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Synthesis and manganese complexes of pentagonal bipyramidal ligands: *N*,*N*′-disubstituted pentaaza macrocycles

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Abstract—Two novel heptadentate ligands, pentaaza macrocycles with two pendant pyridyl and phenol groups, were prepared and the crystal structure of the manganese(II) complex of *N*,*N*′-bis(2-pyridylmethyl)-pentaaza macrocycle revealed a pentagonal bipyramidal geometry.

Seven-coordinated complexes, though not common in transition metal chemistry, are receiving more attention as intermediates in associated reactions of various six-coordinated complexes.[1] Interestingly, some of the metalloenzymes are known to contain hepta-coordinated Mn, Cd, or Mo atoms in the active sites,[2] for example, manganese complexes in glutamine synthetase[3] and inositol monophosphatase,[4] the Mo center in DMSO reductase,[5] or the Cd complex in the cytochrome domain of cellobiose dehydrogenase.[6] Therefore, an understanding of hepta-coordinated complexes provides a broader foundation for the understanding of metalloenzymes.

In order to obtain hepta-coordinated complexes of transition metals, several types of ligands have been utilized, including planar[7,8] or macrocyclic pentadentates[9–11] and tripodal[12–22] or macrocyclic heptadentates.[23–26] Among the geometry of these complexes, the pentagonal bipyramid (PBP) is the most common structure.[2] The complexes of macrocyclic pentadentate ligands, such as [15]crown-5-ether derivatives[10] or their aza analogs such as pentaazacyclopentadecane are mostly PBP where oxygen or nitrogens of the ring occupy the equatorial plane of the bipyramid. Riley et al. have reported pentagonal bipyramidal Mn(II) complexes of C-substituted pentaaza macrocycles as their dichloro complexes.[27,28] They possess high superoxide dismutase (SOD) activity and one of the optimized complexes, M40403, showed in vivo antitumor,[29] antiarthritis,[30] and pain-relieving[31] activities.

For the heptadentate ligands with PBP geometry, there are a few examples of manganese complexes hepta-coordinated by only one ligand: three triaminoethylamine (tren) based tripodal ligand complexes[14,21,22] and two macrocyclic complexes, [21]aneN_7 complex[23] and *N*,*N*′-bis(2-aminobenzyl)-1,10-diaza-15-crown-5 complex.[26] In this letter, we describe an efficient synthesis and manganese complexes of two pentagonal bipyramidal ligands which are pentaaza macrocycles having two N-substituted axial ligands (Fig. 1).

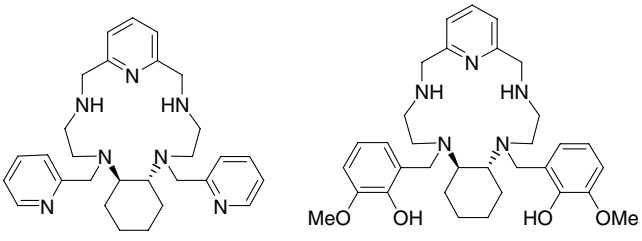

Figure 1. Two heptadentate ligands having two *trans*-axial coordination sites.

Keywords: Manganese; Pentagonal; Bipyramidal; Pentaaza; Macrocycle.
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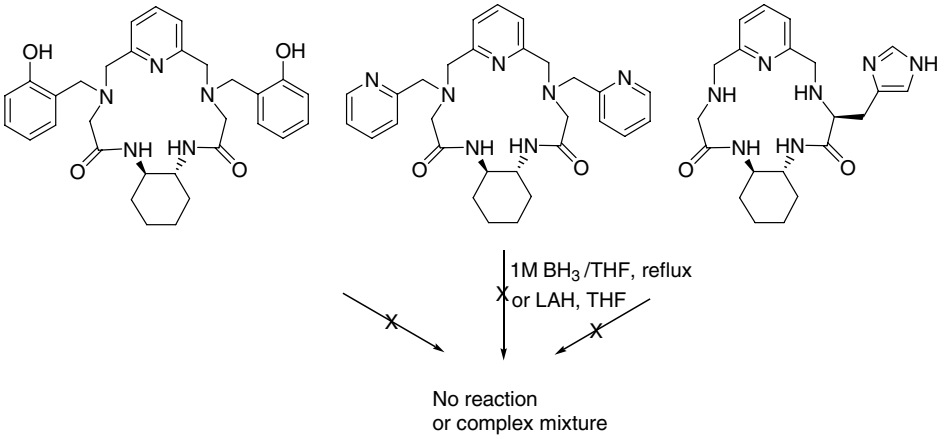
As with the aforementioned macrocyclic pentadentate ligand, the lone pairs of the five macrocyclic nitrogens will occupy the equatorial plane. The two pendant groups, pyridylmethyl or *m*-methoxy-*o*-hydroxybenzyl, are attached to the nitrogens of *trans*-cyclohexyldiamine, so as to be placed in *trans*-diaxial space. These ligands offer a preorganized binding site for one metal ion and can be considered as derivatives of the 15-membered N_5 macrocycles.

