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Macrocyclic polyamines with pendent phenol, catechol, hydroquinone, and pyridine group

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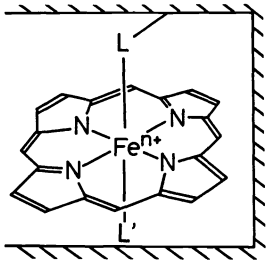
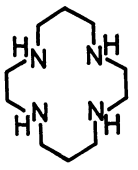
Abstract - Novel synthesis and properties of a new class of macromonocyclic polyamines having pendent phenol, catechol, hydroquinone, and pyridine are presented. The proximity of these potential donors to the center of the macrocyclic cavities renders otherwise (i.e. intermolecularly) unlikely coordination feasible. Those intramolecular axial donors affect the metal complex structure and stability, redox properties of the encapsulated metal ions, and possibly the reactivity of vacant coordination sites. The intramolecular, electroactive ligands such as phenol and catechol couple with electroactive metal ions, and both redox properties are greatly altered.

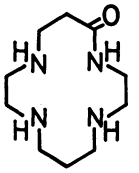
INTRODUCTION

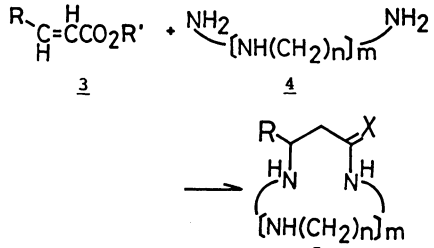
Metal complxes as enzyme models have been intensively studied and played an important role in elucidating enzyme reaction mechanisms. Macrocyclic polyamines offer useful models for redox-related metalloenzymes. One notable example is 16-membered dioxopentaamine complexes with Ni^{II} that activate molecular oxygen to catalyze the conversion of benzene into phenol at r.t. (ref. 1). A 14-membered tetraamine, cyclam 1, (1,4,8,11-tetraazacyclotetradecane) and oxocyclams such as 2 (ref. 2), like porphyrins and corrin, incorporate metal ions into their cavities and form stable, square-planar N_4 complexes. The biological macrocyclic tetraamines are functionalized for their specific activities by having proximate donor ligands such as imidazole, phenolate or cysteine at an axial position. Therefore, it was felt that incorporation of intramolecular axial donor groups into macrocyclic polyamines would attach various enzyme functions to these metal complexes.



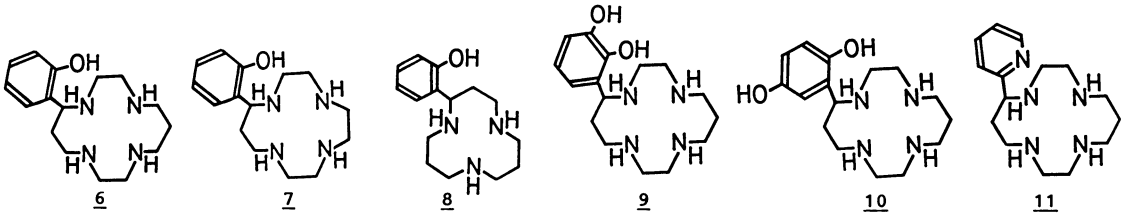
Heme Protein


Cyclam
1


Monooxocyclam
2



Recently we have discovered a new and versatile synthetic method (ref. 3) that leads to a novel class of macromonocyclic polyamines 5 having aromatic donor group-bearing side arms attached at a ring carbon atom. The reaction uses α,β-unsaturated carboxylic acid esters 3 and linear polyamines 4 for a new one-step annelation that successively involves Michael addition followed by intramolecular lactam formation. In the present study, we have applied this method to the synthesis of a new series of macrocycles having phenol (6, 7, 8,), catechol (9), hydroquinone (10), and pyridine (11) as pendents.

