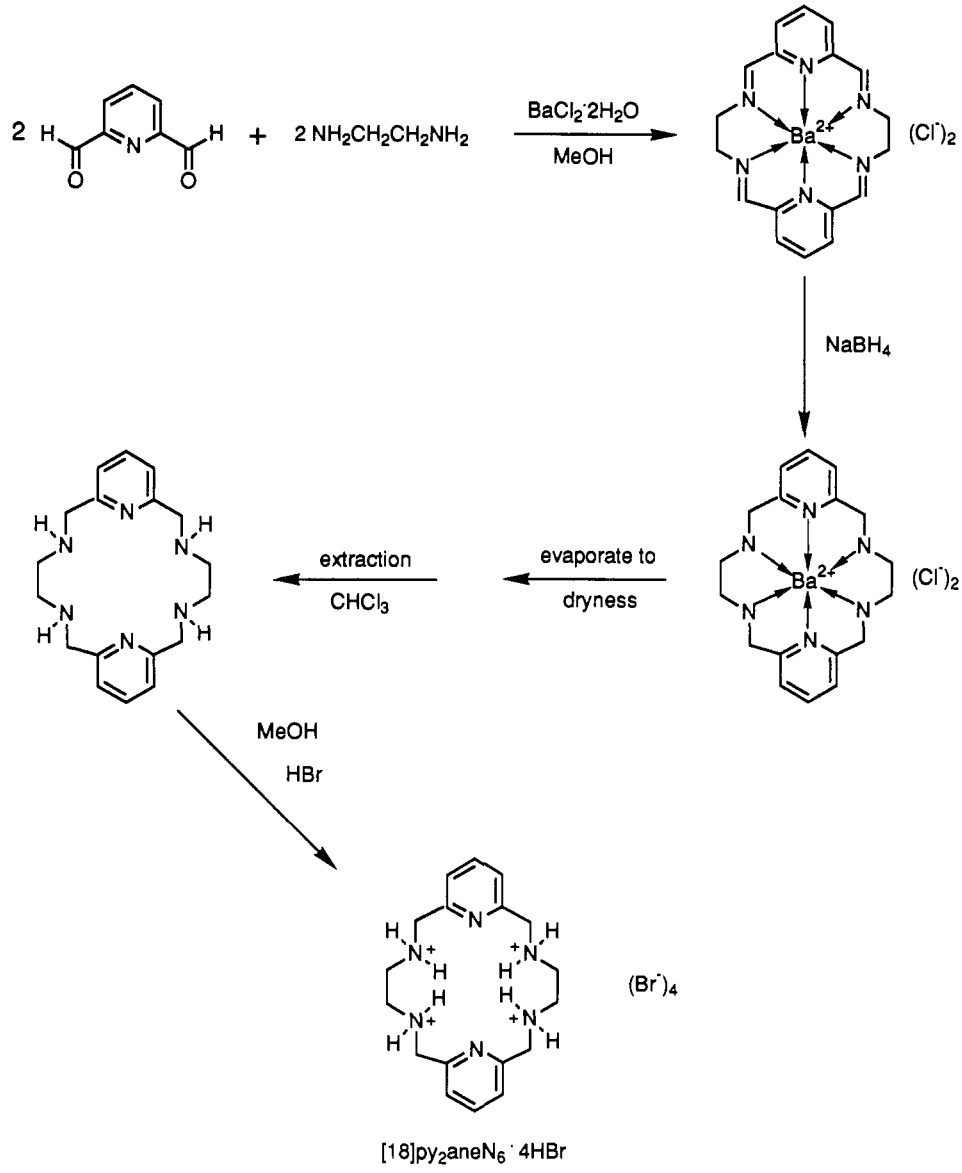
Scheme I. Preparation of $pyo_2[18]dieneN_6 \cdot 4HBr$



