

Developments in functionalization of macrocyclic polyamines

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Abstract - The classical structure of macrocyclic polyamines (*e.g.* cyclam 1) have been renovated by means of (1) conversion of amines into amides (*i.e.* dioxocyclam); (2) replacement of N donors for S donors; (3) replacement of skeletal C-H for C-F; and (4) attachment of intramolecular pendant donors. The characteristics of dioxocyclam 2 is best illustrated by its ability to incorporate Pt^{II}, while the oxo-free cyclam 1 fails to do so. A new version of dioxocyclam 3 containing two S donors in place of N donors of 2 was designed, which astonishingly selectively accommodates noble metal ions Pt^{II} and Pd^{II}, but not Cu^{II}, Ni^{II}, or Co^{II} as 2 does. Furthermore, 3 detracts Pt^{II} much more rapidly than 2 from *cis*-[Pt^{II}(NH₃)₂Cl₂]. The fluorinated polyamines show lower N basicities than nonfluorinated counterparts, and yet, the Cu^{II} complex of 21c (CuH₂L) is more stable than that of 2. The fluorinated polyamine complexes stabilize metal ions with lower oxidation states than nonfluorinated counterparts. Intramolecular pendant donors greatly affect the redox and other chemical properties of the central metal ions, as well as the complex properties.

INTRODUCTION

Macrocyclic polyamines are the most basic and extremely useful ligands as cation as well as anion complexons. Progress in coordination chemistry of macrocyclic polyamines with simple skeleton structure (*e.g.* cyclam) has almost come to the stage of maturation both in basic and applied fields and the time has come for us to address to renovation of polyamine ligands for more needy, extensive, or intelligent applications and for exploration into new macrocyclic fields.

Recently, we have been trying step-by-step to expand the functions of macrocyclic polyamines, which was pursued by chemical functionalization of the classical polyamine structures. We have had several strategies for these objectives: (1) Conversion of amine(s) into amide(s) (*i.e.* oxopolyamines); (2) Replacement of N donors for S donors; (3) Replacement of skeletal C-H for C-F; and (4) Attachment of intramolecular pendant donors. These modifications, with structural simplicities, easy approaches, and broad extensibility, would serve to rejuvenize conventional concepts of macrocyclic polyamines, setting forth for far more sophisticated structures and functions. Fig. 1 represents schematically how we have developed the most classic 14-membered tetraamine, cyclam 1, into the new tetraamine architectures.

DIOXOCYCLAM 2. A HYBRID LIGAND

Dioxocyclam 2 was designed as a hybrid ligand of cyclam 1 and oligopeptides such as triglycine 11 (ref. 1). 2 and 11 interact with M^{II} ions (*e.g.* Cu^{II} (ref. 2), Ni^{II} (ref. 3), Co^{II} (ref.4)) with concomitant dissociation of the

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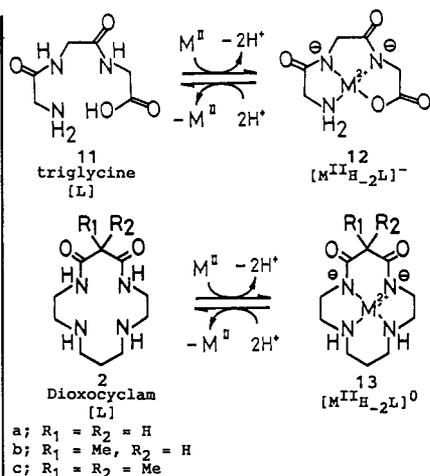
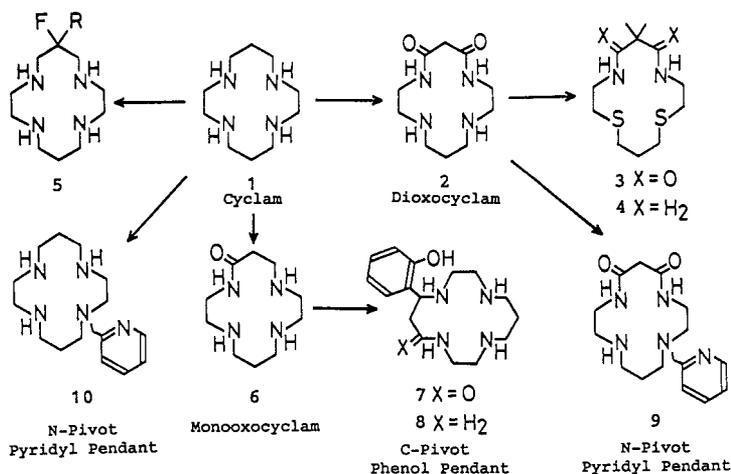


Fig. 1. Summary of recently developed macrocyclic polyamines represented by cyclams

Fig. 2. Metal complexation of triglycine and dioxocyclam

two amide protons to accommodate them, yielding square-planar complexes, 13, 12, respectively (Fig. 2). Advantages of dioxocyclam 2 over cyclam 1 in metal complexation are (i) enhanced selectivities of metal ions to be accommodated, (ii) enhanced reversibilities of metal uptake controlled by pH, and (iii) stabilization of enclosed metals at higher oxidation state, M^{III}.

