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DISSERTATION

SYNTHESIS AND APPLICATION OF DIOXOCYCLAMS

Submitted by
Thomas Andrew Wynn
Department of Chemistry

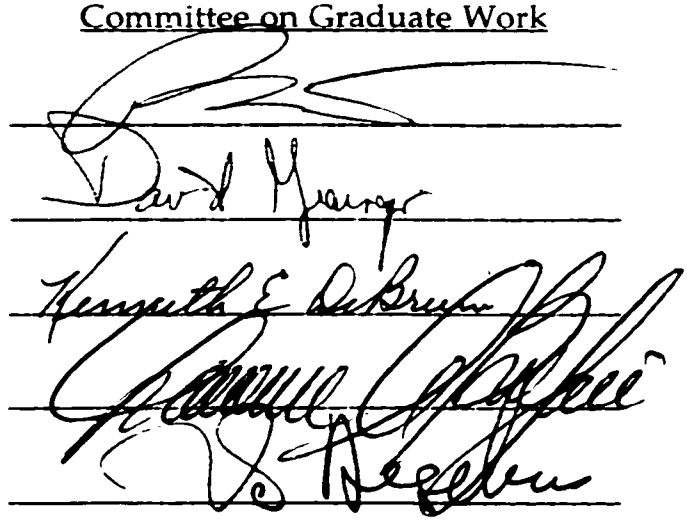
In partial fulfillment of the requirements
for the Degree of Doctor of Philosophy
Colorado State University
Fort Collins, Colorado
Spring 2000

COLORADO STATE UNIVERSITY

December 2, 1999

WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY THOMAS ANDREW WYNN ENTITLED SYNTHESIS AND APPLICATION OF DIOXOCYCLAMS BE ACCEPTED AS FULFILLING IN PART THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work



Adviser

Department Head

ABSTRACT OF DISSERTATION
SYNTHESIS AND APPLICATION
OF DIOXOCYCLAMS

A new class of highly functionalized, penta-coordinate capped dioxocyclams was developed by the alkylation of two secondary amines on the dioxocyclam ring with an aromatic bis-electrophile. An in depth analysis of the complex stereochemistry of the capped dioxocyclams was performed. A new class of bis-dioxocyclams was also developed in which the two dioxocyclam rings were linked by an aromatic bridge. The stereochemistry of the bridged bis-dioxocyclams was analyzed, and it was discovered that from achiral materials a total of 6 different stereoisomers could be produced, of which only two were observed. The different stereoisomers showed substantially different shapes along with different orientations of the two linked dioxocyclam rings.

A copper(II) complex of a capped dioxocyclam was synthesized and the X-ray crystal structures of two different forms of the copper complex were solved. The crystal structures revealed that the differences were due to changes in conformation of the dioxocyclam ligand which changed the coordination geometry around the copper center.

Copper(II) complexes of alkoxy-linked bis-dioxocyclams were used as agents for the hydrolysis of activated phosphate diesters. The different bis-dioxocyclam complexes positioned the two copper centers at different distances and a small correlation between copper-copper distance and rate enhancement

of hydrolysis was seen. Several new alkoxy linked bis-dioxocyclams were synthesized for use as phosphate diester hydrolysis agents.

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CHAPTER ONE

RATIONALE FOR RESEARCH PERFORMED

Two major projects were addressed in the course of this research, both relating to the synthesis and applications of dioxocyclams. Dioxocyclams are macrocyclic ligands capable of coordinating transition metals. Changing the ligands that surround the metal changes the environment around a metal center, and can change the properties of the metal. Changing the properties of the metal can then change the reactivity of the metal, which can lead to novel transformations of molecules in the coordination sphere of the metal. The first project, which is outlined in the third chapter of this document, presents the synthesis of two new classes of dioxocyclam ligands. These new classes of dioxocyclams add several desirable modifications to the core dioxocyclam macrocyclic ligand.