$[18]py_2aneN_6 \cdot 4HBr$

Titrations Followed by NMR. The pH titration of $pyo_2[18]dieneN_6 \cdot 4HBr$ was also followed by proton NMR spectra recorded on a Varian VXR, 200-MHz spectrometer at the ambient temperature of 24.6 ± 0.1 °C. Peak positions are reported relative to HOD at 4.75 ppm. A solution of $pyo_2[18]dieneN_6 \cdot 4HBr$ (0.1 M) was prepared with D_2O as the solvent. KCl (0.5 M) was added to maintain constant ionic strength. NaOD in D_2O (2.5 M) was added in increments to adjust the pD. The pD of the solution was measured with a semimicro combination electrode (Aldrich Chemical Co.) which was previously standardized with aqueous buffer standards and then equilibrated in D_2O. The pH was then calculated from the measured pD values by using the following relationship:[25]

$$pH = pD - 0.40$$

Results and Discussion

Synthesis. The two macrocyclic ligands $pyo_2[18]dieneN_6$ and $furo_2[18]aneN_4O_2$ were prepared using the well established 2 + 2 template condensation method, followed by $NaBH_4$ reduction of the imines as shown in Scheme I. Ba(II) was chosen as the templating ion due to its success in promoting template condensations of macrocycles of this ring size.[15] This adaptation of the synthetic scheme is yield-optimized (83% and 70% yield from pyridinedicarbaldehyde and furandicarbaldehyde, respectively) and convenient in that the condensation and reduction steps are performed in a single step. The ligands are obtained metal-free as the tetrahydrobromide salts. The elemental analyses and determination of hydrogen ion equivalents by potentiometric titration are consistent with these formulations. The NMR and mass spectral data reported in the Experimental Section confirm the structures of the ligands.

Proton Binding Studies. The curve for potentiometric titration of $pyo_2[18]dieneN_6 \cdot 4HBr$ with NaOH is shown in the curve labeled L·4HBr in Figure 1. There are two inflection points, at 2 and 4 equiv of base, indicating successive titration of protons in approximately two-proton steps. A model consisting of four protonation steps was used to fit the potentiometric data using the program BEST. Three data sets each consisting of 53 points (pH, volume) gave very good fits, resulting in the proton binding constants given in Table I. The average deviation between observed and calculated pH was less than 0.015 pH units. There are two protonations with log K_a in the range 8–9 and two in the range 5–7. This protonation behavior contrasts with that of $[18]aneN_6$, for which there are three log K_a's in the range 8–11 and three in the range 1–4, but is similar to that for $pyo_2[22]dieneN_6$, where only four protonations are observed in the log K_a range 3–10.[11] The results for $[18]aneN_6$ have been interpreted in terms of the first three protons being bound in the ring each pairwise

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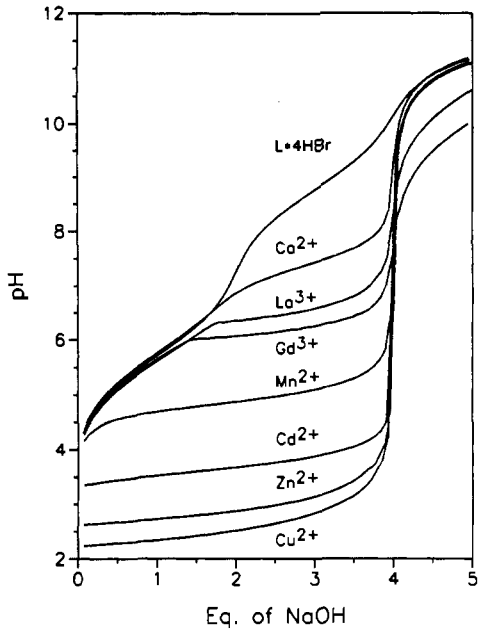


Figure 1. Potentiometric titration curves of $pyo_2[18]dieneN_6 \cdot 4HBr$ without added metal (L·4HBr) and with equimolar amounts of the metal ions specified. Conditions: 0.20 M KCl, 25 °C. Note: Two curves displaced to lower pH in the region above 4 equiv of NaOH are La^{3+} and Gd^{3+}.