Dioxocyclam 2, moreover, can encompass Pt^{II} (ref. 5). The resulting platinum(II) complex 17 is the first Pt^{II}-included macrocyclic N₄ complex. On the other hand, the Pt^{II}-cyclam complex strangely remains unreported. During the mechanistic study of the Pt^{II} incorporation by 2 in pH 6 aqueous solutions (see Fig. 3), an intermediate complex 16 with dioxocyclam acting as a bidentate was also isolated, which is quantitatively converted into the final product 17 with $\tau_{1/2} \sim 6$ hrs at 36°C, pH 7 (ref. 6). The X-ray crystal structure of these two dioxocyclam complexes, 16 and 17' (methyl derivative of 17) are shown in Fig. 3 (ref. 6). In 17, the macrocyclic coordinate geometry is nothing unusual with little constraints seen around Pt^{II}. This result suggests the hypothetical square-planar Pt^{II}-cyclam complex stereochemically to be feasible.

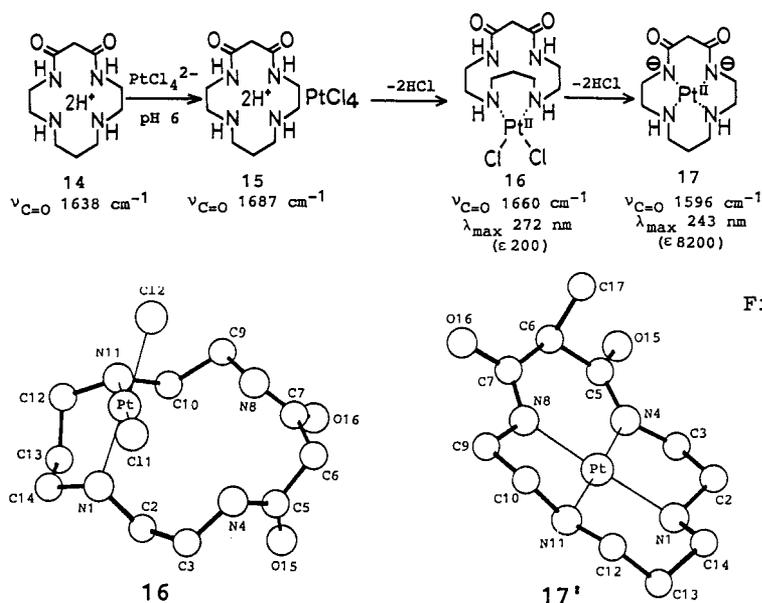


Fig. 3. Mechanism of Pt^{II} (from [PtCl₄]²⁻) uptake by dioxocyclam and X-ray crystal structures of 16 and 17'

DIOXYCYCLAMS WITH (N⁻)₂S₂ DONORS 3. A NOVEL LIGAND SELECTIVE FOR NOBLE METAL IONS

Very recently (ref.7), we have extended 2 to a new version 3, composed of two amides and two thioethers, as a potential tetradentate ligand.

Most interestingly, 3 accommodates only noble metal ions i.e. Pt^{II} and Pd^{II}, but not Cu^{II}, Ni^{II} or Co^{II} in MeOH-H₂O solution (pH < 10). Such a selective recognition of noble metal ions against other metal ions has no precedence. Apparently, this difference is closely relevant to the known M^{II} Lewis acidity to effect deprotonation from the amide nitrogens; Pt^{II} > Pd^{II} > Cu^{II} > Ni^{II} > Co^{II} (ref. 8). The amide-deprotonated structure 18 was established by the similarity in their ir and uv spectral behaviors to those of dioxocyclam complexes 13c, see Fig. 4.