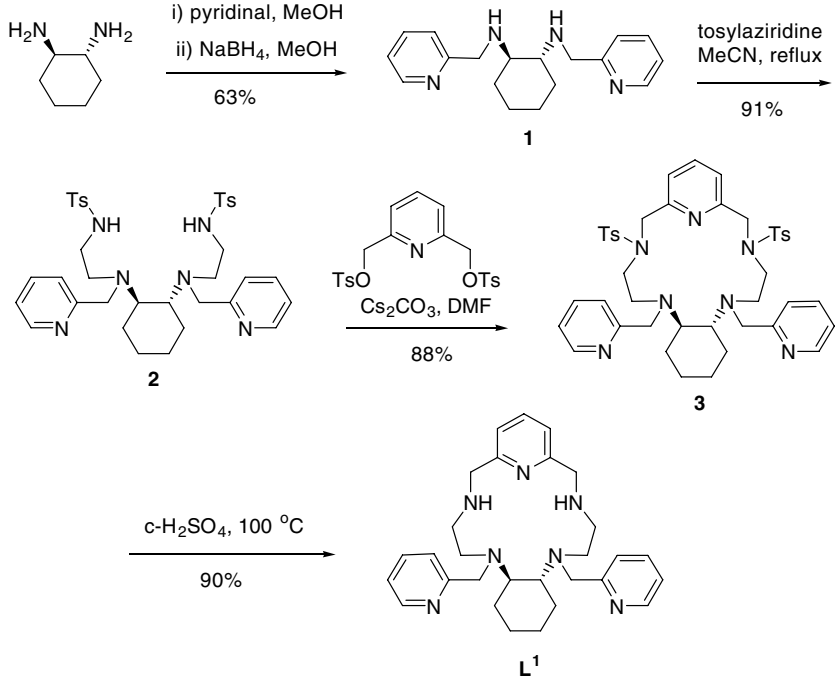
In the synthesis of the pentaaza macrocyclic system, previous study revealed that both Richman–Atkins type cyclization[32–34] and the 'crablike' macrolactam formation/reduction approach[35–37] are useful strategies. For the derivatives of small alkyl groups on carbon, both strategies can be applied, but for large substituents on C or N, especially metal coordinating substituents, the second approach is problematic, because of the difficulty with amide reduction (Scheme 1, unpublished result). Therefore we applied the Richman–Atkins cyclization strategy to synthesize *N*,*N*′-disubstituted cyclic heptadentate ligands.

In order to prepare *N*,*N*′-bispyridyl derivative of pentaaza-macrocycle, reductive alkylation of *trans*-diaminocyclohexane was performed as shown in Scheme 2.

The condensed diimine product from the diamine and pyridine aldehyde was precipitated out from the reaction mixture, and then reduced to the diamine **1** with 63% yield. Incorporation of an additional amine group was performed with tosylaziridine to yield the tetraamine



Scheme 1. Failed reaction condition in the reduction of macrocyclic lactam derivatives.



Scheme 2. Synthesis of bispyridyl pentaaza macrocycle $\mathbf{L^1}$.