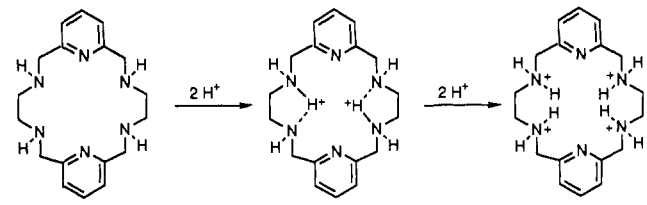
Table I. Proton Binding Constants (log K_n) for Ligands in Aqueous Solution at 25 °C

ligand	log K_n n 1	2	3	4	(ref), note
$pyo_2[18]dieneN_6$	9.13	8.32	6.12	5.24	(this work), *a*
$pyo_2[22]dieneN_6$	9.11	8.32	7.12	3.72	(11), *b*
$[18]aneN_6$	10.19	9.23	8.73	4.09	(7), *c*
$furo_2[18]aneN_4O_2$	8.84	7.73	5.20	4.21	(this work), *a*
trans-$[18]aneN_4O_2$	9.36	8.40	6.27	5.23	(34), *d*
bamp	9.53	9.15			(26), *e*

[a] Measured in 0.1 M KCl ($furo_2[18]aneN_4O_2$) or 0.2 M KCl ($pyo_2[18]dieneN_6$). Standard deviations at the 95% confidence level for the log K_n values are as follows (n, $\pm 2\sigma$): $pyo_2[18]dieneN_6$ (1, 0.12), (2, 0.08), (3, 0.06), (4, 0.12); $furo_2[18]aneN_4O_2$ (1, 0.04), (2, 0.04), (3, 0.06), (4, 0.08). [b] Measured in 0.01 M $NaClO_4$. [c] Two more protons were bound with log $K_5 \approx 2$ and log $K_6 \approx 1$. Measured in 0.2 M $NaClO_4$. [d] Measured in 0.1 M $NaNO_3$. [e] bamp is 2,6-bis(aminomethyl)pyridine. Measured in 1 M $NaNO_3$ at 20 °C.

to adjacent nitrogen atoms with the second three protons being added to form the hexaprotonated ligand having H^+ bound to each amine site.[5] The difference in log K_a's presumably is due to the stability of the favorable hydrogen bonding in the hexaaza cavity for the first three, while, in the latter three, the buildup of positive charge in close proximity destabilizes the protonated forms. The pyridine-containing ligands, $pyo_2[18]dieneN_6$ and $pyo_2[22]dienN_6$, show behavior similar to that of the open-chain analogue, 2,6-bis(aminomethyl)pyridine (bamp),[26] for which the log K_a for proton binding at the amine nitrogen sites is about 9 and at the pyridine nitrogen site is less than 3. In contrast to $[18]aneN_6$ there is no enhancement in proton binding of the first proton in the cyclic ligand as compared to bamp. Thus, in the pyridine-containing macrocycles, the behavior is consistent with protonation occurring only at the amine nitrogen sites, with the first two protons bound pairwise having log K_a in the range 8–10 and the second two protons added to produce four quaternary amines having log K_a in the range of 6 or less. These results are summarized in Scheme II. The species distribution curves indicate that approximately 85% of the species exists in the diprotonated