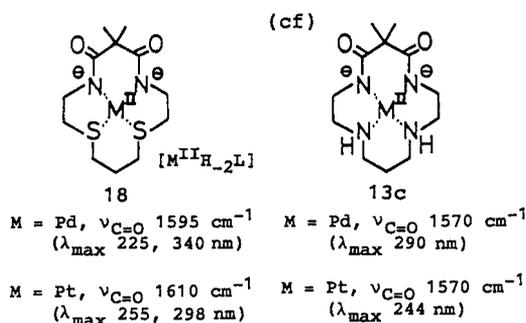


Fig. 4.
Comparison of IR and UV data for dioxocyclam complexes

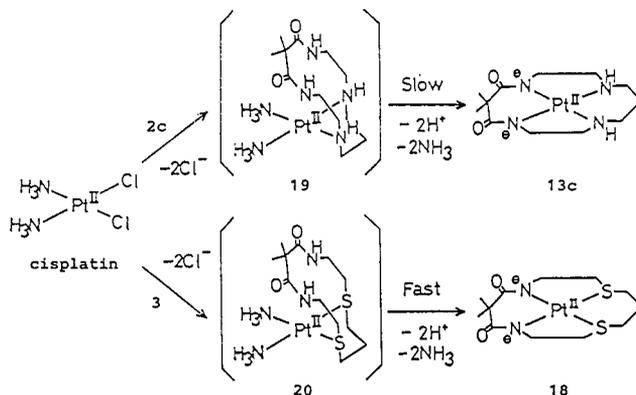


Fig. 5. Mechanism of reaction of cis-[Pt^{II}(NH₃)₂Cl₂] with dioxocyclams 2c and 3

Mechanistically and medicinally more interesting with 3 is that it can detract Pt^{II} out of cis-[Pt^{II}(NH₃)₂Cl₂] (cisplatin) much more efficiently than 2c. For instance, in HEPES buffer (pH 7)-MeOH (1:1) solution at 35°C, the Pt^{II}-uptake yields (from equivalent cisplatin) after one day are 40 % with 3 vs. < 1 % with 2c. This is due to the stronger trans effect by the S donors in 19 than by the N donors in 20, see Fig. 5. In Fig. 5, the second step reaction is reminiscent of anionic (X⁻) replacement of the labilized NH₃ (under the trans effect of Me₂S) in cis-[Pt^{II}(Me₂S)₂(NH₃)₂]²⁺ to cis-[Pt^{II}(Me₂S)₂(X⁻)₂]⁰ (ref. 9). Significance of the amide function as a precursor of the N⁻ donor is well demonstrated by failure of the Pt-incorporation by the oxo-free N₂S₂ homologue ligand 4.

FLUORINATED DIOXYCYCLAMS 21 AND CYCLAMS 5

Recently we have explored easy synthesis and novel properties of fluorinated dioxocyclams 21 and cyclams 5 (ref. 10). A preliminary study has indicated the fluorinated macrocycles to serve not only as a promising means by itself to open new areas of macrocyclic complexes but also as useful aid to evaluate special properties (such as N basicities and solvations) characteristic to macrocyclic ligands. The synthetic route is depicted in Fig. 6.

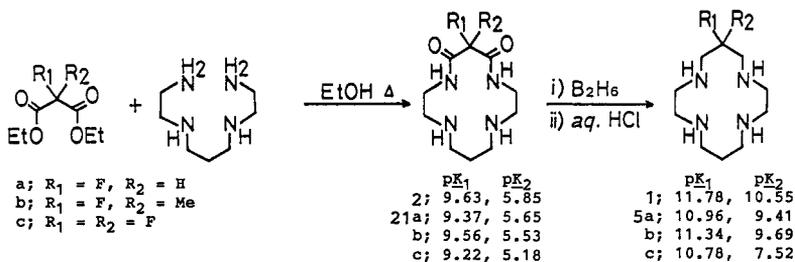


Fig. 6.
A synthetic route to fluorinated cyclams

Here, the cyclization becomes faster as more F atom is substituted, completing within 30 min with the difluorinated malonate as compared to 3 days with nonfluorinated malonate. The protonation constants pK_a for non-fluorinated and fluorinated macrocycles indicate the most dramatic diminution in the amine basicities at the second stage (pK_2), in particular for cyclam series 5. In the light of the remote location of the basic nitrogens from fluorines in dioxocyclams, the observed basicity weakening effect by the F atoms may indirectly occur through the strengthened hydrogen bondings between the acidified (due to the electron-withdrawing effect of F) proximal amide hydrogens and the distal N_4 lone pairs. A similar space effect argument may explain the reduced pK_1 and pK_2 of the distal nitrogens in the fluorinated cyclams.

The complexation of **5c** with Cu^{II} occur at lower $pH \sim 3$ than that of non-fluorinated **2** ($pH > 4$) with stability constant of $\log K_{CuH_2L} (= [CuH_2L][H^+]^2/[Cu][L])$ being 2.5 ± 0.2 for **5c** as compared with 1.0 for **2**. Despite the apparent greater complex stability, the d-d absorption spectrum (λ_{max} 515 nm for **5c** vs 505 nm for **2**) implies a weakened LF by the fluorinations. In **5c** the reduced desolvation energy at the complexation may outweigh the reduced LF strength.

