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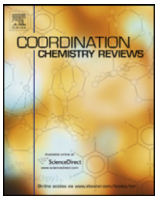

Review

Coordination chemistry of N-tetraalkylated cyclam ligands—A status report

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Contents

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ABSTRACT

N-alkylation of macrocyclic amines has a significant impact on their properties as ligands for metal ions. This article examines the development of the coordination chemistry of N-alkylated cyclam ligands from its inception in 1973 with the first report of tetramethylcyclam. Emphasis is on: (1) the stereochemistry of metal complexation, including the effects of inclusion of functional groups in one or two of the N-alkyl groups; (2) the effect of N-alkylation on the metal–donor interaction; (3) the ability of tertiary amine ligands to stabilize complexes of metal ions in unusual oxidation states.

1. Introduction

During his investigation of the redox chemistry of nickel(III) complexes Mocella discovered that Ni(III) complexes of **1** (cyclam) and related macrocyclic 2°-amine ligands were highly sensitive to base [1]. He determined that proton loss from one of the 2°-amines initiates a reaction sequence that ultimately leads to oxidative dehydrogenation of one of the C—N bonds in up to 50% of the sample [1,2]. We sought a ligand that would prevent such base promoted reactions and decided that **2** (1,4,8,11-tetramethyl-1,4,8,11-tetrazacyclotetradecane, also known as N-tetramethylcyclam or TMC) was an attractive possibility. N-Alkylation of macrocyclic ligands as a means of controlling reactivity and ligand field strength was a new concept. Prior to this time Kalligeros and Blinn [3] had synthesized 1,4,7,10-tetrabenzyl-1,4,7,10-tetraazacyclododecane (N-tetrabenzylcyclen), which can only bind to *cis* positions of divalent metals, and studied some of its metal complexes. Grigg et al. [4] were examining N-alkylated porphyrins and Rusnak and Jordan had synthesized the nickel(II) complex of a mono-N-alkylated tetraaza ligand for comparison with its unalkylated analog [5].

Wagner readily synthesized tetramethylcyclam [6] by methylation of cyclam with formaldehyde/formic acid [7].

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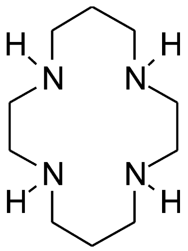

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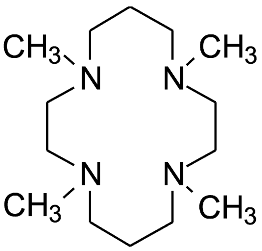

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Kaden independently prepared TMC by the same method and also initiated studies of its metal complexes with an emphasis on the effect of N-alkylation on rates of complexation [8]. It was our naïve expectation at the outset that the nickel complex of TMC would have the same high kinetic stability as that of **1** and that nickel(III) would be stabilized because of the greater intrinsic basicity (proton affinity) of the tertiary amine donors [9]. However, it was immediately apparent that the kinetic stabilities of divalent metal complexes of TMC were low compared to those of cyclam as they decomposed much more rapidly in acidic media and in the presence of excess cyanide (nickel), and all showed a propensity to bind a fifth ligand to form five-coordinate complex ions [6,8], whereas complexes of cyclam typically form six-coordinate complexes. Also the Ni(III)/Ni(II)/Ni(I) [10] potentials for the TMC complex were much more anodic than those for the nickel–cyclam complex [11]. The unique properties of the originally prepared divalent metal complexes of TMC are a result of the stereochemistry of the tertiary nitrogen donors, which is one in which all four methyl groups are on the same side of the metal–nitrogen coordination plane as confirmed by the X-ray structure of [Ni(TMC)N$_3$]ClO$_4$, Fig. 1 [12,13].

To set the stage for discussions of the stereochemistry of metal complexes of TMC and other N-alkylated cyclam ligands to follow recall that there are five possible diastereoisomeric forms for a nominally square planar arrangement of the four nitrogen donors. These are depicted in Fig. 2 with the original isomer designations of Bosnich et al. [14] and the Cahn–Ingold–Prelog designations of the relative absolute configurations of the coordinated nitrogen donors. The + indicates that the substituent on the coordinated nitrogen is above the plane of the nitrogen atoms, − indicates that it is below. Bosnich et al. designated diastereosiomers with planar arrangements of the nitrogen donors as *trans*-I, *trans*-II, etc., and diastereoisomers with *cis* arrangements of the nitrogen donors as *cis*-I, *cis*-II, etc. [14] There has been some lack of consistency in the designation of the relative configurations of the nitrogen donors, particularly for isomer III, which has sometimes been incorrectly referred to as the RSSR isomer. Schematic drawings of structures of the five planar arrangements showing chelate ring conformations are shown in Fig. 3.

Our inability to convert the *trans*-I diastereoisomer to the desired/expected *trans*-III form found for structurally characterized [Ni(cyclam)Cl$_2$] [15], originally considered to be the most thermodynamically stable of the five diastereoisomers, led us to seek alternative routes to its synthesis. Deprotonation/alkylation of [Ni(cyclam)]$^{2+}$ produced the *trans*-III diastereoisomer of nickel(II)-tetramethylcyclam in excellent yield. This diastereoisomer tended to bind two additional ligands to form six-coordinate species in solution and in the solid state; the *trans*-III form was confirmed by the crystal structure of the six-coordinate, azide bridged dimer [Ni(TMC)N$_3$]-μ-N$_3$-[Ni(TMC)N$_3$]I [16]. The kinetic stability of this complex in acidic and cyanide media was even higher than that

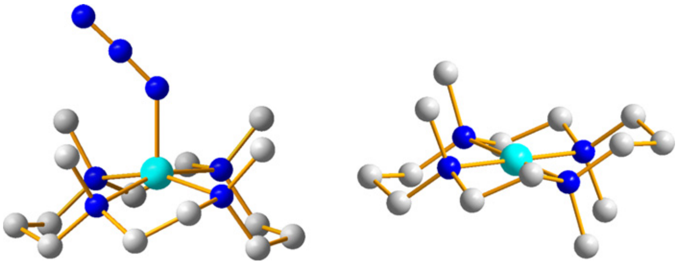


Fig. 1. Structure of the cations of *trans*-I [Ni(TMC)(N$_3$)]ClO$_4$ (left) and *trans*-III [Ni(TMC)](CF$_3$SO$_3$)$_2$ (right). Redrawn with data from references [12,19], respectively.

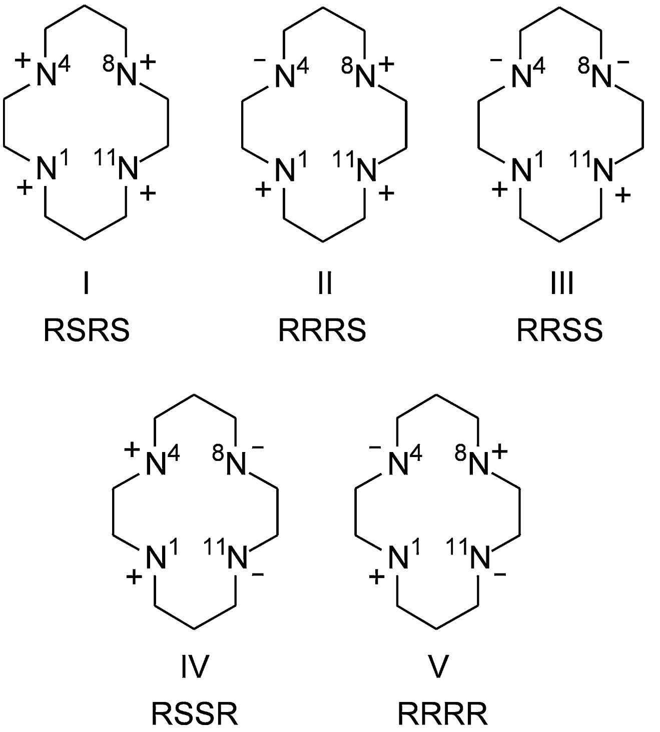


Fig. 2. Designations of the diastereoisomeric forms of coordinated 1,4,8,11-tetraazacyclotetradecane (cyclam) ligands.

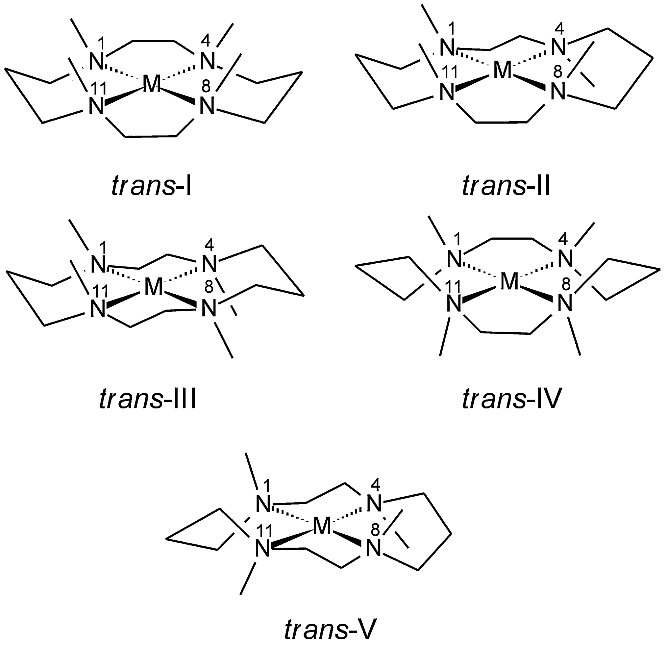


Fig. 3. Schematic representations of the structures of diastereoisomeric forms of coordinated 1,4,8,11-tetraazacyclotetradecane (cyclam) ligands.

of the parent cyclam complex and in sharp contrast to that of the *trans*-I form [17]. However, there was little difference in the $Ni^{3+/2+}$ [10] and $Ni^{2+/+}$ [18] potentials compared to those for the *trans*-I form [19].

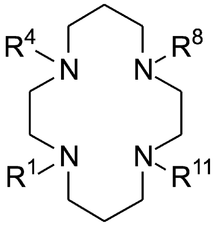
A very substantial area of chemistry involving the synthesis and application of N-alkylated cyclic aza ligands has developed since the first examples of such ligands were reported. The range of ligands known includes a variety of denticities, mixed donor types, and mono-N-alkylated to per-N-alkylated forms of all of these. This review is not intended to be a comprehensive one. In order to keep within the space allowed I will focus primarily on tetra-N-alkylated 1,4,8,11-tetraazacyclotetradecanes (tetra-N-alkylated cyclams) without carbon-substitution. Over 200 examples of tetra-N-alkylated cyclams with unfunctionalized or functionalized aliphatic carbon substituents and or other substituents such as phenyl, pyridyl, and thienyl have been reported. There are dozens more examples that have one or more acyl, sulfonyl or other functional group bonded to nitrogen. To further limit the scope of this article it will be confined to just three fundamental types of tetra-N-alkylated cyclam compounds; those with no functional groups, one functional group and two functional groups. Of particular interest will be (1) the stereochemistry of metal complexation and the interconversion (or lack thereof) of diastereoisomers, (2) the differences in the structural and electronic effects of tertiary amine ligands relative to those of their secondary amine counterparts, and (3) the use of tertiary amine ligands to stabilize complexes of metal ions in unusual oxidation states. Other than limiting the length of this article, the decision to not generally consider the many tri- and tetrafunctionalized ligands was primarily because when they incorporate the metal ion into the macrocycle their behavior with regard to these three points is, in general, not dramatically different from that observed for the difunctionalized ligands [20].

2. Complexes of 3d metals with unfunctionalized tetra-N-alkylated ligands

Complexes of tetra-N-alkylated cyclams have been generated for 3d metals Cr–Zn with the majority of these being prepared from preformed ligand. In this section I will present what is known about the stereochemical course of metal complexation, the interconversion of diastereoisomeric forms, and the relative thermodynamic stabilities of complexes of these ligands. It is appropriate to begin with a discussion of N-tetramethylcyclam for which the most information is available, and then to consider the effect of substituent size, substitution pattern, and finally the impact of incorporation of functional groups into the alkyl substituents.

2.1. trans-I stereochemistry—divalent metals

Most of the complexes isolated from reactions conducted in donor solvents between salts of divalent, first-row, transition metal ions with N-tetramethylcyclam have a *trans*-I type structure [21]. There is a considerable amount of evidence to suggest, however, that the formation of these *trans*-I complexes proceeds via short-lived intermediates that have the *trans*-II structure, *vide infra*. Interconversion of *trans*-I and *trans*-III nickel(II) and copper(II) complexes can also be achieved via M(I) intermediates. Complexes of TMC with the *trans*-I stereochemistry have a marked propensity for five-coordination with multiple structures reported for a variety of metals (Mn [22,23], Fe [24,25], Co [26–28], Ni [12,13,29–35], Cu [36–38], Zn [39–41]). These are generally described as square-pyramidal although in a few cases the relative magnitudes of the *trans* N—M—N angles is such that they may be better considered to be trigonal bipyramidal. The Mn, Fe, Co and Ni complexes are all high-spin. The only structurally characterized four-coordinate, *trans*-I Ni(II) complexes [42,43] show a tetrahedral distortion of the four donors about the metal. Similar distortions were found for four-coordinate complexes of other N-tetraalkylated ligands such as the Cu(II) complex of **3** and the Ni(II) complex of **4** [44,45].



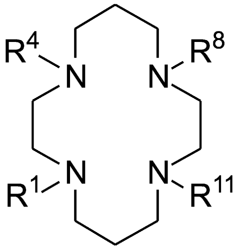
3 R=Et
4 R^1=R^4=Me, R^8=R^{11}=*n*-Pr
5 R=*n*-Pr
6 R=CH_2CH_2CN

In solution $[M(TMC)]^{2+}$ exists as a mixture of 4- and 5-coordinate species with the position of the equilibrium determined by the donicity of the solvent [29,46–50]. Exchange and substitution reactions of the fifth ligand in five-coordinate *trans*-I $[M(TMC)L]^{n+}$ have been examined. In general the reactions are associative in nature [29,47,50,51].

Although six-coordinate complexes of Cr(II) [52] and Ni(II) [6] that probably contain *trans*-I TMC have been reported, none appear to have been structurally characterized. However, six-coordinate complexes of divalent 3d metals with a *trans*-I configuration for the ligand have been structurally characterized with other N-tetraalkylated ligands, i.e., *trans*-[Ni(**5**)$(NCS)_2$] [53] and *trans*-[Ni(**6**)$(NCS)_2$] [54]. Such coordination environments are also frequently found for TMC complexes of 3d metals in higher oxidation states and for 4d and 5d metals in a variety of oxidation states (discussed in subsequent sections).