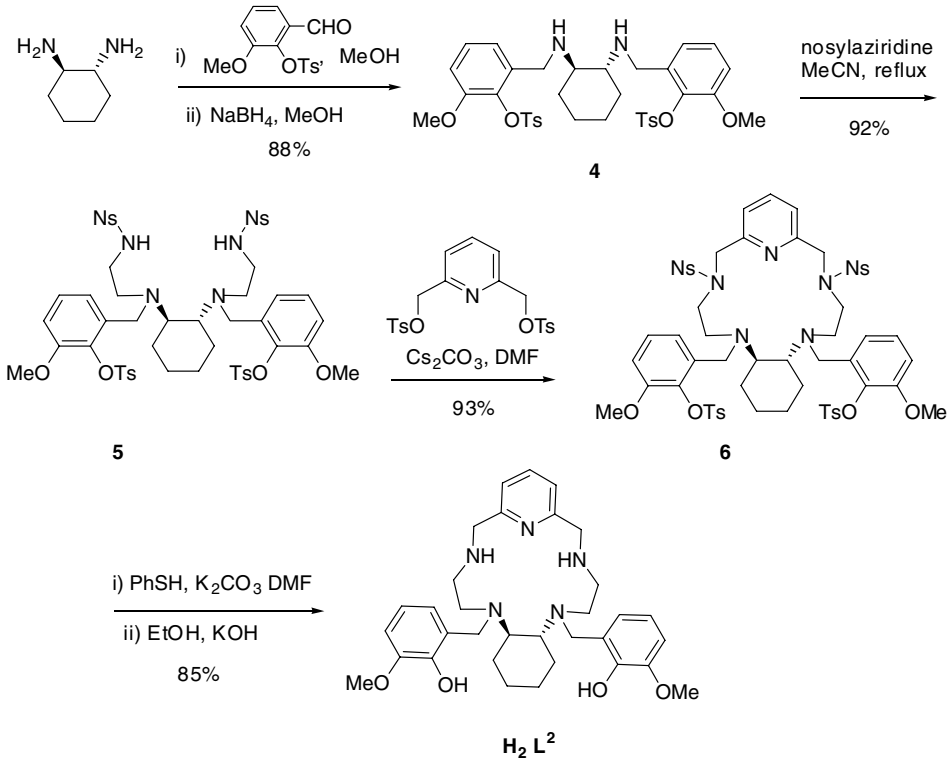
2. Cyclization of the tetraamine **2** with 2,6-pyridinedimethanol bistoluenesulfonate was carried out under cesium carbonate in dimethylformamide with 88% yield. Two tosyl groups of the macrocycle **3** were removed under sulfuric acid to provide the desired heptadentate ligand $\mathbf{L^1}$ (90%).

Synthesis of the *N*,*N*′-bisphenolic derivative of the pentaaza macrocycle $H_2\mathbf{L^2}$ is described in Scheme 3, which takes advantage of the same synthetic strategy as described in Scheme 2. Reductive alkylation of cyclohexyl diamine with tosyl protected phenolic aldehyde afforded the diamine **4** in 88% yield.

Toluene sulfonyl (Ts) was an appropriate protection group for the phenol group. Addition of two aminoethyl groups to **4** was performed with nosylaziridine to yield the tetraamine **5**. In the first trial, we used tosylaziridine in place of nosylaziridine as in Scheme 2, since it is more stable to handle and can be stored for months at room temperature. But a problem occurred when the tosyl group was removed in the last step of the synthesis. Under the usual deprotection condition using sulfuric acid or HBr/AcOH, a complex mixture was obtained, judged by HPLC analysis. One of the side reactions was cleavage of the hydroxy benzyl substituent (Fig. 2).

Therefore, the nosyl group was chosen for the aziridine protection and two hydroxybenzyl pendants were stable under the deprotection condition. Cyclization of the tetraamine **5** with 2,6-pyridinedimethanol bistoluenesulfonate provided the desired product in 93% yield. Finally, the nosyl and tosyl groups of the macrocycle **6** were removed under basic thiophenol and ethanolic KOH conditions, respectively, to provide the desired heptadentate ligand $H_2\mathbf{L^2}$ (85% yield for the two steps).

To prove that the two new ligands are really heptadentate ligands with pentagonal bipyramidal geometry, we



Scheme 3. Synthesis of bisphenolic pentaaza macrocycle $H_2\mathbf{L^2}$.

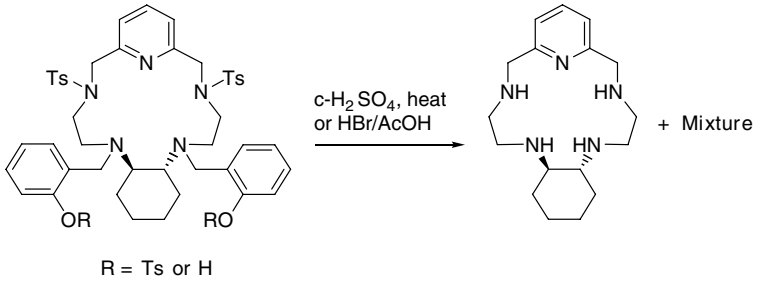


Figure 2. Unsuccessful deprotection of the tosyl group from the bisphenolic derivative.