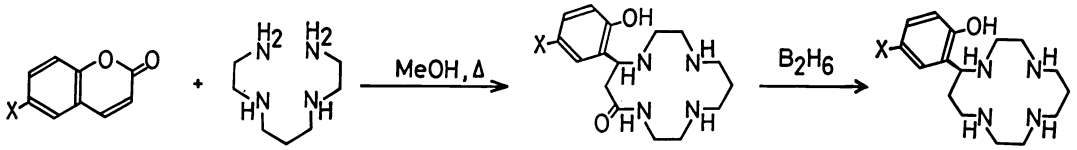


6 7 8 9 10 11

The axial coordination of phenolate was expected to permit 6 having strong interaction with Fe^{III} and provide a simplified model of catalase (ref. 4) or abnormal heme (ref. 5), where the central metal ion Fe^{III} is a more stabilized form than Fe^{II}. The anticipated axial catecholate coordination with 9 may offer a model for the enzyme-substrate interaction at the active site of catechol 1,2-dioxygenase (ref. 6). The axial pyridyl coordination of 11 might keep metal ions held in the macrocycle at lower oxidation state by its π -donor character.

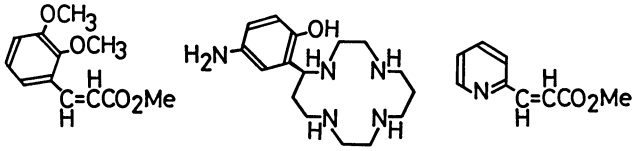
SYNTHESIS

For the synthesis of phenol-pendent macrocycle 6, 7, 8, we have "recycled" coumarin 12. A typical procedure is as follows (ref. 7). Refluxing 12 and 1, 9-diamino-3, 7-diazanonane 13 in MeOH for two weeks afforded the 14-membered monooxocyclam 14 in 20% yield after purification by silica gel column chromatography (eluant CH_2Cl_2-MeOH-28% aq. NH_3, 100 : 5 : 1 in volume). Reduction of 14 with B_2H_6 in THF yielded the cyclam derivative 6 (m.p. 142-143 °C, from CH_3CN) in 50% yield. Use of 1, 8-diamino-3, 6-diazaheptane and 1, 7-diamino-4-azaheptane in place of 13 afforded a 13-membered tetraamine 7 (ref. 8) and 12-membered triamine analogue 8 (ref. 9), respectively.



12 13 14 6

Catechol-pendent cyclam 9 was synthesized in an analogous fashion from 15 and 13. The final demethylation was performed with BBr_3. Hydroquinone-pendent cyclam 10 was so unstable that we prepared it electrochemically in solution from 16, which was originally derived from 6-nitrocoumarin (12, where X=NO_2). Pyridyl-pendent cyclam 11 was synthesized from 17.



15 16 17

SOME NOTABLE PROPERTIES OF NEW LIGANDS

A significant consequence of the phenol pendent proximately bonded to the macro ring in 6 is that in solution and crystals the motion of the phenolic group is restricted with its OH group strongly hydrogen-bonded with the nearest nitrogen of the macrocycle. This is supported by the ^1H nmr spectrum in $CDCl_3$ (35 °C)showing an unusually high chemical shift for OH (δ 0-1.5 ppm) and a well resolved doublet or doublets for the benzylic H signal (δ 3.7-4.0 ppm) owing to coupling with the adjacent CH_2 protons (ref. 7). See also the X-ray crystal structure (Fig. 1) (ref. 10).

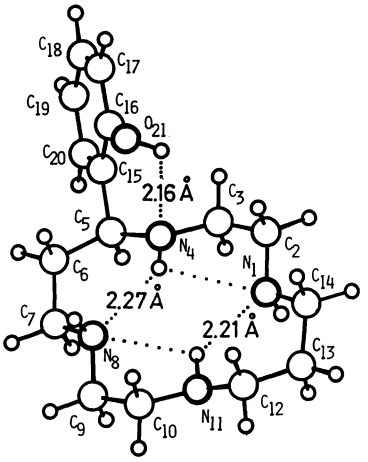


Fig. 1. Crystal Structure of 6.