In aqueous solution complexes of cyclam are more stable than those of *trans*-I tetramethylcyclam complexes, i.e., log *K* values for their Ni(II) complexes are 22.2 (mixture of four- and six-coordinate species) [55] and 11.8 (5-coordinate *trans*-I complex) [46], respectively and for their Cu(II) complexes 27.2 (six-coordinate) [56] and 17.7 (5-coordinate *trans*-I complex) [46], respectively. Similar effects are observed for other metal ions [57]. Complexes of TMC are much more labile than those of cyclam and readily decompose in acidic media and in cyanide (nickel). The Ni(II) complex of cyclam can be boiled for several minutes in 12 M HCl without noticeable change, whereas the complex of TMC has a very short lifetime in 1 M HNO_3 [46]. There is a significant proton-independent dissociation pathway for $[Ni(TMC)]^{2+}$ [46], which probably accounts for the complete transfer of TMC from Ni(II) to Cu(II), which forms a more stable complex, in millimolar aqueous solutions in about 12 h [6]. Similarly, TMC transfers from Ni(II) to Ag(I) in aqueous solution according to $[Ni(TMC)]^{2+}$ + excess $Ag^+ \rightarrow [Ag(TMC)]^{2+} + Ag^0 + [Ni(OH_2)_6]^{2+}$ [6,58]. The X-ray structure of the perchlorate salt of $[Ag(TMC)]^{2+}$ shows it to have the *trans*-III set of nitrogen configurations with weak axial interactions to oxygen atoms of the perchlorate ions [59].

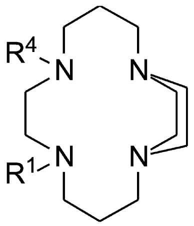
In non-aqueous solvents rates of formation of TMC complexes having the *trans*-I stereochemistry are lower than those of cyclam [46,60], and partially N-alkylated ligands show intermediate behavior [60]. Increasing the size of the N-alkyl groups does not change the stereochemical outcome of the complexation reaction, but does decrease the rate and the thermodynamic stability of the complexes.



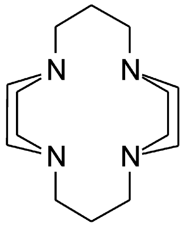
7 R=CH_2Ph
8 R=$CH_2C_6H_4$-*o*-Me
9 R=*i*-Pr
10 R=dodecyl
11 R=$CH_2C_6H_4$-*p*-CN

For example Kaden was unable to generate Cu(II) or Ni(II) complexes of **7–9** in water, ethanol, DMF or DMSO [44]. Dong et al. [61] were successful in isolating and structurally characterizing five-coordinate $[Cu(\mathbf{7})(OH_2)](NO_3)_2{\cdot}2MeOH$ (*trans*-I configuration of donors), but were unsuccessful in obtaining a complex with Ni(II). Comba et al. [62] prepared and structurally characterized the analogous $[Cu(\mathbf{7})(NCMe)](ClO_4)_2$. Alcock et al. [53], found that **10** reacted very slowly with $[Ni(DMSO)_6](ClO_4)_2$ in hot 1-butanol though a reasonable yield (61%) of $[Ni(\mathbf{10})(DMSO)](ClO_4)$ was obtained after 12 h. Complexation of azide in the open axial position becomes less favorable as the size of the N-alkyl group increases [44], and $[Ni(TMC)]^{2+}$ does not bind large ligands such as pyridine and imidazole [49].

Wainwright prepared topologically constrained ligands **12** and **13** by alkylation of cyclam with 1,2-dibromoethane. (Alternative syntheses have been developed [63–65].) Kaden and co-workers [66] expanded on these studies with the synthesis of the copper complexes of **14**, **15** and **16**. The nickel complexes of **14** and **15** were also prepared, but $[Ni(\mathbf{15})]^{2+}$ was prepared from $[Ni(\mathbf{14})]^{2+}$ by a deprotonation/alkylation sequence as it could not be prepared from preformed ligand. Spectral studies suggest that the Cu(II) complexes exist in four-coordinate form in non-coordinating solvents ($MeNO_2$), but become five-coordinate in donor solvents or upon addition of coordinating anions. The nickel complexes of **12**–**15** are four-coordinate under all conditions examined, suggested by Kaden to be a result of the increased strain that would accompany the change in spin-state required for the five-coordinate compounds. X-ray structures of perchlorate salts of cations $[Cu(\mathbf{15})(OH_2)]^{2+}$ and $[Cu(\mathbf{16})(OH_2)]^{2+}$ show them to have structures with the Me or Et groups on the same side of the N4 plane with the water molecule attached to copper on that same side. However, the structure of four-coordinate $[Cu(\mathbf{14})]^{2+}$ has the N—H and N—Me groups on opposite sides of the nominal CuN4 plane. The structure of $[Ni(\mathbf{15})]^{2+}$ is unknown and its method of preparation could lead to either of the possible diastereoisomers. Though the constraints of the piperazine ring result in skewing of the six-membered chelate rings, all of these structures are otherwise largely comparable to those of unconstrained N-tetraalkylated complexes.



12 $R^1=R^4=H$
14 $R^1=Me$, $R^4=H$
15 $R^1=R^4=Me$
16 $R^1=R^4=Et$



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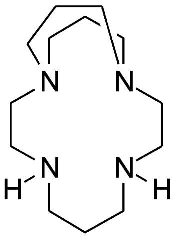

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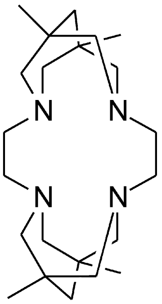

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Available spectral data and M—N bond distances for four-coordinate nickel(II) and copper(II) complexes of **1**, **2** and **12**–**18** are collected in Table 1. To the extent possible these are for nitromethane solutions of complexes of stoichiometry $[M(\mathbf{L})]Y_2$ where Y is a poorly coordinating anion. Under these conditions there is a reasonable expectation that the metal ion will be four-coordinate with a square planar arrangement of donors, at least to the extent allowed by the conformation of the ligand. These data will be considered further in a later section, but it is obvious that compared to cyclam, N-alkylation results in a red-shift of the absorption maximum that is moderately affected by the stereochemistry of the coordinated nitrogen donors, but that topological rigidity imposed by ligands such as **13** and **18** can reverse this trend. This suggests that the relief of steric strain and/or the rigidity of the ligand imparts a stronger ligand field. One expects that the M—N bond distances are shorter, which seems to be supported by the few structural data that are available.

Table 1
Spectral data and M—N bond distances for four-coordinate nickel(II) and copper(II) complexes of some tetra-N-alkylated ligands.

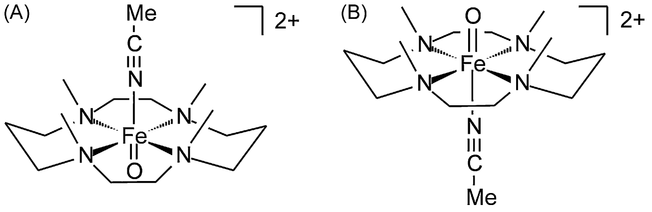
Ligand	Absorption maximum[a] (cm^{-1}), avg. M—N bond distance (Å)			
	Nickel(II)	Reference	Copper(II)	Reference
1	21,980	[67]	20,200	[69]
	1.94	[68]		
2 (*trans*-I)	19,455	[70]	19,080[b,c]	[44]
	1.98	[42]		
2 (*trans*-II)	19,880	[70]		
2 (*trans*-III)	20,325	[70]	18,870, 2.07	[71]
	1.99	[19]	2.08	[38]
12	21,690[b]	[72]		
14	21,097	[66]	19,530, 2.00[d]	[66]
15	20,790	[66]	19,920, 2.03	[66]
16			19,920, 2.04	[66]
13	23,260[b]	[72]		
	22,222[b]	[73]		
17	22,230[b], 1.92[e]	[74]		
18			25,460, 1.98[f]	[75]

[a] Data are for CH_3NO_2 solution unless otherwise indicated.
[b] H_2O.
[c] Data for the tetra-N-ethyl derivative which is believed to be four-coordinate.
[d] While the Cu—N(2°) bond distance is about 0.02 Å shorter than the Cu—N(3°) bond distances, the latter bonds are also shorter than those in **15** and **16**.
[e] Bond distances to N(2°) are hardly distinguishable from those to N(3°).
[f] Calculated value.

2.2. *trans-I stereochemistry—high valent metals*

A number of higher valent 3d metal complexes of tetra-N-alkylated cyclams have been prepared, many of which likely owe their stability to the blocking of acid-base reactions at the nitrogen donors. An early example was $[Fe(TMC)(NO)](BF_4)_2$, prepared by reaction of $[Fe(TMC)(NCMe)](BF_4)_2$ with $NO_{(g)}$ in dry acetonitrile under an inert atmosphere, which has the *trans*-I structure but one with a significant distortion toward trigonal bipyramidal with the NO in an equatorial position [76]. This $\{FeNO\}^7$ compound is best described as Fe^{3+} with an $S=3/2$ ground state [77]. When $[Fe(TMC)(NCMe)](BF_4)_2$ was treated with $[NO]BF_4$ a six-coordinate complex with an hydroxyl group in the sixth position *trans* to the NO was obtained. The same compound can be obtained by reaction of $NO_{(g)}$ with $[Fe(TMC)(NCMe)](BF_4)_2$ in air. The shorter iron–tertiary amine distances in the hydroxo compound (0.07 Å) and the methods of synthesis all suggest that this compound could be considered to contain Fe(IV) [76].

Que and co-workers prepared a series of iron(IV) oxo complexes of TMC including *trans*-$[Fe(TMC)(O)(NCMe)](OTf)_2$ (**A** in Scheme 1) and $[Fe(TMC)(O)(X)](OTf)$ ($X=N_3^-$, NCS^-, and $CF_3CO_2^-$). These were prepared by oxidation of $[Fe(TMC)(OTf)_2]$ [78] or $[Fe(TMC)(X)](OTf)$ ($X=N_3^-$, NCS^-) [25] with PhIO or H_2O_2 in acetonitrile or by substitution of acetonitrile in **A** [79]. The X-ray



Scheme 1.

structure of **A** shows the TMC ligand to have the *trans*-I structure with the oxo group bound to iron on the side *opposite* to the N-methyl groups.

A second diastereoisomer (**B** in Scheme 1) in which the oxo and acetonitrile groups are interchanged was prepared from **A** using excess PhIO in the presence of fluoroborate anion or with two equivalents of $PhI(OAc)_2$ in acetonitrile, possibly via a transient dioxoiron(VI) species [80]. Loss of the oxygen originally present in **A** occurs by insertion into a C—H bond of acetonitrile. Both diastereoisomers react with NCS^- to give isomeric $[Fe(TMC)(O)NCS]^+$. All of these compounds have an $S = 1$ ground state.

Evidence for the generation of $[Fe(TMC)O]^{2+}$ directly from oxygen in mixtures of acetonitrile and other solvents (alcohols, ethers, etc.) and catalyzed aerobic oxidation of substrates has also been reported by Nam and co-workers [81]. The role of the co-solvents may be to change the $Fe^{3+/2+}$ potential. Formation of the oxo complex was suggested to occur by homolytic cleavage in a dioxo-bridged dinuclear $[Fe(TMC)]^{3+}$ complex, i.e.,

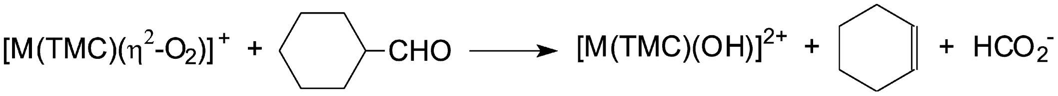
$$2[Fe^{II}(TMC)]^{2+} + O_2 \rightarrow [(TMC)Fe^{III}\text{—}O\text{—}O\text{—}Fe^{III}(TMC)]^{4+}$$
$$\rightarrow 2[Fe^{IV}(TMC)O]^{2+}$$

The absorption spectrum of the species obtained is consistent with that of diastereoisomer **A** in Scheme 1. The reason for difference in the location of the nitrosyl group in $[Fe(TMC)(NO)](BF_4)_2$, which is on the same side as the N-methyl groups, compared to the orientation of the oxo group on the side opposite the N-methyl groups observed in **A** is not obvious.

An intriguing feature of the chemistry of these iron oxo complexes is the impact of variation in the axial ligand on their redox potentials, and their reactivity toward oxygen transfer to PPh_3 and C—H hydrogen atom abstraction from 9,10-dihydroanthracene (DHA). Electrochemical reductions were irreversible, but there was a systematic decrease in peak potential (vs $Fc^{+}/^{0}$) for **A**-NCMe (−0.32 V), **A**-N_3^- (−0.50), **A**-$CF_3CO_2^-$ (−0.60 V) [79]. There was a corresponding decrease in the rate of oxygen transfer to PPh_3 consistent with the notion that the more basic anions stabilize the Fe(IV) center relative to acetonitrile. The observed order of reactivity for H-atom abstraction from DHA was opposite to that for oxygen transfer and was attributed to participation of a low lying quintet state, whose energy dropped as the electron-donating character of the axial ligand increased [79,82]. This behavior was accentuated by replacing one of the N-methyl groups by a tethered thiolate donor as described in a subsequent section. Isomer **B** reacts more rapidly than **A**-NCMe with both PPh_3 and with DHA. Whether this difference in reactivity is substantially kinetic (more accessible oxygen?) or thermodynamic (more positive $Fe^{4+/3+}$ potential?) or a combination is an open question. An iron(II) complex of tetrabenzylcyclam **7**, suggested to be $[Fe(\mathbf{7})(NCMe)_2](OTf)_2$ has been reported to react with PhIO in acetonitrile to generate an oxo complex, which oxidized PPh_3 and anisole [83]. No structural information is available, but the implied six-coordination of the starting Fe(II) complex is surprising.

Prior to the discovery of diastereoisomer **B** incorporation of ^{18}O from labeled water was observed during oxidation of thioanisole (to sulfoxide) by **A** [84]. At the time it was assumed that because the two sides of the coordination plane were different the incorporation of labeled oxygen must involve coordination of water *cis* to the oxo group followed by proton transfers. This may be the case, but the possibility that a *trans*-dihydroxo species could be formed and that the actual oxygen transfer agent is some form of **B** cannot be discounted.