The first of the new classes of dioxocyclams adds that contains a fifth donor atom a group to the macrocycle. Addition of further donor atoms to a ligand can change the denticity of the ligand, which can change the coordination properties of the ligand. The first class of ligands synthesized, capped dioxocyclams, provide a coordination environment which places the metal in a well defined deep pocket in which only one coordination site is left open. With only one coordination site free there is only one approach to the metal center. This approach can be affected by groups attached to the ligand, a factor of importance with optically active complexes in which only one chiral environment

is presented to molecules approaching the metal center. The capping group can be a ligand that allows external communication with the metal center. External communication to complexed metal centers is of interest because the properties of the metal can be changed without direct contact to the metal. The new ligands are also much more rigid than the original dioxocyclams because of the group that is attached to the dioxocyclam ring.

The second new class of dioxocyclams includes many properties of the first class, while joining two dioxocyclam rings in a novel manner. This new way to link two dioxocyclams places the two ligands in very close proximity with a aromatic system separating the two rings. The close proximity and aromatic bridge between the two rings increase the chances of communication between two coordinated metal centers. The communication between the two metal centers can then affect the properties and reactivity of the metal centers. The capped and bridged dioxocyclam ligands that are presented in Chapter 3 possess many of the properties discussed above, and the synthesis and analysis of a copper(II) complex of a capped dioxocyclam is also presented.

The second project, outlined in the fourth chapter, develops bi-metallic complexes to be used as phosphate diester hydrolysis agents. Phosphate diesters comprise the backbone that links the base pairs in DNA. Phosphate diesters are very resistant to uncatalyzed hydrolysis, but nature has developed metalloenzymes that hydrolyze phosphate diesters in seconds. Metal complexes that can effect the hydrolysis of phosphate diesters can be used in the study of how nature hydrolyses DNA. There are several properties that are desired of the bi-metallic complexes to be used as hydrolysis agents which went into the design of the second project.

First, the ligands need to be able to complex to two metal centers simultaneously. These two metal centers can then cooperate to activate the

phosphate diester toward hydrolysis. Next, the distance between the two metal centers needs to be variable to test how metal-metal distance affects the rate of hydrolysis. To gain insight into how orientation of the metals affects the rate of hydrolysis, the orientation of the two metal centers in the complex needs to be controlled. Finally, the complexes must be soluble in the solvent system in which the hydrolysis experiments are run.

Several bis-copper(II) complexes were synthesized that had these desired properties and these were studied as phosphate diester hydrolysis agents. The rate enhancement of the hydrolysis by these bis-copper complexes is presented in Chapter 4. Also presented in Chapter 4 are the syntheses of several new bis-dioxocyclam ligands that can be used in further hydrolysis studies.

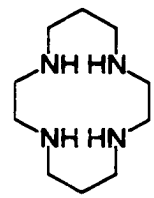
These two projects represent a significant extension of the applications of dioxocyclams. First, two new classes of dioxocyclams were developed, and metal complexes of these new ligands were studies. Second, the novel molecular architectures of dioxocyclam metal complexes was applied to the study of phosphate diester hydrolysis.

CHAPTER TWO

TETRAAZAMACROCYCLES: SYNTHESIS, STRUCTURES AND APPLICATIONS

2.A. INTRODUCTION

The recent interest in a subclass of 14-membered tetraazamacrocycles called cyclams (tetraazacyclotetradecanes) stems of their ability to complex to most transition metals.[1] The metals are mainly divalent, but cyclams also stabilize higher, less stable oxidation states of certain metals (e.g. copper(III), nickel(III)). Cyclams have also shown biological activity, with certain linked cyclams showing high activity towards HIV-1,2.[2]



The cyclam scaffold is also an attractive ligand because of the ease of synthesis of many analogs of the basic tetraazamacrocyclic core. Substitution on the carbon backbone or on the nitrogens of the macrocycle can introduce additional ligands for metal chelation, which can alter the stability of many metal complexes. Substituents on both carbon and nitrogen can affect the conformation of the ring, which can in turn affect the properties of metals coordinated by the cyclams.