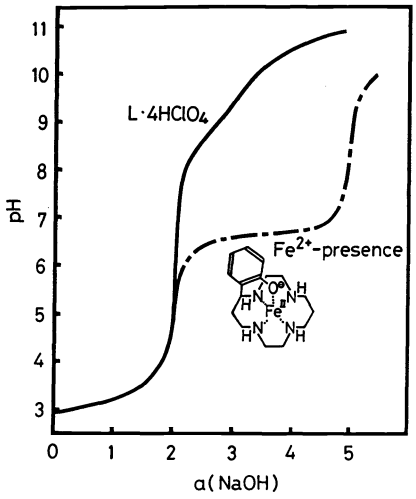
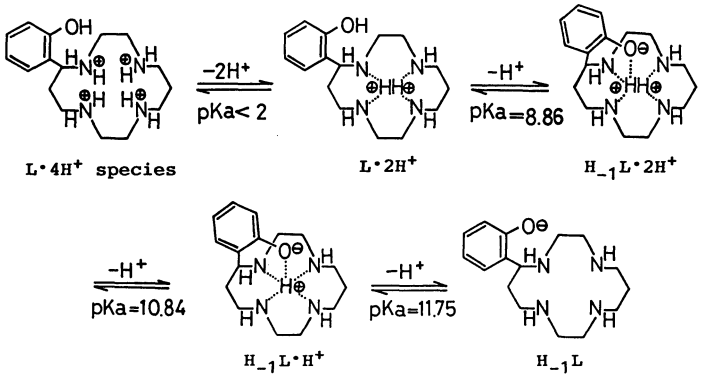


Fig. 2 pH Titration curves for 6 with and without equimolar Fe^{II}.

The protonation constants for new macrocycles are established by pH-metric titrations aided with spectroscopic titrations. The mode of deprotonation for 6 is depicted as follows (ref. 7); the diprotonated species $H_{-1}L{\cdot}2H^+$ is isolable as crystals of mono ClO_4 salt precipitating out of pH 9.5 aqueous solution.



APICAL COORDINATION OF THE PHENOLATE PENDENT

The facile coordination to the metal ions held in macrocycles by the phenol side-arms in 6, 7, and 8 is firmly established by the solution studies and X-ray crystal analyses. As typically illustrated by the pH-metric titration of $6{\cdot}4HClO_4$ in the presence of equimolar Fe^{II} (see Fig. 2), the dissociation of the phenol proton occurs far below the pKa value of free ligand with simultaneous dissociation of all of the four protons attached to the macrocycle amines. This strongly suggests the phenolate interaction with Fe^{II} captured in the macrocycle. From the titration curve, 1:1 complexation constant log $K(Fe^{II}H_{-1}L)$ (= $[Fe^{II}H_{-1}L]/[Fe^{II}][H_{-1}L]$), where $H_{-1}L$ denotes the phenolate form of 6, was determined to be 14.8.

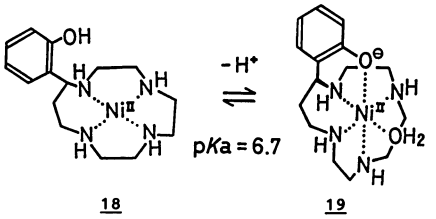
The intramolecular, axial phenolate coordination makes the tetraamine macrocycles a new type of sequestering agents for Fe^{III} in neutral aqueous solution (ref. 7). Cyclam without the phenol side-arm cannot take up to dissolve solid $Fe(OH)_3$ in aqueous solution. The $Fe^{II}H_{-1}L$ (L = 6) complex shows a quasi-reversible (one electron redox) cyclic voltammogram with the redox potential for $Fe^{III/II}$ at -0.16V vs SCE (constant at $7 < pH < 9$)

With triamine 8 (ref. 9) the dissociation of the pendent phenol proton is promoted to aid interaction with Cu^{II}, Ni^{II}, Zn^{II}. The 1:1 complexation constants log $K(MH_{-1}L)$ (= $[MH_{-1}L]/[M][H_{-1}L]$) are 12.6, 14.0, and 18.4, respectively, which are greater than those with phenol-less [12]aneN_3 log K(ML) (= [ML]/[M][L]) = 8.8, 10.9, and 12.6, respectively.