In addition to iron, Nam and co-workers have investigated reaction of a number of other M(II)–TMC complexes with molecular oxygen with notable results. Both the cobalt [26] and manganese [23] TMC complexes react with excess H_2O_2 (5 equiv.) in the presence of base (triethylamine, 2.5 equiv.) to generate $[M(TMC)(\eta^2\text{-}O_2)]^+$, which are characterized as high-spin peroxo complexes. The stoichiometry of the preparative reaction was not established, but the synthetic strategy is based upon that utilized by Kitajima for the preparation of another Mn(III) η^2-peroxo [85]. Nam's TMC complexes do not react with nucleophiles like phosphines and sulfides but do react with electrophiles such as aldehydes leading to deformylation, e.g.,



A number of chromium(III) complexes of stoichiometry $[Cr(TMC)(L)_2]^{n+}$ have been reported [86–88]. Based upon their spectral properties it appears that the monodentate ligands are coordinated in *trans* positions. Structures of these complexes have not been determined although computational studies to investigate their gas and solution phase behavior were done assuming a *trans*-III stereochemistry [86].

2.3. *trans*-III stereochemistry

Because the *trans*-III diastereoisomer was only known for $[Ni(TMC)]^{2+}$ in the early days of N-tetraalkylated ligands and this isomer could be obtained only by derivatization of the cyclam complex our knowledge of the properties and chemical behaviors of these compounds is less than for the *trans*-I forms. Structural data is available for both 6-coordinate (*trans*-$[Ni(TMC)N_3]$-μ-N_3-$[Ni(TMC)N_3]I$ [16], *trans*-$[Ni(TMC)(OH_2)_2]Cl_2{\cdot}H_2O$ [19]), 5-coordinate ($[Ni(TMC)SC_6H_5]OTf$ [32], $[Ni(TMC)(CH_3)]$ B(3,5-$(CF_3)_2C_6H_3)_4$ [89], $[Ni(TMC)(OH)]OTf$ [90]) and 4-coordinate forms $[Ni(TMC)](OTf)_2$ [19]. Recent discoveries, *vide infra*, of ways to systematically achieve interconversion of diastereoisomers have yielded the *trans*-III form of the Cu(II) complex. Salient properties of *trans*-III compounds include:

1. the metal ion sits in the plane of the four nitrogen donors (Fig. 1) in the 4- and 6-coordinate compounds but the M—N bond distances are comparable to those in the *trans*-I isomer,
2. the kinetic stability of the *trans*-III Ni(II) complex in acidic and cyanide media is very high compared to the *trans*-I isomer and even higher than for the cyclam complex [17],
3. the ligand field strength of TMC (est. 1130–1250 cm^{-1}) [17,91] is less than that of cyclam (1480 cm^{-1}) [92,93] in five and six-coordinate Ni(II) complexes and can be inferred to be less in *trans*-I isomers than for *trans*-III isomers based upon the blue shifts for their 4-coordinate Ni(II) complexes in nitromethane (tabulated in Table 1).

We initially concluded, incorrectly, that the *trans*-III diastereoisomer must be thermodynamically more stable than the *trans*-I form and that the latter was the kinetic product of the complexation reaction between metal ion and free ligand, although we were unable to achieve their interconversion. This notion was largely based upon the analysis provided by Bosnich et al. concerning the relative stabilities of the five possible diastereoisomers (Fig. 2) [14], the methods used for the synthesis of the isomers, and their very different stabilities in aqueous acid and cyanide solutions. A decade after the first complexes of tetramethylcyclam was synthesized, Moore and co-workers [94] were able to equilibrate the *trans*-I and *trans*-III forms of $[Ni(TMC)]^{2+}$, and they found evidence for the existence of the *trans*-II diastereoisomer as an intermediate. Moore found that at about 350 K in both DMF and DMSO the ratio of *trans*-III to *trans*-I was in the range of 2-3:1 whereas in nitromethane containing *n*-propylamine the ratio is roughly reversed with the *trans*-I isomer predominating [95]. *Trans*-III $[Ni(TMC)(O_2COCH_3)_2].Et_3NHClO_4$ was isolated by Kato from a CO_2-saturated methanol solution of *trans*-I $[Ni(TMC)](ClO_4)_2$ containing a large excess of Et_3N after the solution stood for several weeks [31]. In 2001 Bucher et al. [71], reported that *trans*-III $[Cu(TMC)]^{2+}$ could be generated directly by addition of $Cu(BF_4)_2$ to a solution of TMC in 3.75 M NaOH maintained at 90 °C. The purple fluoroborate salt, isolated in 50% yield by slow evaporation of the reaction mixture appears to be four-coordinate in nitromethane and in water, but both it and the analogous perchlorate salt [38] have weak axial interactions with the anions in the solid state. When reduced to the monovalent form in acetonitrile these complexes isomerize to the *trans*-I isomer. This phenomenon will be discussed further in a latter section. A 5-coordinate *trans*-III copper complex [Cu(TMC)Br]Br has also been structurally characterized [96].

Following Moore's detection of the *trans*-II isomer, Lincoln et al. [97] found small amounts of the *trans*-II isomer in crude preparations done according to the original preparation of the Ni(II) complex ($EtOH/H_2O$) [6] and that comparable amounts of the *trans*-I and *trans*-II isomers could be obtained when the reaction was done in triethylformate using nickel triflate [97,98] Recrystallization from nitromethane resulted in nearly complete conversion to the *trans*-I isomer. In our lab, Tang [70] found that the *trans*-II isomer could be prepared without detectable contamination from the *trans*-I form (^1H NMR spectroscopy) by addition of an ether solution of TMC to a vigorously stirred DMSO solution of excess $Ni(ClO_4)_2{\cdot}6H_2O$ followed by a rapid work-up [99]. This complex slowly converts to the *trans*-I isomer in neutral aqueous solution but the rate of conversion is greatly accelerated by hydroxide.

The role of the *trans*-II isomer in the reaction of TMC with aquated 3d metal ions was illuminated by Röper and Elias' study of the kinetics of formation of the nickel(II) and copper(II) complexes of the series cyclam, monomethyl, 1,4-dimethyl-, trimethyl-, and tetramethylcyclam in DMF solution [60]. They find conclusive evidence for a two step reaction involving the rapid formation of an intermediate that slowly converts to the final product for all five ligands with Ni(II) and for TMC with Cu(II) (rates of reactions with the other four ligands were too fast to follow the initial step). The final product for both metal ions with TMC was the *trans*-I isomer in the form of $[M(TMC)DMF]^+$. They proposed that formation of the second M—N bond is rate controlling for generation of the intermediate. For the TMC reaction ^1H NMR spectra confirm that the intermediate is the *trans*-II isomer, which is suggested to be four-coordinate in DMF. Kaden had earlier reported a two step reaction sequence for the nickel–cyclam reaction in both DMF and DMSO [100], but reported only a single step for the TMC reaction possibly because the second step was so much slower it was simply not detected.

The question of relative stability of the diastereoisomers of metal–TMC complexes is complicated by their participation in equilibria between species of different coordination number. On the basis of molecular mechanics Hambley [42,101] concluded that the relative stabilities for 4-coordinate Ni(II) complexes is *trans*-I > *trans*-III whereas for 5- and 6-coordinate complexes the order is *trans*-III > *trans* I. A subsequent study of four-coordinate diastereoisomeric forms, which employed an additional term in the force field to account for out-of-plane bending involving the mean plane through the nickel ion and the donor set, reached the opposite conclusion concerning the relative stabilities of the 4-coordinate *trans*-I and *trans*-III isomers [102]. Hambley found that the *trans*-II isomer was also slightly lower in energy than the *trans*-III for the 4-coordinate form, but was higher in energy than either of the other two isomers for 5- and 6-coordinate forms. In all cases the nickel–nitrogen bond distances were longer in the TMC complex than those in the cyclam analog as a result of interactions between the N-methyl substituents or between the N-methyl groups and the metal ion.

2.4. *cis*-V stereochemistry

Reaction of $[Co(TMC)OAc]PF_6$ [103] with 3,5-di-tert-butylcatechol or 9,10-dihydroxyphenanthrene in the presence of base, followed by oxidation with $[FeCp_2]PF_6$ yielded compounds characterized as high-spin $[Co^{II}(TMC)(semiquinone)]PF_6$ [104]. The phenanthrene derivative was structurally characterized along with the related tropononate derivative [105] and found to contain tetramethylcyclam with a folded *cis*-V stereochemistry and chelated catecholate and tropolonate ligands as illustrated for the phenanthrenecatecholate derivative in Fig. 4.

The *cis*-V stereochemistry is forced upon metal ions by ligands such as **19**–**21** were first prepared by Weisman according to Scheme 2 [106,107]. The crystal structure of the Cu(II) complex of $[Cu(\mathbf{20})Cl]Cl{\cdot}H_2O$ shows it to be five coordinate with only one coordinated chloride ion [106,107]. While similar coordination numbers are also observed for the complex of **21** [108] the complex of **20** appears to have a possible coordination position blocked by a novel agostic interaction with the *ortho* hydrogen of one of the benzyl groups. A similar structure was noted for the $[Cu(\mathbf{20})(NCCH_3)]^{2+}$ cation whereas its Cu(I) precursor is four-coordinate [109].

Ligands **19** and **20** are extremely basic ($pK_{a1} > 24$) which makes synthesis of complexes in protic solvents difficult for metal ions with low formation constants. Hubin et al. overcame this difficulty by working in very dry, aprotic solvents and prepared a series of complexes of a variety of di- and trivalent 3d metal ions [110]. Structures of a large number of these complexes have been done. With the exceptions noted above for copper complexes virtually all

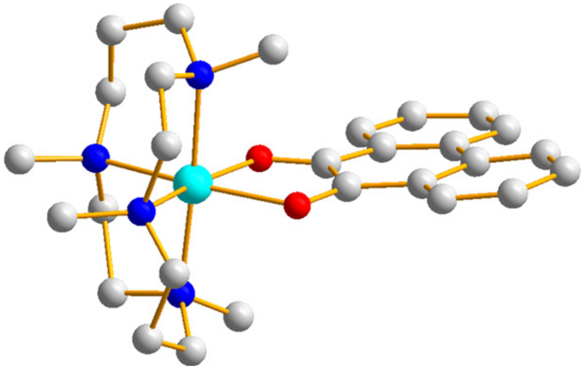
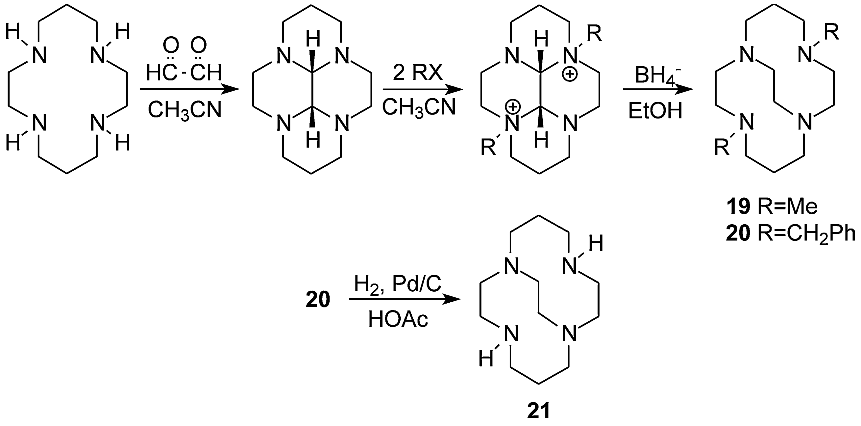


Fig. 4. Structure of the cation of *cis*-$[Co(TMC)(L_2)]PF_6$ (L_2 is 9,10-phenanthrenecatecholate monoanion). Structure redrawn with data from reference [104], obtained from Cambridge Structural Database.



Scheme 2.

the rest are six-coordinate, diacido complexes with the *cis*-V nitrogen stereochemistry for the tetradentate ligand [111]. The kinetic stabilities of complexes of this ligand are extremely high compared to those of TMC. For example, the Cu(II) complex of TMC has a half-life in 1 M acid that is greater than 8 orders of magnitude less than that of the complex of **19**. At the same time the high spin nature of the Mn(II) and Fe(II) complexes result in the chloride ligands being labile and readily replaced by donor solvents [112]. The stability of the manganese complexes and the accessibility of higher oxidation states, $[\mathrm{Mn}(\mathbf{19})(\mathrm{OH})_2](\mathrm{PF}_6)_2$ has been structurally characterized [113], has generated keen interest in their catalytic activity for epoxidation [114] and oxidation by hydrogen abstraction [115].

3. Impact of N-alkylation on electrochemical and spectral properties of 3d-metal complexes

In spite of the high kinetic stability of *trans*-III $[\mathrm{Ni(TMC)}]^{2+}$ its redox behavior is not very different from that of the *trans*-I isomer. However, the redox behavior of both isomers is very different from that of the cyclam complex in that both the $\mathrm{Ni}^{3+/2+}$ and the $\mathrm{Ni}^{2+/+}$ potentials are shifted anodically by significant amounts (up to 590 mV). Fig. 5 presents $E_{1/2}$ values from Freeman's investigation of the electrochemical behavior [19] of the series $[\mathrm{Ni}(\mathbf{L})]^{2+}$ ($\mathbf{L}$ = monomethyl-, 1,4-dimethyl-, trimethyl- and tetramethylcyclam) along with literature data for the cyclam complex under the same conditions [11].

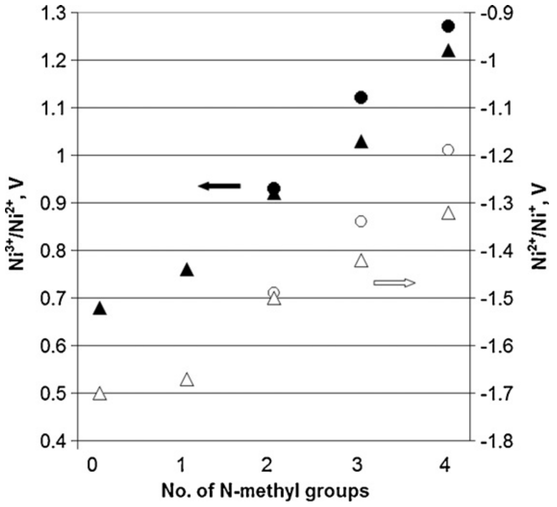


Fig. 5. Variation of reduction potentials for $[\mathrm{Ni(N\text{-}Me}_n\mathrm{cyclam)}]^{3+/2+/1+}$ as a function of n for *trans*-I diastereoisomers (circles) and *trans*-III diastereoisomers (triangles). Acetonitrile solution, 0.1 M Ag^+/Ag reference electrode.