Scheme II. Protonation of $pyo_2[18]dieneN_6$



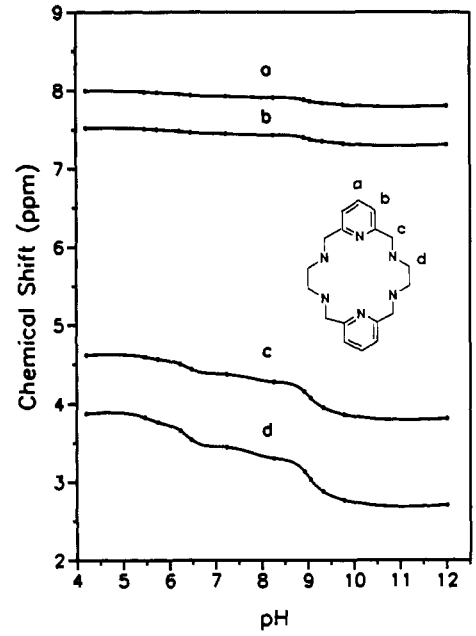


Figure 2. Plot of the ^1H NMR chemical shifts of protons in $pyo_2[18]dieneN_6$ versus pH of the solution. Conditions: D_2O solvent with pD adjusted by additions of NaOD, 25 °C.

form at pH 7. Accordingly, the diprotonated form of this ligand can be isolated from neutral solution.[27]

Further evidence in support of this protonation scheme for $pyo_2[18]dieneN_6$ was obtained from ^1H NMR spectra taken during the titration of the tetrahydrobromide salt in D_2O with NaOD. As shown in Figure 2, the chemical shifts of the methylene group protons change as a function of pH corresponding to the deprotonation steps observed in the potentiometric titrations, whereas the chemical shifts of the pyridine protons are nearly invariant. In view of the known sensitivity of the chemical shift at the four position on pyridine to N-protonation,[28] these results clearly indicate protonation of the amine nitrogens in analogy to $[18]aneN_6$ and nonparticipation of the pyridine nitrogens in protonation over the pH range 3–12.

The potentiometric titration of $furo_2[18]aneN_4O_2 \cdot 4HBr$ with NaOH is shown in the curve labeled L·4HBr in Figure 3. As in the case of the pyridine analog, there are two breaks at 2 and 4 equiv of base, indicating successive titration of protons in approximately two-proton steps. The proton binding constants (Table I) of $furo_2[18]aneN_4O_2$ are seen to be almost the same as those of $pyo_2[18]dieneN_6$, consistent with an analogous protonation scheme for the furan-containing ligand. This result is quite reasonable in view of the low basicity of the furan oxygen atoms.

Metal Ion Binding Studies. The curves for the potentiometric titrations of $pyo_2[18]dieneN_6 \cdot 4HBr$ with added equimolar metal ions, Ca^{2+}, La^{3+}, Gd^{3+}, Mn^{2+}, Cd^{2+}, Cu^{2+}, and Zn^{2+}, are shown in Figure 1. In comparison with the titration curve of the free ligand, the pH values of the metal-containing solutions all are shifted to lower pH by the release of protons according to the

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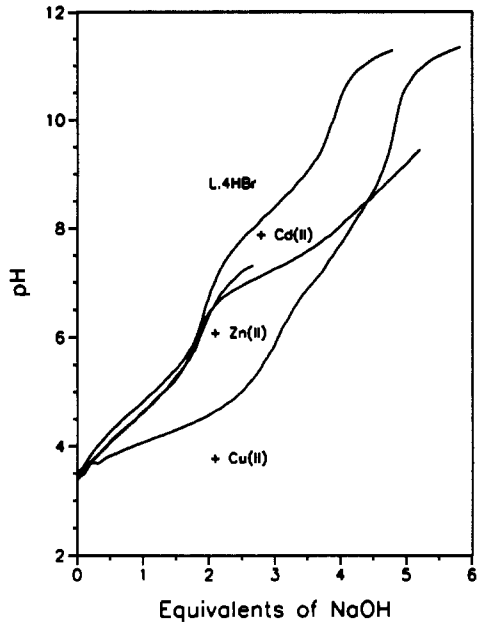


Figure 3. Potentiometric titration curves of furo$_2$[18]aneN$_4$O$_2$·4HBr without added metal (L·4HBr) and with equimolar amounts of the metal ions specified. Conditions: 0.10 M KCl, 25 °C.