The apical phenolate coordination is unequivocally proven by an X-ray crystal study of Ni^{II}-6 complex (Fig. 3) (ref. 10). The square-pyramidal coordination geometry with the five donors of 6 is evident. The four nitrogen atoms on cyclam moiety are coplanar and the Ni stays in this plane. The Ni-N bond distances are in the normal range consistent with high-spin Ni^{II}. The phenolate oxygen O_{21} is nearly at the apex of the pyramid with the very short apical Ni-O_{21} bond distance 2.015 Å. The other axial Ni-O_1 (of perchlorate) distance is very long at 2.402 Å. The cyclam moiety takes the normal trans-III conformation (ref. 12). The strong axial coordination of the phenolate should contribute to fix Ni^{II} in the high-spin state.

The strong σ- donation by the intramolecular axial phenolate coordination leads to stabilization of the encapsulated metal ions with higher oxidation state: e.g. the $Ni^{III/II}$ redox potential is +0.35 V vs SCE for Ni-6, as compared with +0.50 V for Ni^{II}-cyclam 1 under the same conditions (at pH 7.5, 25 °C) (ref. 10). Interestingly, the coordinated (with Ni^{III}) phenolate becomes robust toward oxidation : its $E_{1/2}$ is raised to - +0.9 V from - +0.4 V of the uncoordinated phenolate. This system may be used to account for the effect of the axial phenolate (tyrosine)-coordination in biological porphyrin complexes, catalase and abnormal heme that favor Fe^{III} over Fe^{II}.

The firm phenolate coordination is most dramatically demonstrated by the Ni^{II}-7 complex structure. In the absence of the phenol side-arm, the 13-membered macrocyclic complex overwhelmingly takes a low spin, square planar trans form over a high-spin, folded cis form (ref. 11). However, upon the phenolate coordination, Ni^{II} becomes high-spin in a folded macrocycle, as proved by an X-ray crystal structure (ref. 8). In aqueous solution , the equilibrium of phenol ⇄ phenolate directly determines low-spin, square-planar 18 or high-spin, folded complex structure 19 (ref. 8).



18
square-planar
yellow
low-spin
Ni^{II}-L (L = 7)

19
folded
blue
high-spin
Ni^{II}-H_{-1}L (L = 7)

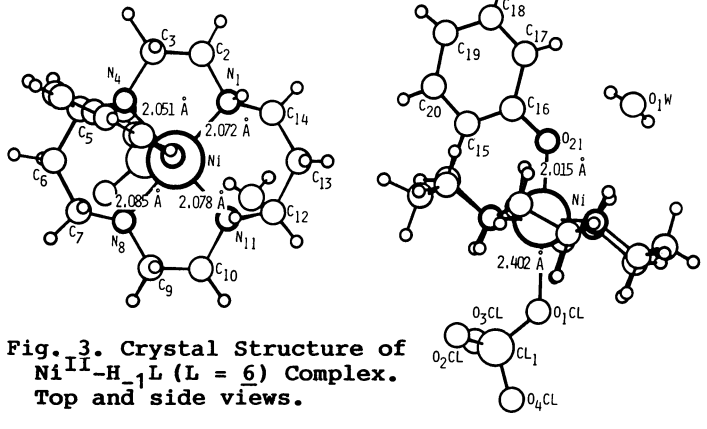


Fig. 3. Crystal Structure of Ni^{II}-H_{-1}L (L = 6) Complex. Top and side views.