Dong et al. [61], have investigated the redox behavior of a series of nickel and copper complexes of N-benzylated cyclam ligands and find similar trends for both the $\mathrm{M}^{3+/2+}$ and $\mathrm{M}^{2+/+}$ potentials to those with the various N-methylated cyclam ligands. The following conclusions can be drawn:

(1) N-alkylation results in a progressive anodic shift in both the $\mathrm{Ni}^{3+/2+}$ and the $\mathrm{Ni}^{2+/+}$ potentials with the difference being largest for oxidation of the *trans*-I TMC complex where the potential is 590 mV greater than that for the cyclam complex.
(2) There is only a small difference in the $\mathrm{Ni}^{3+/2+}$ potentials for the *trans*-I and *trans*-III TMC complexes, but the $\mathrm{Ni}^{2+/+}$ potential is considerably more anodic for the *trans*-I isomer than for the *trans*-III isomer (−1.19 V vs −1.32 V).

Table 2 compares the values for the $\mathrm{M}^{3+/2+}$ and $\mathrm{M}^{2+/+}$ potentials for cyclam and TMC complexes of nickel and copper, the two 3d metals for which the most information is available on structurally characterized compounds. The potentials for the TMC complexes are shifted anodically relative to those for the cyclam complexes in every case where a comparison can be made. Note that data are included for both the *trans*-I and *trans*-III forms of $[\mathrm{Ni(cyclam)}]^{2+}$ in aqueous acid, which were first characterized by Billo in solution [116] and then isolated and studied independently [117]. It is interesting that there is a greater difference in the $\mathrm{Ni}^{3+/2+}$ couple there the two diastereoisomers than for the TMC analogs. Although the $\mathrm{Ni}^{3+/2+}$ and the $\mathrm{Ni}^{2+/+}$ processes for the *trans*-I and *trans*-III TMC complexes are both substantially reversible at CV scan rates of >200 mV s^{-1} the nickel(I) complexes equilibrate at longer times in a variety of media. This phenomenon was first observed by Bakac and Espenson [118,119] and later exploited by Riordan to isolate and structurally characterize *trans*-III [Ni(TMC)]OTf·NaOTf [32]. This complex was isolated from a mixture of the two diastereoisomers, obtained by sodium amalgam reduction of either Ni(II) complex, by preferential crystallization. The coordination environment is rigorously planar but with two somewhat different Ni—N distances of 2.120(5) and 2.095(5) Å. These are on the average 0.12 Å longer than the Ni—N distances in the Ni(II) analog (1.99 Å) [19]. A similar difference in Ni—N bond distance was observed for the Ni(II)/Ni(I) forms of a C-alkylated cyclam ligand (2.068 Å vs 1.959 Å) [120]. Note that Ni—N bond distances for the N-alkylated ligand are slightly longer in both oxidation states.

Recent detailed chemical and electrochemical studies on copper complexes show that they undergo a much more rapid, and possibly more complex, redox induced isomerization. As described

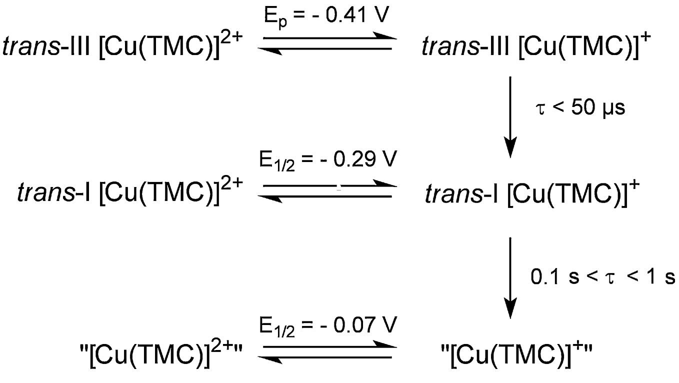
Table 2
Redox potentials for Ni(II) and Cu(II) complexes of cyclam and TMC in acetonitrile and water.

Metal	Solvent	$M^{3+/2+}$, V vs SCE[a]				$M^{2+/1+}$, V vs SCE[a]			
		Cyclam	Ref.	TMC	Ref.	Cyclam	Ref.	TMC	Ref.
Ni	CH_3CN	1.01	[11]	*trans*-I 1.61	[19]	−1.36	[11]	*trans*-I −0.85	[19]
		0.98	[10]	*trans*-III 1.56				*trans*-III −0.98	
	H_2O	0.65[b]	[121]			−1.58	[67]	*trans*-I −1.04	[123]
		trans-I 0.92[c]	[117]			−1.54	[123]	*trans*-III −1.15	[67]
		trans-III 0.77[c]	[122]						
Cu	CH_3CN	1.42	[10]	*trans*-I ca. 2.0 (irrev)	[125]	−0.90	[61]	*trans*-I −0.29	[126]
		1.35	[124]			−1.1 (E_p)	[124]	*trans* III −0.41(E_p)	
	H_2O	0.77[b]	[121]			−0.73	[127]	$Cu^{2+/0}$only	[38]

[a] Values converted from other reference electrodes as necessary unless otherwise indicated; +0.34 for 0.1 M Ag^+/Ag, +0.38 for ferrocenium/ferrocene, −0.045 for Ag/AgCl, −0.241 for NHE.
[b] 10 M $HClO_4$.
[c] Values vs 3.5 M NaCl calomel.

above Amatore et al. [126], were able to directly synthesize *trans*-III $[Cu(TMC)]^{2+}$, but an investigation of the electrochemical behavior (cyclic voltammetry) of this complex indicated that upon reduction in acetonitrile it very rapidly converted to the *trans*-I isomer, which more slowly converted to a species of unidentified composition/structure. These results are summarized in Scheme 3. One can infer from later electrochemical studies by this group of related complexes that "$[Cu(TMC)]^{2+}$" in the above Scheme may be a tetrahedral complex possibly with an η^3-TMC and a solvent molecule as ligands.

The stability of the *trans*-III isomer of $[Cu(TMC)]^+$ is apparently greatly affected by medium as Meyerstein and co-workers were able to generate and isolate the *trans*-III form of $[Cu(TMC)]^{2+}$ by Cu^0 reduction of *trans*-I $[Cu(TMC)]^{2+}$ in the presence of excess TMC in aqueous solution at reflux. The stoichiometric reaction is $[Cu(TMC)]^{2+} + Cu^0 + TMC = 2[Cu(TMC)]^+$ [38]. Exposure of the reaction mixture to air generates the Cu(II) complex, which is largely the *trans*-III isomer. *trans*-III [Cu(TMC)Br]Br has also been obtained from an atom transfer radical polymerization (ATRP) reaction mixture, which employed a 1:1 ratio of CuBr/TMC and a radical initiator in a solution of the monomer, after standing for at least 3 days at room temperature [96]. These reactions involve a reversible switching of copper between the 1+ and 2+ oxidation states and formation of the product may be driven by the insolubility of the Cu(II) complex. The difference in the apparent relative stabilities of the isomeric forms of the Cu(I) complex in water and methanol compared to acetonitrile is striking, as is the further conversion of the *trans*-I isomer to a new species. Finally, if the mechanism of isomerization of the monovalent species involves formation of the *trans*-II isomer its lifetime must be extremely short.



Scheme 3.

4. Reactions of mono-valent 3d metal complexes

As indicated above, generation of mono-valent complexes of nickel and copper, provide a means for interconversion of *trans*-I and *trans*-III stereochemistries. Some of these mono-valent complexes also participate in interesting reactions with electrophiles such as alkyl halides, sulfur and molecular oxygen, which will be briefly summarized.

Reaction of reduced *trans*-III $[Ni(TMC)]^+$ with alkyl halides was first reported by Pletcher and co-workers [18], whose group had already studied similar reactions with macrocyclic secondary amine nickel(I) species, which behave as electrocatalysts for alkyl halide reduction. A mechanism involving formation of a Ni(III) intermediate via oxidative-addition and its subsequent reactions with alkyl halide was proposed. Espenson and co-workers investigated stoichiometric reactions of both the *trans*-I and *trans*-III $[Ni(TMC)]^{2+}$ in aqueous solution and observed the following stoichiometry for reactions with alkyl halides [118,128]:

$$2[Ni(TMC)]^+ + RX \rightarrow [Ni(TMC)(R)]^+ + [Ni(TMC)]^{2+} + X^-$$

which proceeds in two steps:

$$[Ni(TMC)]^+ + RI \rightarrow [Ni(TMC)]^{2+} + I^- + R^\bullet$$

$$[Ni(TMC)]^+ + R^\bullet \rightarrow [Ni(TMC)(R)]^+$$

In a slower reaction the alkyl complexes hydrolyze such that the overall stoichiometry is:

$$2[Ni(TMC)]^+ + RI + H_2O \rightarrow 2[Ni(TMC)]^{2+} + R{-}H + OH^- + I^-$$

There was precedent for the alkyl nickel(II) complexes as paramagnetic *trans*-III $[Ni(TMC)CH_3]^+$ was earlier prepared by D'Aniello from $[Ni(TMC)]^{2+}$ and $Mg(CH_3)_2$ in THF [129] and its B(3,5-$(CF_3)_2C_6H_3)_4{}^-$ salt has been structurally characterized [89]. When excess alkyl halide (other than methyl halide) is present the following reaction occurs [130]:

$$[Ni(TMC)R]^+ + RX \rightarrow [Ni(TMC)]^+ + X^- + \text{hydrocarbons (coupling and disproportionation products)}$$

Since the initial electrocatalytic studies [18] were done with excess alkyl halide Bakac and Espenson [118] suggested that the electrocatalytic results might be explained by a similar set of reactions and that Ni(III) species need not participate. Methyl-Ni(III) species have been suggested to form from reactions of several macrocyclic secondary amine-nickel(II) complexes with methyl radicals generated by pulse radiolysis [131–133].

Espenson noted that *trans*-III $[Ni(TMC)]^+$ reacted with oxygen to form a yellow specie(s) [118] but did not investigate its properties. Recently Riordan has investigated the reaction of *trans*-III [Ni(TMC)]OTf with oxygen in MeCN and THF and finds that two species are formed, a 1,2-μ-dioxo bridged Ni(II) dimer, $[[Ni(TMC)]\text{-}O_2\text{-}[Ni(TMC)]]^{2+}$ [90], and a monomeric, "end-on" Ni(II) superoxo complex, $[Ni(TMC)(O_2)]^+$ with the ratio determined by the amount of oxygen present [134]. The latter complex can also be generated from H_2O_2 in the presence of triethylamine although the precise mechanism/stoichiometry of this reaction has not been established. Characterization of these dioxygen complexes is based upon extensive spectroscopic, magnetic and computation studies. Thermal decomposition of the dioxo bridged dimer in MeCN yields the structurally characterized [Ni(TMC)(OH)](OTf) [90]. The superoxo complex reacts in a 1:1 ratio with triphenylphosphine to give the oxide; however, the fate of the second oxygen is unknown [135]. Through reaction of *trans*-III $[Ni(TMC)]^+$ with elemental sulfur Riordan has also generated a complex believed to be the 1,2-μ-disulfido bridged Ni(II) dimer, $[[Ni(TMC)]\text{-}S_2\text{-}[Ni(TMC)]]^{2+}$ analogous to the dioxo complex [136].

5. Differences in M—N (tertiary) and the M—N (secondary) bonding interactions in 3d metal complexes

As described earlier, M—N bond distances in complexes of 3d metals with 3°-amine ligands are invariably longer than those for comparable 2°-amine ligands. This is also the case for 4d and 5d metals, although the percent increase is generally not as large, *vide infra*. It is not surprising then that ligand field strengths are lower for 3°-amine donors relative to those for 2°-amine donors. Redox potentials indicate that lower oxidation states are stabilized for complexes of tertiary amine ligands relative to their secondary amine counterparts. This has resulted in the availability of many complexes of metal ions in lower oxidation states. Higher oxidation states are not stabilized in a thermodynamic sense, but because there are no ionizable protons in the tetra-N-alkylated ligands, decomposition pathways available to complexes of secondary amines are blocked such that high oxidation state complexes are often kinetically more stable for the 3°-amine ligands, which often allows for their isolation. Except for the possible limitation on intramolecular redox processes none of the above effects of N-alkylation were predicted by us when we first synthesized tetramethylcyclam though our notions were based entirely on the increase in intrinsic basicity (proton affinity) of $(CH_3)_nNH_{3-n}$, $n = 0–3$, which increases with n [137].

The reasons for the differences in M—N(3°) and the M—N(2°) interactions have been addressed by others with sometimes conflicting conclusions. Three major factors are suggested: (1) steric effects resulting from the introduction of the N-alkyl substituents; (2) intrinsic differences in donor properties (basicity) of 3°-amines compared to 2°-amines; (3) differences in solvation [86,138–140]. Each of these will be briefly considered.

Good arguments can be made that the equilibrium metal–nitrogen distance is ultimately determined by the balance between steric strain within the ligand and the strongest possible metal–nitrogen interaction. This is supported by the many molecular mechanics studies that have been done on macrocyclic systems, especially for Ni(II) systems [42,101,102,141–144], and supported by DFT calculations [145]. The ideal unconstrained Ni—N distance is suggested to be 1.91 Å [146] whereas the strain-free hole sizes for cyclam and TMC would suggest ideal Ni—N bond distances of 2.05 Å [142] and 2.20 Å [42], respectively. These hole sizes are determined from calculated minimum energy structures for the ligands with constrained locations for the nitrogen donors and orientations of the donor pairs, a point that has been noted [147,148]. On this basis it would seem that the shorter Ni—N distances in the cyclam complex result because less strain is introduced in the ligand in achieving the equilibrium Ni—N distance. The orientation of the nitrogen lone pairs will be affected by the nitrogen stereochemistries and this effect is evident in the differences in the absorption maxima for the three diastereoisomeric TMC complexes (Table 1). Copper(II) is better matched to the hole sizes of cyclam or TMC, but there is still a significant effect of N-alkylation on ligand field strength. Given the propensity of copper to bind additional ligands, even poorly coordinating ones, some of the examples in Table 1, such as the *trans*-I complex of N-tetraethylcyclam [44] may not be four-coordinate. The absorption maximum for $[Cu(\mathbf{14})]^{2+}$ seems lower than it should relative to those of **15** (and **16**) in comparison with the behavior of the of the nickel(II) complexes of **14** and **15**. This suggests that there may be structural differences between the nickel and copper compounds. The Cu complex of the most highly constrained ligand **18** has an extremely high energy absorbance, consistent with the calculated Cu–N bond distance.