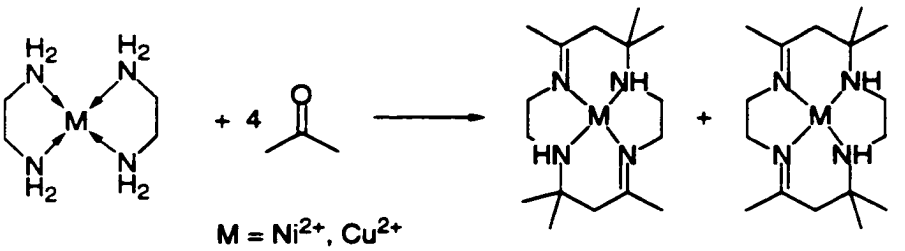
2.B. SYNTHESIS OF TETRAAZAMACROCYCLES.

Several different methods for the synthesis of tetraazamacrocycles have been developed. Generally, the synthetic methods involve the condensation of diamines with bis-electrophiles. This is, however, the classic method for the synthesis of linear polymers, and a major issue is the competition of cyclization of the polyamine with linear polymerization. For the synthesis of macrocycles two major methods to suppress linear polymerization have been developed: template assisted macrocyclization and direct condensation.

2.B.1. Template synthesis

One way to promote macrocyclization over linear oligmerization is to use a metal to either preorganize the reactants (kinetic) or complex the macrocyclic product (thermodynamic), removing it from the reaction equilibrium. As is often the case, the product distribution depends upon whether kinetic or thermodynamic effects predominate. In most cases the metal ions of choice for macrocyclization of tetraazamacrocycles are nickel(II) or copper(II). These ions form stable square planar amine complexes, favoring macrocyclization. Several different synthetic routes for the synthesis of macrocyclic tetraamines via transition metal templates have been reported.[3-9]

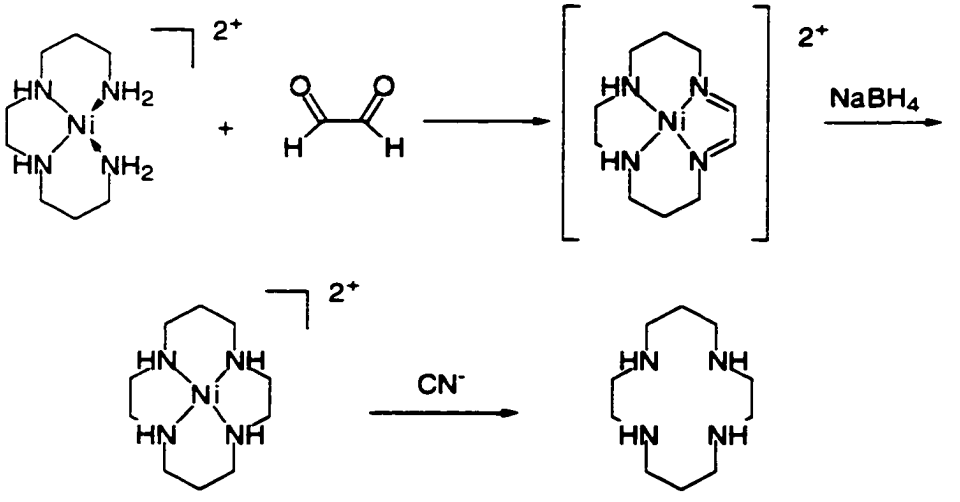
One of the first examples of a useful synthesis of a cyclam was reported by Curtis[3] in 1962 (Equation 2.1). This synthesis takes advantage of the kinetic



(2.1)

template effect in which coordination of the primary amines to the metal center predisposes the condensation reaction toward cyclization, limiting the amount of polymer produced. In the absence of the template ion, the reaction does not produce the macrocycle. When different 1,2 diamines or methyl ketones are used, many different analogs of this bisimine-cyclam can be produced.[1a] A limitation of this synthesis is that often the free imine cyclam is not stable to the reaction conditions used to remove the copper(II) or nickel(II), thus other metal centers cannot be introduced with this method.