The effect of the F substitution is most evident in electrochemical properties of Cu and Ni complexes. The fluorinated $[NiL]^{2+}$ and $[CuH_2L]^0$ gave quasi-reversible voltammograms for Ni^{III}/Ni^{II} and Ni^{II}/I , and Cu^{III}/II , respectively. In either Cu or Ni system, the higher oxidation states Cu^{III} and Ni^{III} , become successively destabilized with respect to Cu^{II} and Ni^{II} , while the lower oxidation state Ni^I becomes successively stabilized with respect to Ni^{II} , see TABLE 1.

CYCLAMS WITH C-PIVOT PENDANTS

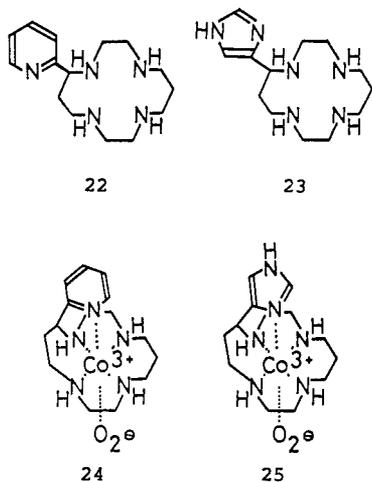
Earlier (ref. 11) we have discovered a new annelation method by refluxing cinnamate, coumarin or substituted α,β -unsaturated esters with linear tetraamines, which created numerous new cyclams with C-pivot pendants (e.g. **8** (ref. 12), **22** (ref. 13), **23** (ref. 14)).

These donor pendants are located at the most favorable position for axial coordination, which were proved by X-ray crystal studies. An effect of such intramolecular axial coordination is recently demonstrated by isolation of 1:1 O_2 adducts (superoxo) **24** and **25** from Co^{II} -**22** and Co^{II} -**23** as perchlorate

TABLE 1. Half-wave potentials (V vs SCE)^a for Cu^{III}/II -(**2**, **21a-c**) and Ni^{III}/II - and Ni^{II}/I -(**1**, **5a-c**) complexes.

Complex	$E_{1/2}$ (V vs SCE)		
	for Cu^{III}/II , b	for Ni^{III}/II , c	for Ni^{II}/I , d
$[CuH_2L]^0$			
L = (2)	+0.64		
(21a)	+0.69		
(21b)	+0.71		
(21c)	+0.83		
$[NiL]^{2+}$			
L = (1)		+0.50	-1.56
(5a)		+0.52	-1.52
(5b)		+0.53	-1.53
(5c)		+0.63	-1.46

^a All solutions were deaerated by purified Ar and a Pt wire was used as auxiliary electrode. ^b 0.5 M (Na_2SO_4), 25 °C, pH = 7.0. Working electrode (W.E.); glassy carbon. ^c 0.5 M (Na_2SO_4), 25 °C, pH = 6-7. W.E.; glassy carbon. ^d 0.1 M ($NaClO_4$), 25 °C, pH = 7.0. W.E.; hanging-mercury-drop electrode.



salts from aqueous solution at room temperature. Under the same condition, Co^{II} -cyclam produces a 2:1 O_2 adduct (μ -peroxo) (ref. 15). The optical and ESR spectra of these dioxygen complexes **19** and **20** are in accord with a monomeric species of the superoxo $\text{Co}^{\text{III}}\text{-O}_2^-$ type.

Our annelation method is also applicable to macrocyclic triamines. Thus, a 12-membered N_3 **26** was synthesized (ref. 16), which has an ideal structure for N_3O^- tetrahedral coordination. The crystal structure of its Zn^{II} complex **27** has revealed a distinct trigonal bipyramidal structure with an additional apical water molecule (Fig. 7)(ref. 17). The deprotonation of the pendant phenol group ($\text{pK}_a = 6.8$) is promoted by the proximity to $\text{Zn}(\text{II})$ to become the fourth donor, which renders the basicity of the $\text{Zn}(\text{II})\text{-OH}$ higher to pK of 10.7 from pK 7.5 of the pendant-less [12]ane N_3 complex **28**. Our Zn complex thus may offer a simple model of anion-additive effect around Zn^{II} in carbonic anhydrase which is ligated by three imidazoles and a H_2O molecule and whose four coordination is transiently expanded or by anion inhibitor binding.