What about intrinsic differences in the donor properties of 3°-amines vs 2°-amines? There is a common conception that alkyl groups bonded to nitrogen are electron donating and that these inductive effects result in a greater basicity. This is most likely not the case. That the enhanced proton affinities of the methyl amines observed in the gas phase [149] are not due to electron donation by the alkyl groups was suggested in the early 1970s when it was demonstrated that the *acidities* of the methyl amines increased in the same order as their basicity [150]. A similar substituent effect on the acidity of alcohols was also established, i.e., $Me_3COH > Me_2CHOH > MeCH_2OH > MeOH$ [151]. Brauman suggested polarizability stabilization [150] as a possible explanation, which has been supported by subsequent investigations. In fact, electron withdrawal by alkyl substituents bonded to nitrogen relative to hydrogen has experimental and theoretical support [152–155]. For conventional Lewis acids such as borane the experimental order of basicity is again $NH_3 < MeNH_2 < Me_2NH < Me_3N$, which is supported by computational studies [156]. The boron–nitrogen bond distances for the methylated amine boron adducts are similar, but slightly less than that of the adduct with ammonia, a result that is again supported by the computational studies. An energy decomposition analysis (EDA) by Bessac and Frenking [157] of the bonding in both borane and alane adducts of ammonia and trimethylamine indicates that Pauli repulsion (steric repulsion) is greater in the trimethylamine compounds but that this is compensated for by greater electrostatic and covalent interactions. Steric repulsions are significantly less in the alane compounds as a result of the much longer Al—N bond (ca. 2.1 Å vs ca. 1.65 Å in the boron compounds).

Given the behavior of ammonia and alkyl amines towards various acids described above what can we make of the behaviors of macrocyclic secondary and tertiary amines in their interaction with transition metal ions? Bessac and Frenking provide some interesting computational results in their EDA analysis of the bonding in $[Cr(CO)_5NH_3]$ (structurally characterized [158]) and $[Cr(CO)_5NMe_3]$, which is not known. Their results suggest a significantly longer Cr—N bond distance in the trimethylamine complex (2.33 Å) vs 2.23 Å for the ammonia complex, which is comparable to the experimental value. The Cr–N bond dissociation energy in the trimethylamine complex is calculated to be smaller, 22.5 kcal mol^{-1}, than that of the ammonia complex, 27.3 kcal mol^{-1}. While the calculated Pauli repulsion energies are quite similar for the minimized geometries they conclude that it is relief of these repulsive interactions in the trimethylamine complex that results in the longer and weaker bond [157]. This conclusion appears to accord nicely with observations of the behavior of compounds of tetramethylcyclam and cyclam where bonds are invariably longer in the former and observations of their complex behaviors (ligand field strengths, redox potentials) suggest that the metal–donor interactions are intrinsically weaker for the tertiary amine donor.

Variations in the covalent/electrostatic contributions to the metal–nitrogen interaction and the degree of charge transfer to nitrogen may play an important role, which could conceivably result in a reversal of basicities. This possibility is suggested by gas phase measurements and calculations on two-coordinate, monovalent copper, nickel and silver amine complexes. Deng and Kebarle [159] indicate that for the reaction $CuL_2^+ = Cu^+ + 2L$ ΔG°_{393} increases in the order $NH_3 < n\text{-}PrNH_2 < n\text{-}Bu_3N$. Kappes and Staley [160] found a similar effect upon alkylation for the corresponding Ni(I) reactions with ammonia and the methyl amines. Both of these studies suggest that in the gas phase N-alkylation leads to stronger interactions. However, this may not hold for silver(I) since calculations for the analogous Ag(I) amine complexes suggest that the Ag—N bond distances increase with alkylation and that their stabilities decrease by 11–12% (ammonia vs trimethylamine).

That there are likely to be significant differences in solvation energies, including hydrogen bonding, between cyclam and tetramethylcyclam and their metal complexes is not unexpected and these differences are likely to play a significant role, particularly in determining differences in the magnitude of formation constants. But hydrogen bonding cannot be invoked in the solid state or in aprotic solvents where spectral and redox potential differences are equally apparent.

6. Complexes of 4d and 5d metals with unfunctionalized tetra-N-alkylated ligands

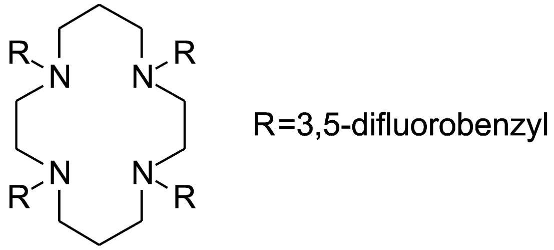
Tetramethylcyclam has been used as a ligand for a variety of 4d and 5d metals although they have in general not yet received the same systematic study as many of their 3d metal counterparts. In the following sections I will attempt to summarize the most notable features of the chemistry of 4d and 5d metals focusing on the observed wide range of ligand stereochemistries and metal oxidation states and where appropriate, comparison with 3d metals. This discussion will began with Group 11 since the first complex of a heavy metal was prepared with silver, and progress to the left in the 4th and 5th periods.

The first complex of TMC with a metal other than those of the third period was with Ag(II), prepared by disproportionation of Ag(I) in aqueous solution and isolated as the perchlorate salt [58]:

$$2Ag_{(aq)}{}^+ + TMC \rightarrow [Ag(TMC)]^{2+} + Ag^0$$

Disproportionation of Ag(I) in the presence of macrocyclic tetraamines in aqueous solution is a general reaction first reported for a C-methylated cyclam analog by Kestner and Allred [161]. The structure of the $[Ag(TMC)](ClO_4)_2$ shows it to be the *trans*-III diastereoisomer [59]. The average silver–nitrogen bond distance of 2.195(3) Å is slightly longer than the distance in the analogous *trans*-III cyclam complex of 2.158(2) Å [162]. Both show weak axial interactions with the oxygen atoms of the perchlorate ions (2.788(2) Å in the cyclam complex vs 2.889(4) Å in the TMC complex). Interestingly, Ito found that the cyclam complex as originally prepared [58] was the *trans*-I diastereoisomer, which slowly converted to the *trans*-III form in 10^{-3} M $HClO_4$ and more rapidly at higher pH. Ito speculates that a Ag(I) complex is initially formed with the *trans*-I configuration, which is retained upon oxidation to the Ag(II) complex. This hypothesis is corroborated by the report of a compound containing both *trans*-III and *trans*-I forms of $[Ag(TMC)]^{2+}$ in a 1:2 ratio, which was prepared by the standard aqueous disproportionation method [163]. The *trans*-I form is five-coordinate with a coordinated water. A related compound had a disordered arrangement of *trans*-III and *trans*-I cations in a 2:1 ratio [164]. The Ag–N bond lengths for the two forms in both compounds are in the range 2.18–2.22 Å. Cyclic voltammetry studies in acetonitrile show that both the Ag(II)–TMC and cyclam complexes can be oxidized to Ag(III) at 0.96 V (irrev) and 0.71 V (quasi-reversible with $\Delta E_p = 300$ mV), respectively (vs the 0.1 M Ag^+/Ag electrode) [58]. Reductions are irreversible $2e^-$ processes. A diamagnetic silver(III)–cyclam complex could be isolated.

Silver(I) complexes of macrocyclic tetramines, including TMC, can be prepared in anhydrous, aprotic solvents [165], though the complex of **22** was prepared in a $CH_3OH/CHCl_3$ mixture [166].



22

The X-ray structure of this compound shows it to have the *trans*-I stereochemistry with Ag—N distances averaging 2.42 Å. One of the aromatic rings sits above the Ag ion and the authors suggest that there is a weak interaction with one of the C—C bonds. The steric bulk of the N-alkyl groups probably slow/prevent oxidation to the Ag(II) form.

Kimura et al. [167] has reported the synthesis of a Au(III) TMC complex of composition $Au\cdot TMC\cdot Cl\cdot (ClO_4)_2$. Neither the coordination environment or macrocycle stereochemistry are known. Three reductions were observed by DC polarography in DMF at 0.17 V, −0.09 V and −0.90 V (vs SCE). The first of these processes was quasi-reversible by cyclic voltammetry. An analogous cyclam complex was also prepared; after recrystallization from nitric acid a mixed nitrate-perchlorate monohydrate salt was obtained, whose X-ray structure showed it to contain four-coordinate *trans*-III $[Au(cyclam)]^{3+}$ cations with average Au—N bond distances of 2.04 Å. The CV and DC polarogram show only a single $3e^-$ reduction at −0.64 V in DMF vs SCE.

The palladium chemistry of TMC has been investigated [168–170]. Blake prepared $[Pd(TMC)](PF_6)_2.CH_3NO_2$ which has the *trans*-I stereochemistry both in solution and in the solid state. The average Pd—N bond distance of 2.058(11) Å is essentially the same as that in the analogous cyclam complex ion (*trans*-III stereochemistry) [171], but with the Pd atom 0.08 Å above the mean plane of the nitrogen donors toward the methyl groups. Electrochemical studies indicated that the $Pd^{2+/+}$ potential (−1.53 V vs $Fc^{+/0}$) for the TMC complex was 0.57 V more positive than for the cyclam complex, a similar difference to that found for the Ni(II) complexes, *vide supra*. In parallel studies the Pd(I) complex of **7** ($Pd^{2+/+}$ potential −1.27 V vs $Fc^{+/0}$) was isolated and structurally characterized. This complex has the *trans*-I ligand stereochemistry with Pd—N bond distances averaging 2.096(8) Å and the Pd atom almost 0.1 Å above the mean N_4 plane toward the benzyl groups though there is a significant tetrahedral distortion of the four nitrogen donors (*trans* pairs of nitrogen donors are ca. 0.2 Å above and below the mean plane). One of the benzyl groups lies somewhat over the Pd atom in the solid state.

Both Pt(II) and Pt(IV) complexes of TMC have been prepared. The former is predominately the *trans*-II form, based upon its ^{13}C NMR spectrum, with a small amount of a species exhibiting a single methyl resonance (<15%). The crystal structure of $[Pd(TMC)](ClO_4)_2.CH_3CN$ has the cation on a mirror plane and was

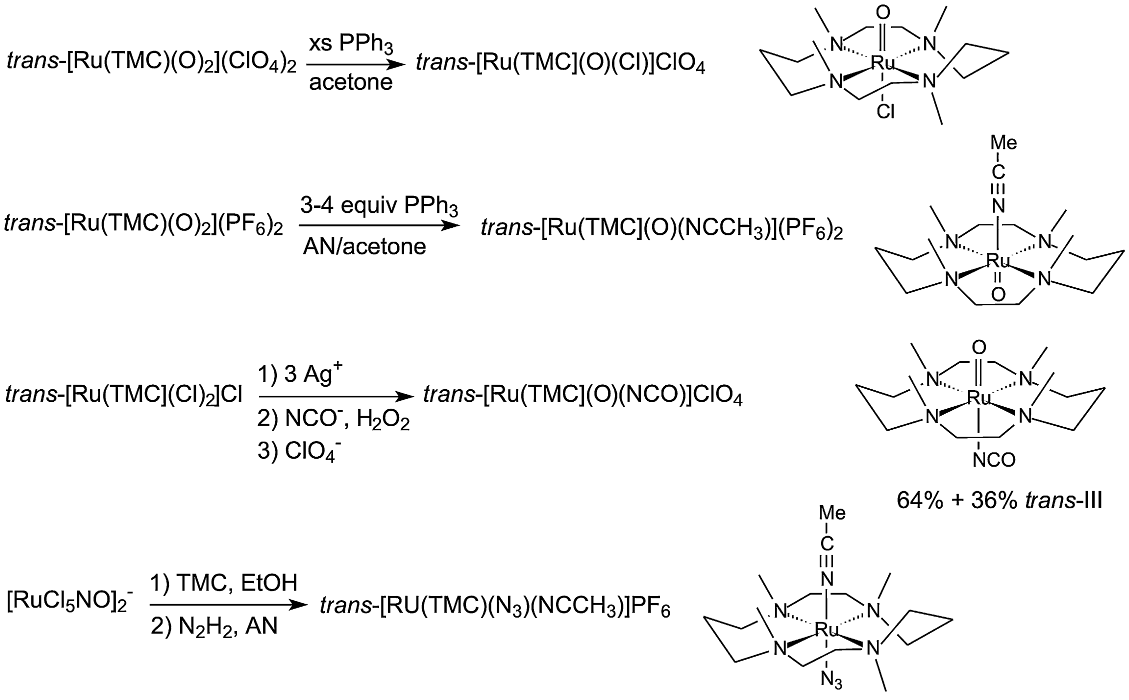


Fig. 6. Preparative route to four structurally characterized Ru–TMC complexes and schematic representation of their gross structures.

refined as the *trans*-I diastereoisomer [172]. However, one of the N-methyl carbons and the adjacent methylene carbons were disordered so that it appears that the crystal contains some of the *trans*-II form. Unlike the corresponding $[Pd(TMC)]^{2+}$ cation the platinum atom appears to be in the plane of the four nitrogen atoms, though this may be an artifact of the disorder. The Pt(II)—N distances (average ca. 2.05 Å) for the TMC and cyclam (*trans*-III diastereoisomer) complexes are essentially identical and comparable to those for the analogous Pd(II) complexes. Oxidation of $[Pt(TMC)]^{2+}$ with $NOBF_4$ in the presence of Cl^- produced $[Pt(TMC)(Cl)_2](BF_4)_2$ [173], whose ^{13}C NMR spectrum suggested the same composition of diastereoisomers as the starting Pt(II) complex. Reaction of the $[Pt(TMC)]^{2+}$ cation with hydroxyl radicals generated by pulse radiolysis proceeded by [173]:

$$[Pt(TMC)]^{2+} + HO\bullet \rightarrow [Pt(TMC)(OH)]^{2+}$$

$$[Pt(TMC)(OH)]^{2+} + H^{+} \rightarrow [Pt(TMC)(H_2O)]^{3+}$$

$$[Pt(TMC)(H_2O)]^{3+} + Cl^{-} \rightarrow [Pt(TMC)(Cl)]^{2+} + H_2O$$

The corresponding cyclam species $[Pt(cyclam)(OH)]^{2+}$ reacted to produce a long-lived $[Pt(cyclam\text{-}H)]^{2+}$. In contrast, similar studies on the Pd(II)–TMC and Pd(II)–cyclam complexes were interpreted in terms of ligand attack at C—H positions, a difference which the authors suggest is most likely kinetic and not thermodynamic in origin [170].

Relative to Group 10 there is little chemistry for the heavier metals of Group 9 with N-tetraalkylated cyclam ligands where the only complex appears to be *trans*-$[Rh(TMC)Cl_2]PF_6$ [174]. This complex was prepared by heating a equimolar amounts of $RhCl_3{\cdot}3H_2O$ and TMC in methanol under aerobic conditions. Both ^1H and ^{13}C NMR spectra of the isolated product indicates it to be 1:1 mixture of *trans*-II (four methyl resonances) and a species having only one methyl resonance. The X-ray structure of the selected crystal shows the cation to lie on a mirror plane but to be substantially disordered. The major component has the *trans*-III ligand stereochemistry with a Rh—N distance of 2.11 Å and Rh—Cl distance of 2.36 Å. The average Rh—N bond distances in *trans*-$[Rh(cyclam)(Cl)(H)]_2ZnCl_4$.DMSO (*trans*-III ligand stereochemistry) are 2.04 Å [175].