Barefield developed an alternate metal template synthesis of a unsubstituted cyclams (Equation **2.2**).[4] This synthesis produced the cyclam in high yield and, once the imine intermediate was fully reduced to the saturated cyclam, the metal template could be easily removed by excess cyanide without the destruction of the macrocycle. Once the nickel(II) template was removed, a range of other metals could be introduced.



(2.2)

Another metal template synthesis of a tetraazamacrocycle was developed by Comba (Figure **2.1**).[5] This cyclization is thought to proceed by attack of the

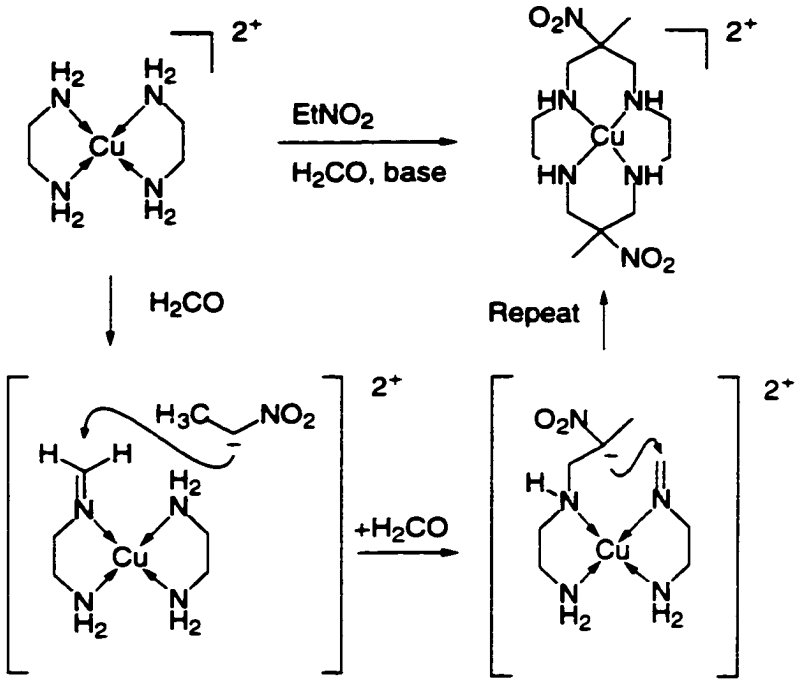
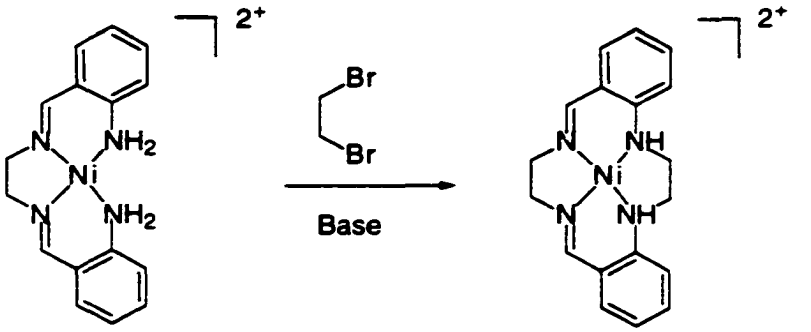