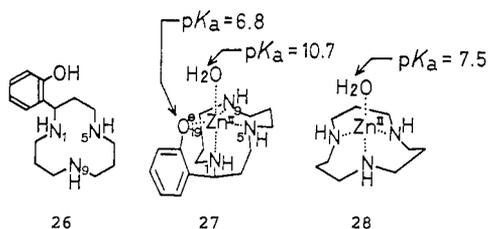


TABLE 2. Comparison of redox potentials $E_{1/2}$ for $\text{M}^{\text{III}}/\text{II}$ (V. vs SCE)

Complex	13a	32	33	30	31	34	35	36
M=Ni	0.81	0.86	0.54	0.44	0.30	0.35	0.61	0.54
M=Cu	0.64	0.83	~ 0.81	0.82	0.82	-	-	-

(irrev.)

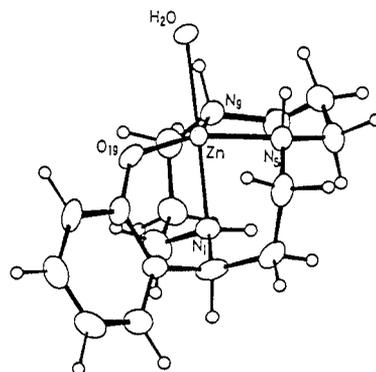
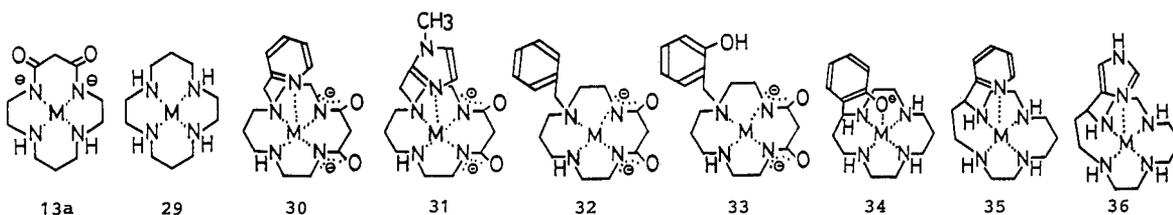


Fig. 7. X-Ray crystal structure of **27**

OXOCYCLAMS WITH N-PIVOT PENDANTS

Dioxocyclam **2** is a rigid square-planar ligand with a stronger LF strength than that of cyclam **1**; thus Ni^{II} complex **13a** is low-spin, while the cyclam complex **29** is a mixture of low-spin and high-spin (ref. 3). Addition of external ligands to **13a** fails to convert the square-planar geometry (yellow-colored) into octahedral one (pink-color), indicating that access to axial sites is extremely hindered due to the strong tetragonal distortion. It is thus tempting to attach potential axial donors such as pyridyl (*i.e.* **9**) or imidazolyl to one of the secondary nitrogen atoms.



The nickel(II) complexes with those dioxocyclams **30** and **31** are both pink-colored, high-spin to substantiate axial interaction by the closely located intramolecular pendant donors. It is of interest to measure the redox potentials for $\text{Ni}^{\text{III}}/\text{II}$ to see the influence of the fifth coordination. The results in comparison with the values for previous systems and for $\text{Cu}^{\text{III}}/\text{II}$ are summarized in TABLE 2.

Although alkyl substitution for a NH tends to slightly raise the $E_{1/2}$ values, the appended donors greatly stabilize the higher oxidation state of Ni^{III}. When it comes to the copper complexes, both Cu^{II} (by the Jahn-Teller effect of d⁹) and Cu^{III} (square planar d⁸) would not warmly welcome such axial interaction and hence the $E_{1/2}$ values are not significantly affected.

CONCLUSION

Renovation of macrocyclic polyamines are performed by (1) conversion of amines into amides (*i.e.* dioxocyclam); (2) replacement of N donors for S donors; (3) replacement of skeletal C-H for C-F; and (4) attachment of intramolecular pendant donors. The syntheses of these new macrocycles are relatively easy. Moreover, the modified structures are simple. Nevertheless, dramatic changes in functions are achieved, as disclosed by complexes of a few exemplified metal ions Pt^{II}, Ni^{II}, Cu^{II}, or Zn^{II}; *i.e.* enhanced efficiency and selectivity in metal uptake, enhanced complex stability, or alteration in redox or other important chemical properties of metal complexes. In future, these smart ligands will be used to create a variety of interesting complexes with other metal ions, which would open a new generation of macrocyclic complexes both in basic and applied fields. Moreover, because of simplicities these new molecules will serve as "leading" or "founding" compounds for even more sophisticated, value-added, and intelligent materials that the coming age demands.

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