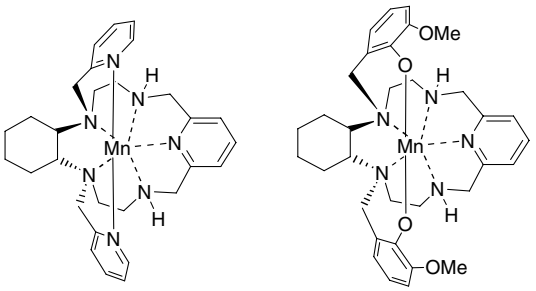


Figure 3. Manganese complexes of the two ligands.

prepared manganese complexes of each in anhydrous MeOH (Fig. 3). Complexation of ligand $\mathbf{L^1}$ with $MnCl_2$ required a refluxing temperature to form a stable complex while the complexation of $H_2\mathbf{L^2}$ proceeded at room temperature to produce a purple solid. These two manganese complexes gave clear separate peaks at later retention times with RP-HPLC (0.1% TFA in CH_3CN/H_2O, pH 2, see Supplementary data) and were soluble in H_2O, CH_2Cl_2, CH_3CN.

Crystal structure analysis of the complex obtained using $\mathbf{L^1}$ revealed the salt form complex, $[Mn\mathbf{L^1}][MnCl_4]$, of the cationic manganese(II) complex ion with hepta-coordinated pentagonal bipyramidal geometry and the anionic manganese(II) complex ion with tetrahedral geometry. As depicted in Figure 4, the cationic hepta-coordinated manganese(II) complex ion has two pyridyl pendant arms located in *trans*-axial positions with the pentagonal macrocycle in the quasi-plane. The two pivotal cyclohexyl diamines are slightly twisted from the macrocyclic plane that probably facilitates the coordination of two axial pyridines. Overall, the structure of the manganese(II) complex of ligand $\mathbf{L^1}$ can be described as a slightly distorted pentagonal bipyramid with C_2 symmetry.

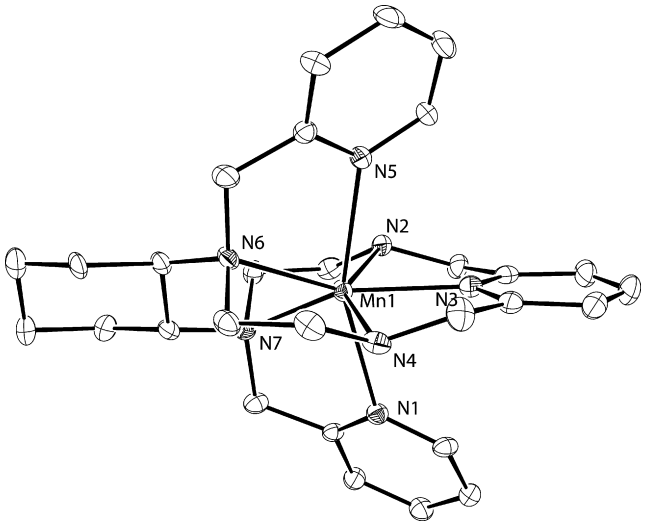


Figure 4. X-ray crystal structure of the cationic complex ion, $[Mn\mathbf{L^1}]^{2+}$. Hydrogen atoms are omitted for clarity.

The manganese complex of $H_2\mathbf{L^2}$ was stable during silica gel column purification and the electronic spectrum exhibits three broad bands at 325 nm ($\varepsilon = 2600\ M^{-1}\ cm^{-1}$), 505 nm ($\varepsilon = 2150\ M^{-1}\ cm^{-1}$), and 640 nm ($\varepsilon = 1810\ M^{-1}\ cm^{-1}$) in acetonitrile. The absorption bands at 505 and 640 nm can be assigned to phenolate → Mn charge-transfer transitions.[38,39]

In summary, we have efficiently prepared two novel heptadentate ligands that are pentaaza macrocycles having two pendant arms. The crystal structure of the manganese(II) complex revealed that a slightly distorted pentagonal bipyramidal conformation is favored.

Acknowledgements

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Supplementary data

Experimental procedures, spectral characterization of new compounds and crystallographic data for $[Mn\mathbf{L^1}][MnCl_4]$. The crystal structure have been deposited with the Cambridge Crystallographic Data Centre with CCDC reference number 618926. Copies of the data can be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk or www: http://www.ccdc.cam.ac.uk). Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2006.10.063.

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