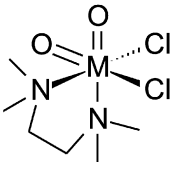
The chemistry of Group 8 was developed early by Che and Poon as part of their extensive investigation of high-oxidation state ruthenium and osmium chemistry [176,177]. They turned to macrocyclic tertiary amines as ancillary ligands after demonstrating that ruthenium macrocyclic secondary amines undergo facile oxidative dehydrogenation reactions [178] like those of their iron counterparts [179]. Starting with *trans*-$[Ru(TMC)(Cl)_2]^+$ [180], successful syntheses of salts of *trans*-$[Ru(TMC)(O)_2]^{2+}$, *trans*-$[Ru(TMC)(O)(X)]^+$ ($X = Cl^-$, NCO^-, $N_3{}^-$) and *trans*-$[Ru(TMC)(O)(NCCH_3)]^{2+}$ were developed [181]. The Ru(V) complex *trans*-$[Ru(TMC)(O)_2]^+$ can be generated by electrochemical reduction of the analogous Ru(VI) complex in acetonitrile [182]. The spectroscopic and electrochemical behaviors of these complexes are in general well-behaved and consistent with expectations for the series of compounds and several 15- and 16-membered macrocyclic analogues. However, X-ray structures on three of the oxo Ru(IV) complexes *trans*-$[Ru(TMC)(O)(X)](ClO_4)$ ($X = Cl^-$, NCO^-) [181,183] and *trans*-$[Ru(TMC)(O)(NCCH_3)](PF_6)_2$ [184] and the Ru(II) complex *trans*-$[Ru(TMC)(N_3)(NCCH_3)]PF_6$ [185] reveal the most diverse stereochemical behavior for the TMC ligand of any other systems investigated to date. Fig. 6 shows the synthetic route to each complex and a schematic drawing of the structure, or major component, for each compound.

Because single crystal X-ray determinations only reveal the structure of the molecules in the crystal that is examined, it is impossible to know based on the data available whether these structures are representative of the bulk sample. In addition, the isomeric contents of *trans*-$[Ru(TMC)(Cl)_2]^+$ and *trans*-$[Ru(TMC)(O)_2]^+$ are unknown so it is also not possible to know whether the observed structures correlate in any way with those of the precursor complex or if inversion of nitrogen configurations occur during the conversion to products.

The only comparison of structural parameters for tertiary and secondary amine ligands in a common oxidation state appears to be for *trans*-$[Ru(TMC)(N_3)(NCCH_3)]PF_6$, where the average Ru—N bond distance is 2.14 Å (*trans*-II ligand stereochemistry) [185] and *trans*-{Ru(cyclam)(Cl)[NC_5H_4-*p*-C(O)CH_3]}BF_4 (*trans*-III ligand stereochemistry) [186] where the Ru—N distances average 2.09 Å. It should be noted that neither complex has crystallographically imposed symmetry for the cation and both show a range of Ru—N distances; however, the average Ru—N distance in the tertiary amine is longer than that in the secondary amine complex.

Osmium also forms high oxidation state TMC complexes $[Os(TMC)O_2]^{n+}$ in the VI, V and IV oxidations states with $n = 2$, 1, 0, respectively. The former two complexes have been isolated and their spectroscopy, and electrochemical behavior well studied [187]. The Os(IV) complex is highly reactive in protic media and has only been generated in acetonitrile by electrolysis [188]. In addition, *trans*-$[Os(TMC)(NCCH_3)_2](PF_6)_2$ was prepared in low yield by reduction of the Os(VI) complex with PPh_3 [187]. NMR studies of $[Os(TMC)O_2]^{2+}$ indicated that it was predominately the *trans*-II diastereoisomer with a smaller amount of a second diastereoisomer [189]. A subsequent X-ray structure indicated the crystal to contain the *trans*-IV diastereoisomer [190], which is unexpected as this the most highly strained of the five possible forms. The standard deviations for bond distances and angles for the structure are quite large and displacements of the carbon atoms to relieve steric strain was suggested as the best explanation, but the possibility that other disordered forms are also present was not discounted. This result illustrates that the material that preferentially crystallizes from solution (or the individual crystal chosen for analysis from a bulk sample) may not be representative of the major component. Also the possibility that crystallization drives a labile system to a single solid state form, while unlikely, also cannot be ruled out based on the available information.

A few attempts have been made to prepare TMC complexes of Group 6 metals. Reaction of MoO_2Cl_2 with TMC yielded a six-coordinate complex in which the TMC served as a bidentate ligand with 1,4-coordination [191]. The X-ray structure of this complex indicated the same arrangement of donors as in the TMEDA adducts of both MoO_2Cl_2 and WO_2Cl_2, i.e., [192],



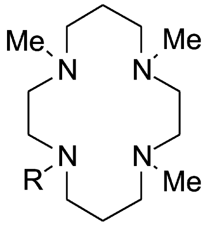
Reaction of TMC with Cr, Mo or W carbonyls yielded complexes of the *cis*-$M(CO)_4L_2$ type based upon their infrared and ^{13}C spectra [193]. Coordination of TMC as a bidentate ligand in the same fashion as for the MoO_2Cl_2 adduct was confirmed by the X-ray structure of the molybdenum complex. Cyclam forms complexes of the type *fac*-$M(CO)_3L_3$ in which the macrocycle is tridentate based upon their composition and infrared spectral properties.

These results simply reinforce the notion that a greater variety of diastereoisomeric forms of TMC complexes can be isolated for 4d and 5d metals than is generally the case for 3d metals. This surely reflects the greater kinetic stability of compounds of the heavier metals, but raises interesting questions concerning the relative stabilities of the various isomers and especially the processes by which they form and interconvert.

7. Complexes of 3d metals and tetra-N-alkylated ligands containing functionalized substituents

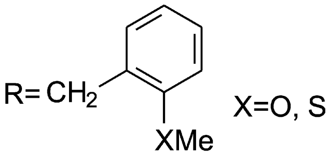
7.1. One functionalized substituent

An extensive series of ligands based upon N-alkylated trimethylcyclam has been reported. These are generally prepared by alkylation of the secondary amine with a Michael acceptor or with a functionalized alkyl halide [194]. The first of these (**23**) was prepared by Schibler and Kaden [195] by cyanomethylation of trimethylcyclam who found that in water it reacted with Cu^{2+} ion to produce a complex of **24,** which resulted from hydrolysis of the nitrile group.



23 R=CH_2CN
24 R=$CH_2C(O)NH_2$
25 R=$CH_2CH_2NH_2$
26 R=$CH_2C(O)OR'$ (R'=Me, Et)
27 R=CH_2CO_2H
28 R=$CH_2CH_2C(O)OEt$
29 R=$CH_2CH_2CO_2H$
30 R=$CH_2CH_2P(O)(OEt)_2$
31 R=CH_2CH_2OH
32 R=CH_2CH_2CN
33 R=$CH_2CH_2C(O)NH_2$
34 R=$CH_2CH_2CH_2NH_2$
35 R=$CH_2CH_2NMe_2$
36 R=$CH_2C(O)NMe_2$
37 R=CH_2CH_2SH
38 R=CH_2CH_2SMe

39



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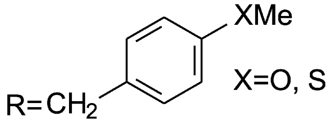

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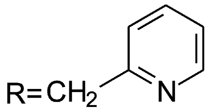


Nickel(II), copper(II) and zinc(II) complexes of **23** could be obtained in DMF; however, once formed all hydrolyzed more or less rapidly to the carboxamide in water, but further hydrolysis to the carboxylate was not observed The pH profile for the reaction and inhibition by thiocyanate suggest that hydrolysis occurs via a five-coordinate hydroxo complex, with intramolecular attack at the carboxyl group. At sufficiently high pH the amide nitrogen is deprotonated and becomes coordinated to the metal ion. Over two decades these studies were expanded to include a number of other hydrolyzable functional groups including **26, 28, 30, 32** whose Cu(II) complexes demonstrated similar behavior [196–200], Complexes of ligands such as **28**, **30**, **32** or **33** prepared by nucleophilic conjugate addition of trimethylcyclam to Michael acceptors are subject to de-alkylation under basic conditions and/or at high temperatures [201], a reaction also observed for complexes of ligands with multiple N-alkyl groups of this type [202,203].

Kaden also reported the synthesis of ligands **25** (by hydrogenation of **23**) and **35** (by Eischweiler–Clarke methylation of **25**) and investigated their Co(II), Ni(II) and Cu(II) complexes [204]. Spectral studies indicated that the primary amino group in **25** coordinated to the metal, but that the dimethylamino group in **35** did not, presumably because of steric interactions between its methyl groups and the methyl groups of the macrocycle, which is expected to be coordinated in the *trans*-I form as found for copper(II) complexes of ligands **28** and **30** [198]. Complexes of **35** reacted with N_3^-, SCN^- and OCN^- in aqueous solution but those of **25** did not. Addition of acid to nickel or copper complexes of **25** resulted in decomposition of the complexes, but addition of acid to suspensions of these complexes in ethanol yield 4-coordinate complexes with a protonated primary amino group [201]. A study of the on/off rates for the appended amino groups in the Co(II), Ni(II) and Cu(II) complexes of **25** and the Ni(II) complex of **34** found little difference with metal ion, but a strong dependence on the length of the carbon chain with the C3 chain being more reactive and less stable in its chelated form [205].

Wainwright succeeded in preparing hydroxyethyl derivative **31** in pure form only by reaction of trimethylcyclam with 2-bromoethanol [206], whereas other hydroxyethyl derivatives of cyclam [207] and less highly N-methylated forms [208] are readily prepared in high yield with ethylene oxide. Determination of formation constants for **31** (and its unmethylated analog) with divalent 3d metal ions by potentiometric titration revealed a very slow rate of equilibration. This was attributed to a low rate of complexation, which is quite unlike the behavior observed for cyclam ligands having multiple hydroxyethyl substituents [207,208].

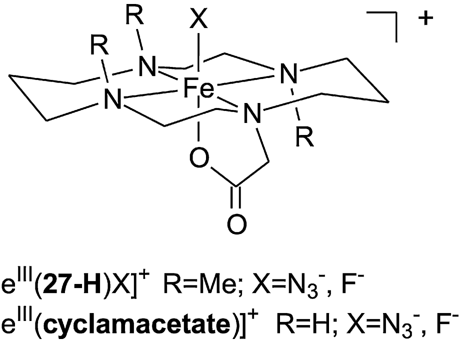
There is nothing to suggest that the nickel(II), copper(II) or zinc(II) complexes of any of these ligands have a stereochemistry other than *trans*-I, which has also been confirmed for **37-H** (prepared from trimethylcyclam and thiirane) (Ni, five-coordinate with chelated ethylthiolate) [209]. Coordination of the ethylthiolate group in **37-H** to copper(II) was also observed spectroscopically by Kaden [210]. The nickel(II) complexes of ligands **39S** and **40S** are four coordinate with a *trans*-I ligand stereochemistry in the solid state with nearly identical structures except for the position of the thiomethyl substituent [211]. The similarity of their absorption spectra in H_2O, MeCN and DMF suggests that the thiomethyl group in $[\mathrm{Ni}(\mathbf{39S})]^{2+}$ does not interact with the nickel ion. The nitrile groups in ligands **23** and **32** also do not bind to metal ions.

Discoveries of the high oxidation state chemistry of iron–TMC complexes stimulated similar studies of iron complexes with (**37-H**) [212] and with **41** [213], (synthesized by alkylation of trimethylcyclam with picolyl chloride). Both of these ligands form five-coordinate Fe(II) complexes, confirmed to have the *trans*-I ligand stereochemistry and a square pyramidal geometry by X-ray crystal structures [24,212]. Both can be converted to Fe(IV) oxo species analogous to that first prepared for TMC, using similar reagents (PhIO, H_2O_2, *meta*-chloroperbenzoic acid). In addition, $[\mathrm{Fe}(\mathbf{41})]^{2+}$ reacts with oxygen in the presence of a proton source and a reductant to give the oxo complex. The $[\mathrm{Fe}(\mathbf{37\text{-}H})(\mathrm{O})]^+$ species does not transfer oxygen atom to triphenylphosphine, but abstracts hydrogen atom readily from dihydroanthracene. Information about the reactivity of $[\mathrm{Fe}(\mathbf{41})\mathrm{O}]^{2+}$ as an oxidant has not yet been reported.

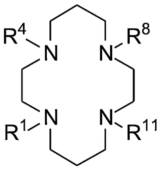
Both *trans*-I and *trans*-III stereoisomers of the Cu(II) complex of **36** and **41** have been prepared [126]; the former diastereoisomer by direct reaction of the ligands with copper salts in water and the latter by the same high temperature/base process used to directly prepare *trans*-III $[\mathrm{Cu(TMC)}]^{2+}$, *vide supra* [71]. These are not interconvertible by thermal processes. However, cyclic voltammetry studies of these complexes show that there is *trans*-I/*trans*-III interconversion in their Cu(I) forms with the *trans*-I form predominating A third species is formed from the *trans*-I isomer in the case of $[\mathrm{Cu}(\mathbf{36})]^{2+}$, which is suggested to be a tetrahedral complex, most likely with an N3O coordination environment. Why the stereochemical course of the complexation reaction of copper by N-tetraalkylated cyclam ligands is different in strongly basic solution compared to other preparative conditions is unknown. Aside from the obvious fact that the ligands will not be protonated under these conditions, the speciation of copper will be very different. Margerum and co-workers [214] demonstrated early that the kinetic and apparent mechanism of complexation of cyclam were very different for simple aquated copper and the "$\mathrm{Cu(OH)_3}^-$" and "$\mathrm{Cu(OH)_4}^{2-}$" species present at high pH.