Table II. Metal Ion Binding Constants (log K^{ML})[a]

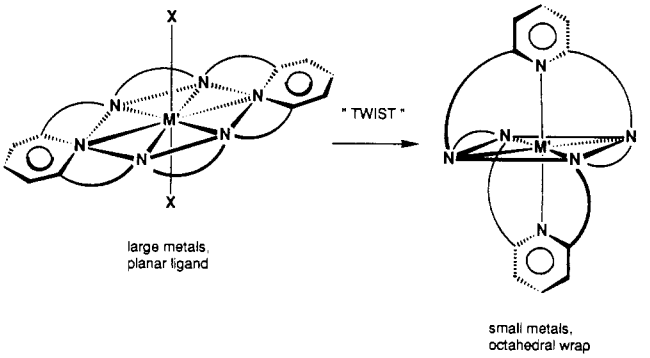
	ligand			
metal	pyo$_2$-[18]dieneN$_6$	[18]aneN$_6$[35]	furo$_2$-[18]aneN$_4$O$_2$	*trans*-[18]aneN$_4$O$_2$[34]
Mn^{2+}	12.5		*b*	
Cu^{2+}	[25]	*c*	*d*	16.3
Zn^{2+}	[21.1]	17.8	*e*	10.5
Cd^{2+}	17.2	17.9	*e*	10.9
La^{3+}	7.4	5.7		
Gd^{3+}	8.1	8.4		
Ca^{2+}	4.4	2.5	*b*	
Mg^{2+}	*b*	*b*	*b*	

[a] Measured in 0.1 M KCl (furo$_2$[18]aneN$_4$O$_2$) or 0.2 M KCl (pyo$_2$[18]dieneN$_6$), aqueous solution, 25 °C. Standard deviations at the 95% confidence level for the log K^{ML} values for pyo$_2$[18]dieneN$_6$ are as follows (M, $\pm 2\sigma$): (Mn^{2+}, 0.20), (Cu^{2+}, 0.52), (Zn^{2+}, 0.16), (Cd^{2+}, 0.08), (La^{3+}, 0.10), (Gd^{3+}, 0.08), (Ca^{2+}, 0.10). [b] No complex formation found. [c] Strong complex formation, K^{ML} not reported. [d] Extensive hydrolysis present. [e] Precipitate formed.

different abilities of the metal ions to bind to pyo$_2$[18]dieneN$_6$. All metal–ligand curves have a break at 4 equiv of base. The displacement of the La^{3+} and Gd^{3+} curves to lower pH above 4 equiv of base is presumably due to hydrolysis. Titrations of solutions containing metal in excess of ligand gave no indication of 2:1 binding (up to 2 equiv of metal/ligand). Accordingly, the binding constants for the metal complexes were evaluated from the curves using a 1:1 binding model. The average deviation between the observed and calculated pH was less than 0.02 pH units in all cases, except for the lanthanides, which were less than 0.08 pH units in average deviation.