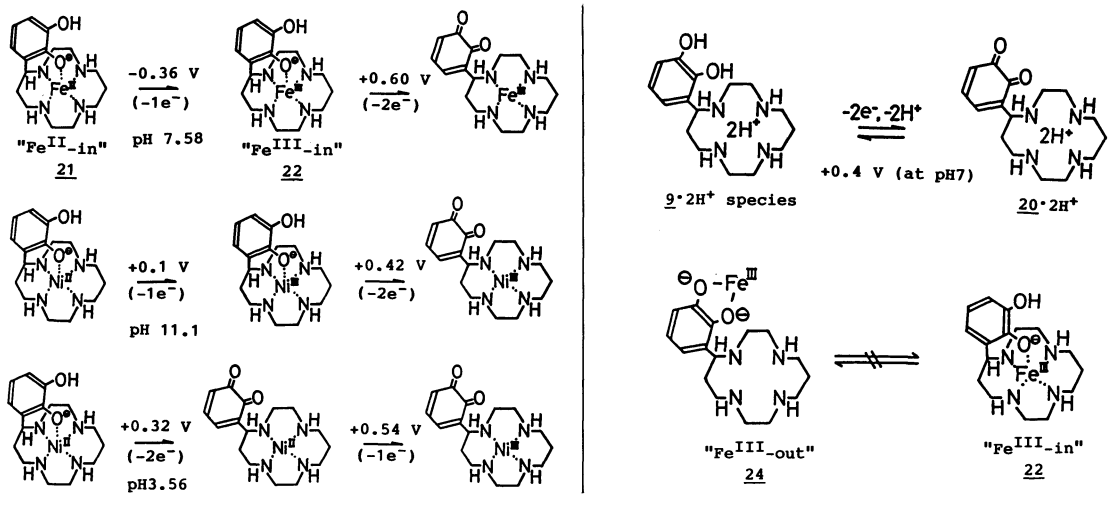
APICAL COORDINATION OF THE MONODENTATE CATECHOL PENDENT

The most interesting aspect of the complexes with redox-active catechol-pendent cyclam 9 is how the axial coordination of its catecholate as a monodentate influences the redox properties of itself and the metal ion. The study is of great interest in relevance to the action of Fe^{III}-containing catechol 1, 2-dioxygenase that catalyzes the oxidative cleavage of catechol to cis, cis-muconic acid. One mechanism is for a substrate catechol to initially act as a reductant to convert the Fe^{III} center into Fe^{II} for activation of O_2 (ref. 12). Another mechanism is coordination of catechol to Fe^{III} for activation of catechol itself to be attacked by O_2 (ref. 13). Accordingly, we have undertaken electrochemical study of Ni^{II}, Fe^{II}, and Cu^{II} complexes.

Like catechol itself that undergoes 2e⁻oxidation to o-quinone at +0.31 V vs SCE on a glassy carbon (by cyclic voltammetry, pH 5.40), the uncoordinated

catechol-cyclam 9 is oxidized to o-quinone 20 at +0.4 V at pH 7. The pKa values of the catechol moiety are >12 and 8.56 (25°C, I = 0.2). In a similar fashion to phenol-pendent cyclam 6, 9 forms 1:1 complexes with Fe^{II} and Ni^{II} at pH 6-7 with dissociation of one proton from the catechol. K($Fe^{II}H_{-1}L$) (= $[Fe^{II}H_{-1}L]/[Fe^{II}][H_{-1}L]$) is determined to be 2.5 X 10^{16} M^{-1} (at 25 °C, I = 0.1). We consider a square-planar macrocyclic structure with a monodentate catecholate at an axial position.

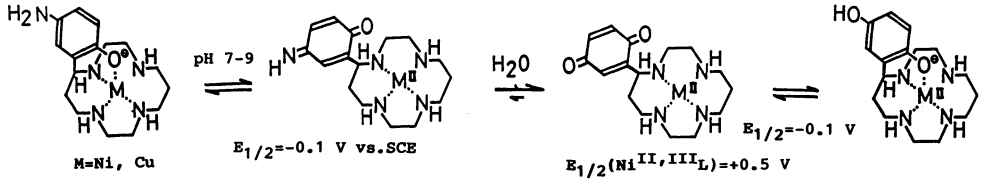
The redox behaviors of its Fe and Ni complexes in aqueous solution are measured with rotating ring disk voltammetry. Our conclusions are schematically summarized as follows. Note that the redox properties of the complexes gravely varies with pH. By the catecholate coordination Fe^{II} is more easily oxidized, while the oxidation of the catechol moiety is more difficult. In the Ni^{II} complex, the sequence of the catechol and Fe^{II} oxidation reverses with the media pH change.