It is worth noting that five-coordinate complexes of nickel(II) [215] and copper(II) [216] complexes of the non-methylated analog of **41**, 1-(2-pyridinylmethyl)-1,4,8,11-tetraazacyclotetradecane, with the *trans*-I ligand stereochemistry were isolated from reactions of the ligand with hydrated metal salts in methanol. In the case of nickel a six-coordinate complex with the macrocycle in the *cis*-V form and *cis*-coordination of the pyridinylmethyl and a water molecule was also formed. In the case of copper, preparation from $[\mathrm{Cu(NCCH_3)_4}]^+$ in methanol under aerobic conditions yields the *trans*-III isomer. However, reduction of the *trans*-III isomer of the Cu complex (peak potential at −1.05 V vs $\mathrm{Fc}^{+/0}$ in acetonitrile) is irreversible with rapid conversion to the *trans*-I form (reversible reduction at −1.15 V). The greater ease of reduction of the *trans*-III complex may be a result of the weaker interaction with the pyridine donor (Cu—N(py) distance 2.250 Å) compared to that of the *trans*-I form (Cu—N(py) distance 2.220 Å) The nickel complexes slowly interconvert in aqueous solution but also show interesting redox behavior, with interconversion of isomers occurring rapidly under both oxidative and reductive conditions in acetonitrile and under oxidative conditions in aqueous solution. The pH of the aqueous experiments was not controlled so it is not possible to exclude proton dissociation from N—H as a contributing process. However, in this context it is important to note that Billo has reported a pH independent conversion of the *trans*-I Ni–cyclam complex to the *trans*-III form after oxidation to the +3 oxidation state [117].

Wieghardt and co-workers have done a comparative investigation of a series of iron complexes of **27-H** and its unmethylated analog **cyclamacetate** starting with the Fe(III) forms, which are prepared by reaction of Fe(III) reagents with the free ligands. Both ligands yield six-coordinate complexes with a *trans*-III macrocycle stereochemistry shown schematically in Scheme 4 [217–219]. This appears to be the only example of a stereochemistry other than *trans*-I for a complex of **27-H** although previous examples were all prepared indirectly by hydrolysis of a carboxylate ester as Wieghardt reported the first synthesis of **27** (by Eschweiler–Clarke methylation of **cyclamacetate**) [218]. No explicit information concerning the formation of other diastereoisomers as precursors is available, although the description of the progress of the reaction



Scheme 4.



I R^1, R^4 functionalized; R^8, R^{11} non-functionalized
II R^1, R^{11} functionalized; R^4, R^8 non-functionalized
III R^1, R^8 functionalized; R^4, R^{11} non-functionalized

Scheme 5.

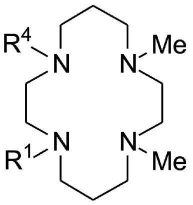
states that combination of **27**.4HCl with $FeCl_4^-$ in water in the presence of 4 equiv of Et_3N "...results in immediate complexation of the iron, yielding a brown solution, which slowly becomes red upon heating" [219]. One might speculate that changes in stereochemistry accompany the change in color. Wieghardt reports that photolysis of [Fe^{III}(**27-H**)N_3]$^+$ yields high-spin [Fe^{II}(**27-H**)($NCCH_3$)]$^+$, presumably with the *trans*-III stereochemistry [220]. Direct interaction of the ligand with Fe(II) should give the *trans*-I stereoisomer based on the established chemistry with divalent 3d ions and other monofunctionalized N-tetraalkylated ligands. If so, it would be most interesting to examine the stereochemical and redox behavior of the Fe(II) complex to determine whether the same type of electrochemically stimulated interconversions occur with iron.

Magnetic studies indicate that the **cyclamacetate** complexes have $S = 1/2$ ground states but the fluoro complex exhibits spin crossover behavior above 250 K. The **27-H** complexes have magnetic moments consistent with $S = 5/2$ spin states at room temperature, but the N_3^- complex converts to a 60:40 mixture of 5/2 and 1/2 spin states at 80 K. Structural studies of the four complexes indicate that Fe–donor distances are generally longer in the low-spin complexes than in the high-spin complexes as expected given the occupancy of sigma-antibonding metal centered orbitals in the latter. The greatest differences are for the Fe—N distances, which are about 0.14 Å longer for the tertiary amines than for the secondary amines. Comparative DFT calculations on the fluoro complexes, which correctly predict the difference in spin state and most structural parameters, suggest that a portion of this difference is likely due to steric interactions between the N-methyl hydrogen atoms and the axial fluorine donor and with other non-bonded hydrogen atoms. These calculations also indicate that the N-methyl groups are electron withdrawing, not electron donating, and suggest that the longer bonds in the complex of the methylated complex could also have an electronic contribution [219].

Electrochemical studies on the azido complexes show the same trend observed for complexes of TMC, namely that oxidation is more difficult and reduction is easier for the complex of the N-tetraalkylated ligand; potentials (vs $Fc^{+/0}$)for $Fe^{4+/3+/2+}$ are 1.14 V and −0.36 V for **27-H** and 0.99 V (irrev) and −0.75 V for **cyclamacetate**, respectively. The effect of N-alkylation on the kinetic stability of higher oxidation states and the thermodynamic stability of lower oxidation states of Ni(II) and Cu(II) complexes is well established, *vide supra*. The stability of [Fe^{IV}(**27-H**)N_3]$^{2+}$ is sufficient that solutions prepared by electrolysis and frozen can be photolyzed to induce loss of molecular nitrogen in a formal oxidative process that produces only the second known Fe(VI) complex [Fe^{VI}(**27-H**)(N)]$^{2+}$ [220]. Photooxidation of [Fe^{III}(**cyclamacetate**)N_3]$^+$ yielded [Fe^{V}(**cyclamacetate**)(N)]$^+$ [217] but [Fe^{III}(**27-H**)N_3]$^+$ was photoreduced to [Fe^{II}(**27-H**)($NCCH_3$)]$^+$ under the same conditions.

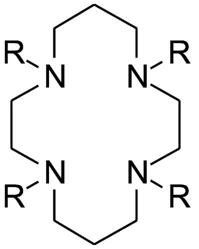
7.2. Two functionalized substituents

Introduction of the second functionalized group can occur at the 4, 8 or 11 positions to produce three structural isomers as shown in Scheme 5. Examples of type **I** were prepared early on by alkylation of the secondary amines in 1,4-dimethylcyclam. Kaden prepared **42** by cyanomethylation found that while the cyano groups did not coordinate in its Cu(II) complex, one cyano group was hydrolyzed at higher pH. The resulting carbamoylmethyl group then coordinated to the copper ion, by the carbonyl oxygen at intermediate pH values and by the deprotonated amide nitrogen at higher pH, which blocked hydrolysis of the second cyano group. In a subsequent expansion of this work the metal promoted hydrolysis of one cyano group was used as a synthetic route to unsymmetrically substituted ligands **43,** and by catalytic reduction of the cyano group **44** [200]. Copper(II) forms five-coordinate complexes with **44**. Two forms of the complex were isolated by crystallization at pH 5 and pH 9 and were structurally characterized. Both have the *trans*-I macrocycle stereochemistry. In the low pH form the amino group is protonated and the carbonyl oxygen is coordinated, whereas in the high pH form the amino group is coordinated and the carbamoylmethyl substituent is pointing away from the metal. The pH dependent spectral behavior observed for [Cu(**44**)]$^{2+}$ in water is consistent with varying amounts of these two structural isomers.



42 R=CH_2CN
43 R^1=$CH_2C(O)NH_2$, R^4=CH_2CN
44 R^1=$CH_2C(O)NH_2$, R^4=$CH_2CH_2NH_2$
45 R=$CH_2CH_2C(O)NH_2$
46 R=CH_2CH_2SMe
47 R=CH_2CH_2OMe
48 R=$CH_2C(O)OH$
49 R=$CH_2CH_2NH_2$
50 R=$CH_2CH_2CH_2NH_2$
51 R=CH_2CH_2OH

Another early example of a type I ligand **45** was studied by Freeman who found that two forms of its nickel(II) complex could be isolated [54].



52 R=$CH_2CH_2C(O)NH_2$
53 R=CH_2CO_2H

A green product whose absorption spectrum was consistent with a high-spin, five-coordinate similar to those formed with other functionalized ligands, was prepared by reaction of the ligand with nickel perchlorate in methanol. Heating this green product in aqueous solution for extended periods resulted in partial conversion to a blue product whose absorption spectrum was essentially identical to the structurally characterized *trans*-III isomer of tetra-functionalized ligand **52**. Based upon these observations *trans*-I and *trans*-III structures were proposed for the green and blue forms of the nickel complex of **45** (**A** and **B** in Fig. 7).

It both surprising and noteworthy that the structure of the complex of **52** (Fig. 7) has the 1,4-carbamoylethyl groups coordinated rather than those in the 1,8-positions, which has been observed for the tetracarboxymethyl analog **53-2H** in its Cu(II) [221,222] and Zn(II) [223] complexes [224].

Ligand **46**, prepared by Kaden and co-workers [225], forms five coordinate, *trans*-I complexes with both Ni(II) and Cu(II) with one of the thiomethoxy groups coordinated, confirmed by X-ray crystallography. The Cu(II) complex of the analogous tetraalkylated ligand has an identical coordination environment and very

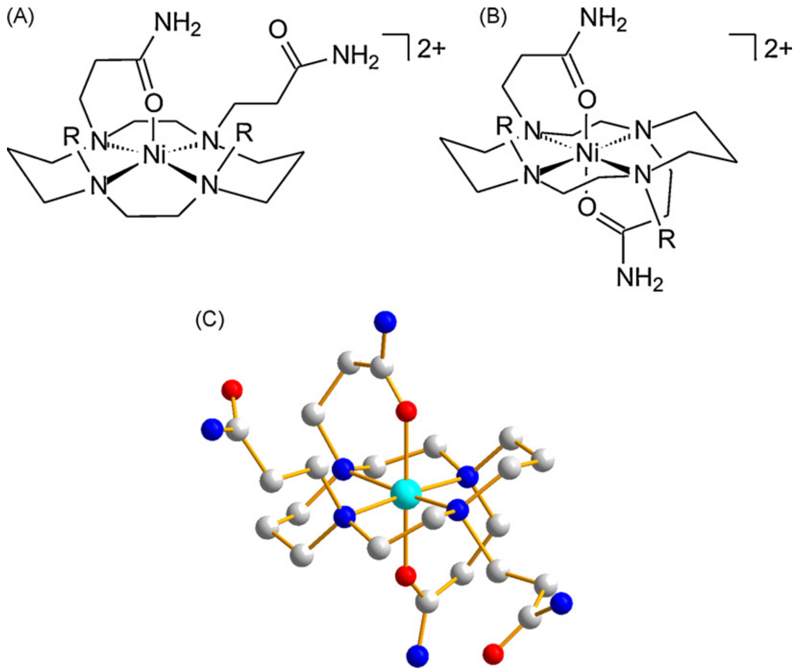
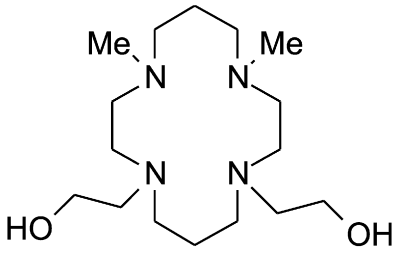


Fig. 7. Proposed *trans*-I (**A**) and *trans*-III (**B**) structures for the two forms of the nickel(II) complexes of ligands **45** (R = Me) and **52** (R = $CH_2CH_2C(O)NH_2$). The *trans*-III structure confirmed for [Ni(**52**)]$(ClO_4)_2$ (**C**) by X-ray crystallography (structure drawn with data from reference [54]).

similar metric parameters. The X-ray structure of [Ni(**47**)]$(ClO_4)_2$, however, shows the cation to be four-coordinate with the *trans*-I ligand stereochemistry. Electrochemical studies on the Ni(II) complex of **46** (acetonitrile, HMDE, SCE) indicate that it undergoes reversible reduction to a Ni(I) species at −0.76 V; the same value was observed for the nickel(II) complex of the corresponding mono-functionalized analog, **38**.

Subsequently Kaden investigated ligands **48**–**50** with the carboxymethyl ligand showing very different behavior from the aminoalkyl ligands. Ligand **48-2H** forms complexes with both Ni(II) and Cu(II) whose spectra are consistent with six-coordinate structures. The similarity of the spectrum of the copper complex to that of the analogous 1,8-derivative, *vide infra*, whose structure has been established by crystallography [73], suggests that these compounds probably have a *trans*-III stereochemistry as it seems unlikely that six-coordination could be achieved in any other way. However, both **49** and **50** produced Ni(II) and Cu(II) complexes whose spectra were consistent with five-coordination as prepared, but exhibited pH dependent spectral behavior. Investigations of the Cu(II) complexes showed that two protons were consumed, the first at pH values suggesting protonation of a free amine, but the second at much lower values. Concomitant with the second protonation was a conversion of the absorption spectrum from that of a five-coordinate complex to one resembling a four-coordinate complex. The conclusion was that the complexes had the *trans*-I ligand stereochemistry, which puts both aminoalkyl groups on the same side of the coordination plane such that only one is coordinated. Under the conditions studied neither the *trans*-III or *cis*-V stereochemistries were apparently accessible although either would have allowed coordination of both amino groups.

Wainwright and co-workers [208] prepared the nickel(II) complex of ligand **51** and concluded on the basis of a combined X-ray and molecular mechanics analysis (crystals were severely disordered) that the complex was six-coordinate with a *trans*-III ligand stereochemistry and coordination of the hydroxyl groups. As part of this study Wainwright also prepared the nickel(II) complex of the analogous type **II** difunctionalized ligand **54**, apparently the only example of a ligand of this type, although there are a number of potential routes to the synthesis of such ligands using existing 1,11-derivatives of cyclam [63,226–230]. Crystals of this complex were also disordered, but a similar combined X-ray/molecular mechanics method indicated that the complex was also six-coordinate with *trans*-coordination of the hydroxyl groups, which requires that the ligand have the *trans*-II stereochemistry. As far as I am aware the type **III** analog of this ligand has not been prepared; however, the tetrahydroxyethyl analog is well known and the X-ray structure of its nickel(II) shows the ligand to have the *trans*-III structure with coordination of 1,8-hydroxyl groups, one of which is deprotonated [231]. The presence of two or more hydroxyethyl groups facilitates much more rapid rates of complexation of metal ions than is observed for cyclam or its unfunctionalized tetra-N-alkylated forms, but one hydroxyethyl group does not enhance complexation rates [206], *vide supra*.