The metal binding constants for pyo$_2$[18]dieneN$_6$, shown in Table II, follow the order $Ca^{2+} < La^{3+} < Mn^{2+} < Cd^{2+} < Cu^{2+} > Zn^{2+}$, which is the order of the Irving–Williams series. The same order was seen for [18]aneN$_6$ and was interpreted by Kodama and Kimura[4,8] as indicative of hexacoordination in all cases with little interference from steric hindrance of the ligand. This conclusion is consistent with the ability of [18]aneN$_6$ to perform an octahedral wrap about a metal ion. Whereas [18]aneN$_6$ is capable to an octahedral wrap in two modes, corresponding to meridional and facial disposition of adjacent nitrogen donors,[4,8] pyo$_2$[18]dieneN$_6$ can wrap only in the meridional mode due to the planarity and rigidity imposed by the pyridine groups. Additionally, in order to accommodate larger metal ions, the ligand must be able to "untwist", ultimately to its largest cavity size, which corresponds to a planar macrocycle as shown in Scheme III. Preliminary results[29] from the X-ray crystal structure determination of Zn(pyo$_2$[18]dieneN$_6$)(CF$_3$SO$_3$)$_2$ reveal that the macrocycle is hexacoordinate in an approximate octahedral wrap about the Zn^{2+} ion. Furthermore, the ligand is present in only one of the five possible isomeric forms involving stereochemistry at the amine nitrogen sites corresponding to *RSRS* chirality at the coordinated amine sites. The manipulation of space filling models of this isomeric form of pyo$_2$[18]dieneN$_6$ reveals that it is indeed capable of twisting without steric hindrance to accommodate all sizes of metal ions ranging from its largest cavity size in its planar form to its smallest size in the D_2 symmetry octahedral wrap (see Scheme III). These observations provide a basic understanding of why pyo$_2$[18]dieneN$_6$ binds well to metal ions representing a large range of sizes. The tetra-N-methylated analogue of pyo$_2$[dieneN$_6$ has been reported by Newkome et al.,[30] and the crystal structures of its Co(II) and Cu(II) complexes show that its coordinates analogously to pyo$_2$[18]dieneN$_6$.

Scheme III. Limiting Coordination Geometries for [M(pyo$_2$[18]dieneN$_6$)]$^{n+}$



It is seen from the constants in Table III that pyo$_2$[18]dieneN$_6$ binds to all of the metal ions at least as well as [18]aneN$_6$ does, to within 1 order of magnitude in log K. And in several cases involving the filled-shell ions Ca^{2+}, Zn^{2+}, and La^{3+}, pyo$_2$[18]dieneN$_6$ binds stronger by up to 3 orders of magnitude. Thus, for this group of ions, pyo$_2$[18]dieneN$_6$ forms the stronger complexes of the two ligands. There are several potential sources for the enhanced stability of complexes of the pyridine-containing macrocycle. One is from increased enthalpy of binding due to the higher dipole moment of pyridine (2.19 esu cm, gas phase) as compared to secondary amines (1.03 esu cm for dimethylamine, gas phase).[31] This effect is seen in the relative free energies of formation of pyridine and alkyl amine complexes.[32] Second, the incorporation of pyridine into the macrocycle linked through the 2- and 6-positions relieves potential steric interactions of the ortho hydrogen atoms. Another source could be due to entropic contributions arising from the rigidity of pyridine and the potential ability of pyridine to stabilize the free ligand in a conformation closer to that of the coordinated ligand. These preorganizational effects were reviewed by Hancock and Martell.[33] Further thermodynamic studies will be necessary to identify which of these potential contributions is most important.

In contrast to the pyridine-containing analog, the potentiometric titration curves for furo$_2$[18]aneN$_4$O$_2$ with 1:1 mole ratio of metal

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(33) Hancock, R. D.; Martell, A. E. *Chem. Rev.* **1989**, *89*, 1875–1914.
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ions showed little evidence of binding (Figure 3). The higher stability of *trans*-[18]aneN_4O_2 complexes is not likely to be due to free energy of bonding of ether oxygen as compared to furan oxygen since the gas-phase free energies of formation of both types of complex are comparable.[32,33] Another source of instability of the macrocyclic complexes could be due to unfavorable enthalpic or entropic contributions, where the increased rigidity of the furan ring system does not allow either of the lone pairs of electrons on furan to overlap favorably with the metal ion orbitals. Finally, the furan-containing macrocycle could experience steric strain in twisting to accommodate the size of the metal ion due to the smaller size of the furan ring and the larger angle between substituents, thus necessitating more twisting to accommodate a given size metal ion. A more thorough understanding of the differing abilities of these ligands to bind metal ions awaits further structural and thermodynamic studies on the complexes.

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