We can electrochemically (at +0.2 V) oxidize the pink Fe^{II} complex 21 ["Fe^{II}-in" complex, λ_{max} 500 nm (ε 490)] in pH 7 aq. solution to a violet "Fe^{III}-in" complex 22 [λ_{max} 558 nm (ε 2000)] without much harming the catechol moiety. Interestingly, mixing 9 with Fe^{III} in pH 7 solution yields a red 1:1 "Fe^{III}-out" complex 24 displaying absorption maximum at λ_{max} 490 nm (ε 1200), where the catechol is oxidized at $E_{1/2} \sim +0.4$ V. The "Fe^{III}-out" complex does not interconvert to the "Fe^{III}-in" complex. We are now investigating the reactivities of these complexes toward O_2 to see if the catechol cleavage occurs in a similar fashion to the catechol 1, 2-dioxygenase.

APICAL COORDINATION OF HYDROQUINONE PENDENT

Neither p-quinone- nor p-hydroquinone-pendent cyclam 10 was isolable as a stable compound. Accordingly, we have electrochemically generated them in situ from p-aminophenol-pendent cyclam 16. The cyclic voltammograms for the Ni^{II}- and Cu^{II}-16 complexes permit the following interpretation of the redox equilibrium.



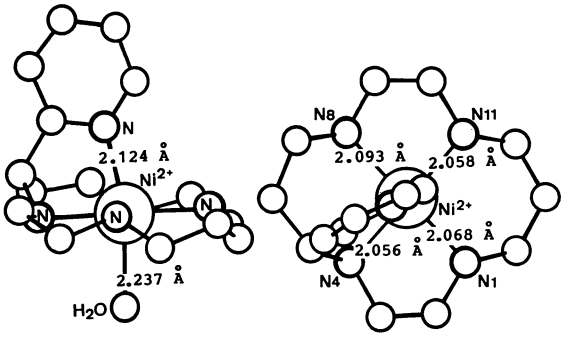


Fig. 4
Crystal Structure of Ni^{II}-11 Complex. Top and Side Views.

An almost identical cyclic voltammogram was obtained for p-aminophenol-pendent cyclam in the absence of metal ions. The conclusion is that the side-arm p-quinone and p-hydroquinone (which interconvert at a potential as low as $E_{1/2}$ = -0.2 V vs SCE) have minor interactions with Cu^{II} and Ni^{II} held in the cyclam. This interpretation is supported by the redox potential of ~ +0.5 V vs SCE for $Ni^{III/II}$ held in the macrocycle, nearly the same value for Ni^{II}-cyclam complex. With Fe^{II} or Fe^{III} rapid decomposition of the ligand 16 occurs.

APICAL COORDINATION OF PYRIDYL PENDENT

The pyridyl coordination of 10 at an axial position is unequivocally established by an X-ray crystal study of the Ni^{II} complex (See Fig. 4) (ref. 14). The Ni-N(pyr) bond distance of 2.124 Å is longer than those of the equatorial Ni-N bonds. The average Ni-N(cyclam) bond distance of ~2.07 Å is compatible with Ni^{II} in high-spin state. The cyclam configuration is similar to that of phenol-pendent-cyclam (Fig. 3). The $Ni^{III/II}$ redox potential is raised to +0.61 V vs SCE (pH 7) from +0.5 V of the cyclam complex. Recall that the phenolate coordination in 5 lowers it to +0.35 V. The higher $Ni^{III/II}$ potential illustrates an effect of pyridine (as π-acceptor) coordination. In a similar fashion, $Fe^{III/II}$ redox potential of +0.12 V with the pyridyl coordination is positive-shifted from -0.16 V with phenolate coordination (both at pH 7, 25 °C, and I = 0.1 M $NaClO_4$).

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