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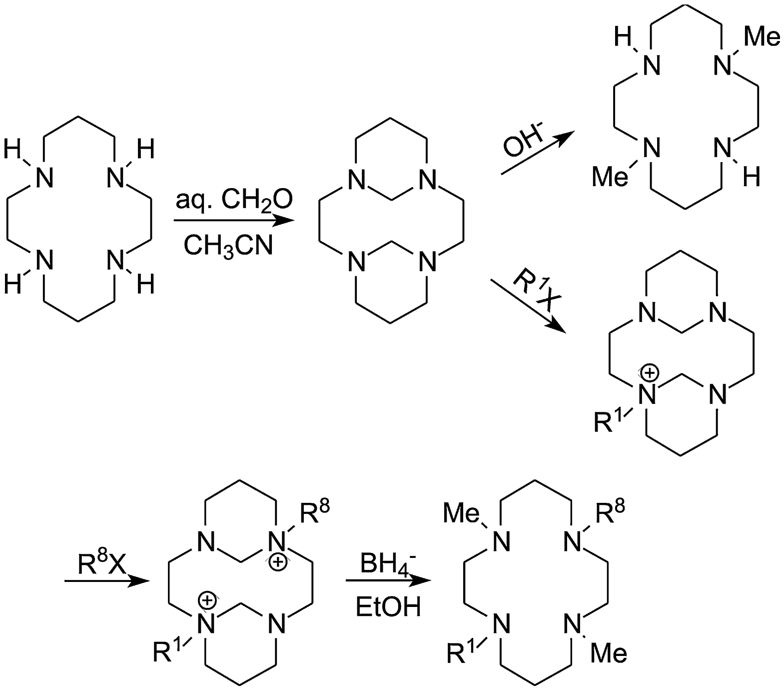
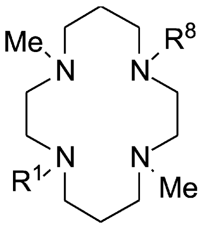
There are more examples of 1,8-difunctionalized derivatives because they can be made from the diaminal of cyclam according to Scheme 6 [232–234]. Alkylation of the diaminal or of 1,8-dimethylcyclam leads to ligands of type **III**.

Kaden also pioneered in the development of type **III** ligands as a follow-on to his work with those of type **I**. Most of the synthetic methods used to prepare **55**–**61** are the same as those used for their type **I** analogs using 1,8-dimethylcyclam as the starting material. In general the observations made for the copper(II) and/or nickel(II) complexes of their type **I** analogs also apply to the complexes of **55**–**61** [200,235]. Of these ligands only **61** appears to give a six-coordinate complexes. To the extent they have been investi-



Scheme 6.

gated, all of the others appear to bind nickel(II) and copper(II) to give five-coordinate complexes, which most likely have the *trans*-I stereochemistry. This was confirmed for the Cu(II) complex of **56**, which was prepared by hydrolysis of one of the cyano groups in [Cu(**55**)]$^{2+}$ [200].



55 R=CH_2CN
56 R^1=$CH_2C(O)NH_2$, R^8=CH_2CN
57 R=$CH_2C(O)NH_2$
58 R=$CH_2CH_2NH_2$
59 R=CH_2CH_2CN
60 R=$CH_2CH_2CH_2NH_2$
61 R=CH_2CO_2H
62 R=$CH_2P(O)(OH)_2$
63 R=CH_2-(2-pyridinyl-6-CH_2OH)
64 R=$CH_2C(O)NMe_2$
65 R=CH_2-(2-pyridinyl)
66 R=CH_2-ferrocenyl
67 R^1=$CH_2C(O)NMe_2$, R^8= CH_2-(2-pyridinyl)

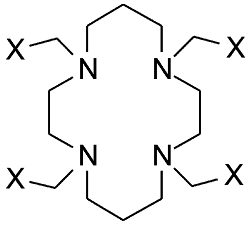
Chapman isolated the copper(II) complex of **61,** which crystallized over 48 h after combination of copper perchlorate with the protonated ligand in water and adjusting the pH to 3. The X-ray structure of [Cu(**61**)](ClO_4)$_2$·$2H_2O$ shows the copper to be six-coordinate with protonated carboxyl groups coordinated in the axial positions and the macrocycle having the *trans*-III stereochemistry [73]. In contrast, the copper(II) complex isolated with diphosphonic acid **62** [236] has the *trans*-I ligand stereochemistry with one of the phosphonic acid groups coordinated to give a five-coordinate species. The sample used for the structural analysis contained two different copper species; one was a neutral species in which both the coordinated and uncoordinated phosphonic acid groups were mono-deprotonated whereas only the coordinated group was deprotonated in the second form.

Bradshaw and co-workers [237] prepared and structurally characterized the Ni(II) complex of ligand **63**, where the ligand has the *trans*-I stereochemistry, but the nickel ion is six-coordinate with one of the pyridines and its hydroxymethyl group coordinated. This is a rare arrangement, but suggests that ligands could be designed with a single nitrogen substituent that can function as a bidentate ligand, which might routinely provide for a six-coordinate environment for the metal ion.

Five-coordinate and six-coordinate complexes of the copper(II) complexes of **64** [126,238] having the *trans*-I and *trans*-III ligand stereochemistries (X-ray structures), respectively, were prepared in the same fashion as for the monofunctionalized analog **36**. The electrochemical behavior of these compounds was also similar to that those of **36** with the reduced forms interconverting, but the rate of conversion of the *trans*-III form of [Cu(**64**)]$^+$ to *trans*-I was even more rapid. Likewise, two forms of the copper(II) complex were isolated for **65** using the same preparative methods as for **64** [126]. Reference is made to a crystal structure confirming a *trans*-III, six-coordinate structure for the compound prepared under strongly basic conditions with maintenance of six-coordination in acetonitrile confirmed by absorption spectroscopy. The properties of the other isomer are consistent with the *trans*-I stereochemistry. Again electrochemical studies show that reduction results in interconversion of the diastereoisomers with much more rapid conversion of the *trans*-III isomer to *trans*-I than the reverse.

Both copper(I) and copper(II) complexes of ligand **66** have been isolated and structurally characterized with the former being very stable in air [239]. The copper (I) complex has the *trans*-V stereochemistry and with a significant tetrahedral distortion of the four nitrogen donors. The copper(II) complex was isolated as a five-coordinate, acetonitrile complex with a *trans*-I stereochemistry. Both complexes exhibit reversible reductions at $3\,\mathrm{V\,s^{-1}}$ at room temperature (and at slower scan rates at lower temperatures) with $E_{1/2} = -0.56\,\mathrm{V}$ for the *trans*-I redox couple and $-0.24\,\mathrm{V}$ for the *trans*-V couple, but at lower scan rates both exhibit irreversible electrochemical behavior with interconversion between the two forms. The half-lives of the *trans*-I Cu(I) species and the *trans*-V Cu(II) species were estimated to be $0.35\,\mathrm{s^{-1}}$ and $6.30\,\mathrm{s^{-1}}$, respectively. Surprisingly, an electrochemically stimulated interconversion between two forms also occurred in the solid state.

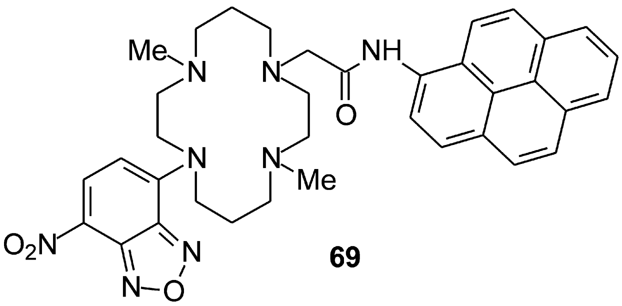
Copper(II) and nickel(II) complexes of **68** have also been prepared and structurally characterized [240]. Combination of **68** with copper acetate in methanol yielded a complex, isolated as the perchlorate salt, whose crystal structure shows it to have the *trans*-III stereochemistry for the ligand. With nickel(II) acetate a five-coordinate complex with the *trans*-I ligand stereochemistry and coordinated acetonitrile was isolated upon recrystallization from acetonitrile. In a separate investigation [241], both Cu(II) and Cu(I) complexes of **68** were prepared and undergo electrochemically induced chemical processes similar to those for the copper complexes of **66**. The two forms of [Cu(**68**)]$^{+}$ are in equilibrium in acetonitrile. The electronic spectrum for [Cu(**68**)]$^{2+}$ complex, prepared by combination of $\mathrm{Cu(ClO_4)_2{\cdot}6H_2O}$ and the ligand in methanol, compared favorably with that for the complex of **66** suggesting that it is most likely five-coordinate, which would be consistent with what is expected for a *trans*-I ligand stereochemistry. If true, then it appears that both *trans*-III and *trans*-I isomers of [Cu(**68**)]$^{2+}$ exist. Whether a third stereoisomer also exists cannot be determined on the basis of the information available.



68 (X=ferrocenyl)

The complex [Cu(**67**)]$\mathrm{(ClO_4)_2}$ [233,242] is five-coordinate with the *trans*-I ligand stereochemistry and the oxygen of the dimethylcarbamoyl group bonded to the copper ion rather than the pyridinyl group. In nitromethane the absorption spectrum is very similar to that for the *trans*-I copper complex of **64**, which has one dimethylcarbamoyl group coordinated, and the EPR of the frozen nitromethane solution exhibits no nitrogen superhyperfine coupling, which suggests that the structure observed in the solid state persists in solution.

Chang and co-workers have recently synthesized a series of ligands such as **69**–**71** for use as fluorophores for metal ion detection, including Cu(II). No complexes have been isolated, so it is not clear how these ligands bind to metal ions, but it would be very interesting to see how the size of the large dipyrenyl substituents affect the stereochemistry of complexation, the ability of the amide group to coordinate, and whether interconversion of diastereoisomers via Cu(I) forms is possible [243–245].



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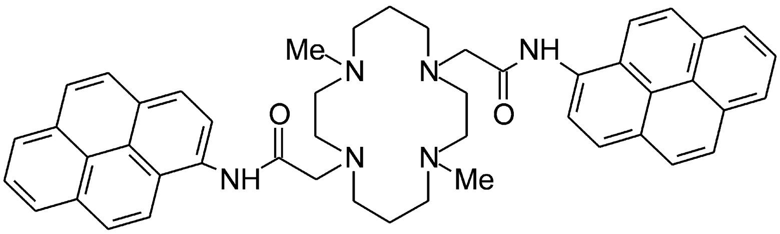

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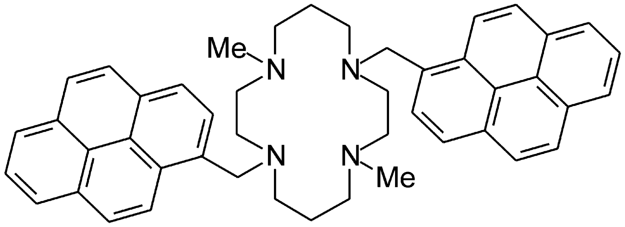

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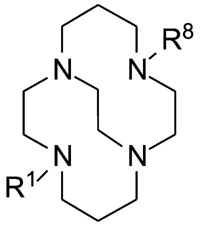
Finally, there are numerous examples of difunctionalized ligands based upon **72** where R^1 and R^8 are functionalized substituents.



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These ligands can be expected to generally form six-coordinate complexes with the macrocycle having the *cis*-V stereochemistry. Because these ligands necessarily have a fixed set of nitrogen configurations their complexes will not be discussed here. However, they are of considerable current interest for binding ^{64}Cu in radiopharmaceutical applications [108,246–248].

8. Concluding remarks on the stereochemistry of metal complexation reactions

The last few sections were intended to focus attention on the complexity of the stereochemical outcomes of reactions of N-tetraalkylated cyclam ligands with transition metal ions. For ligands with unfunctionalized N-alkyl substituents it seems pretty safe to conclude that complexation of a solvated divalent 3d metal will generally result in a complex with the *trans*-I stereochemistry, probably by a pathway that involves an intermediate with *trans*-II stereochemistry. What prevents conversion of the *trans*-II form to the *trans*-III under these conditions is not obvious. A change in donor configuration requires four steps: (1) M—N bond cleavage, (2) nitrogen inversion, (3) C—N bond rotation to bring the nitrogen electron pair back into position, and (4) M—N bond (re)formation. Steps 2 and 3 could be in reverse order, or, more likely, occur in parallel and there may be a requirement for participation of an additional donor during the process. Once formed *trans*-I complexes are not easily converted to *trans*-III although Moore's results with $[Ni(TMC)]^{2+}$ show that such interconversions can be achieved under forcing conditions, at least for nickel(II). How the complexation process is redirected under basic conditions, i.e., Cu(II) or for monovalent metal ions is a fascinating question. In the latter case weaker bonds make bond dissociation easier and tetrahedral species energetically less unfavorable. Both of these most likely play a role. At this point there is enough information available to be able to prepare multiple diastereoisomeric forms of nickel and copper complexes in a systematic fashion. Whether some of the techniques that work for these metals can be adapted to other 3d metals remains to be seen.

It is fair to say that the role of functionalized N-alkyl groups on the stereochemistry of complexation of 3d metals is not yet known. The likelihood of obtaining a *trans*-I complex from the reaction of a monofunctionalized ligand and a solvated metal ion under "normal" preparative conditions is high. Few of these complexes have so far been demonstrated to thermally isomerize. A notable exception is the formation of the *trans*-III diastereoisomer of Fe^{III} with **27-H**. This is the only complex of this ligand prepared from preformed ligand; other examples were generated by hydrolysis of nitrile or carboxylic acid esters in preformed metal complexes. Addition of a second functional group does not greatly diminish the likelihood of initial formation of a *trans*-I complex with most functional groups, with the exception of carboxylate and hydroxyl groups, where *trans*-III complexes were generated directly. (The 1,11-dihydroxyethylcyclam generated the *trans*-II isomer, which is the only way that the hydroxyl groups can coordinate to axial positions.) But the second functional group may promote thermal isomerization processes. The same techniques that allowed for preparation of *trans*-I and *trans*-III isomers of copper–TMC complexes also work for mono- and difunctionalized ligands.

About the only thing that can be said with certainty with regard to stereochemistry and 4d and 5d metals is that it is complicated and much remains to be done in this area. There appears to be some parallel between the chemistry of silver and copper, but otherwise patterns of behavior are not obvious. Given that metal–donor bonds should be stronger with the heavier metals one would expect isomerization reactions to be less likely than for the 3d metals. Assuming that this is the case then the conformational space available to the ligand during complexation must be greater than previously expected because a much wider range of donor stereochemistries is observed in complexes of the heavier metals. How ancillary ligands impact the stereochemistry of complexation, including functionalized N-alkyl substituents, has received little consideration up to this point.

Acknowledgements

My initial exposure to macrocyclic ligands and their metal chemistry came from my association with Professor Daryle Busch as a graduate student at The Ohio State University, a time that I remember fondly. I would like to sincerely thank my former students and other co-workers for their hard work and intellectual input into our studies on N-tetraalkylated cyclam ligands and their metal complexes.

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