Figure 2.1 Comba's template assisted synthesis

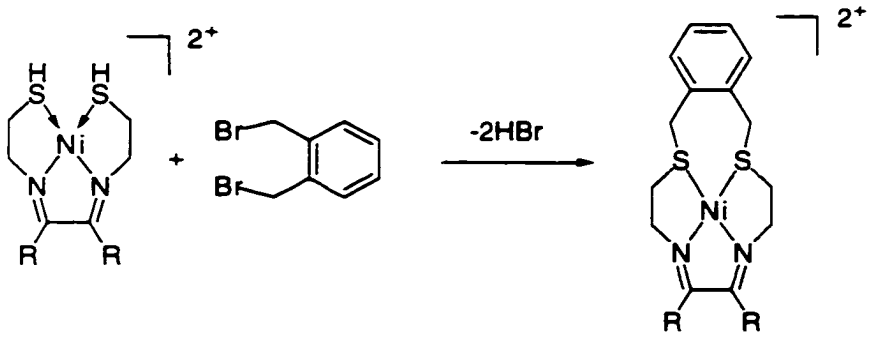
nitroethane anion on the imine formed from condensation of formaldehyde and the coordinated amine. Once again, the copper center could be removed from this cyclam freeing the ligand for coordination to other transition metals.

A third cyclization method directly alkylates the coordinated amines instead of forming the Schiff bases. This method has, however, seen limited success because of the low nucleophilicity of the coordinated amines. Deprotonation of the coordinated amines prior to addition of the electrophile facilitates this process (Equation **2.3**).[6] The aromatic groups, which increase the



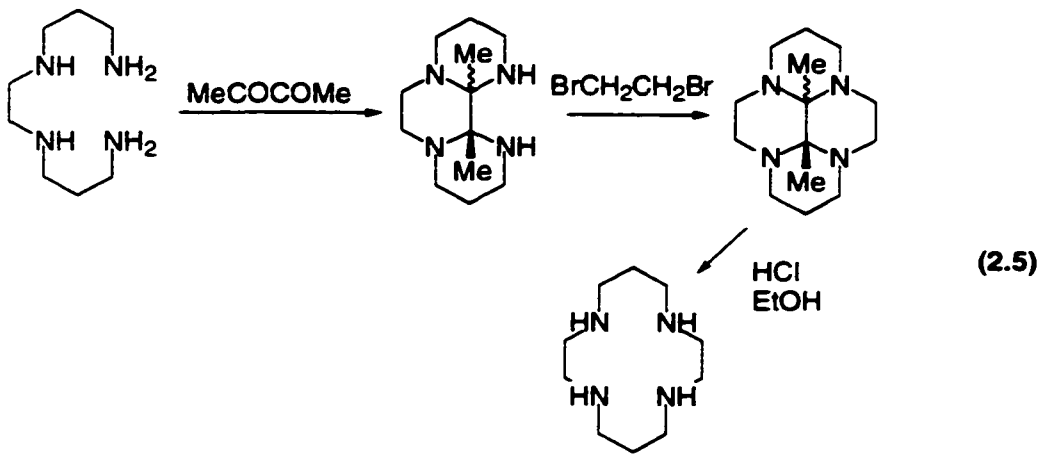
(2.3)

acidity of the coordinated amines, are necessary for this reaction to proceed. The coordinated nitrogens must be deprotonated because the lone pairs of the nitrogens are coordinated to the metal center and unavailable to attack an electrophile. If sulfur is substituted for two of the coordinated nitrogens, direct alkylation of the heteroatom can be accomplished without prior deprotonation (Equation **2.4**).[7]



(2.4)

A method analogous to the metal template synthesis utilized a carbon chain to preorganize a linear tetraamine (Equation **2.5**).[8] This brought the two nitrogens that were to be alkylated closer together in a rigid tricyclic system while leaving the nitrogen lone pairs free to attack the incoming electrophile.



(2.5)

A limitation of this synthesis was the harsh conditions needed to hydrolyze the bis aminals to free the cyclam. This synthesis was previously attempted using glyoxal as the template but the resulting tetracyclic bis-aminals proved very resistant to hydrolysis.[9]

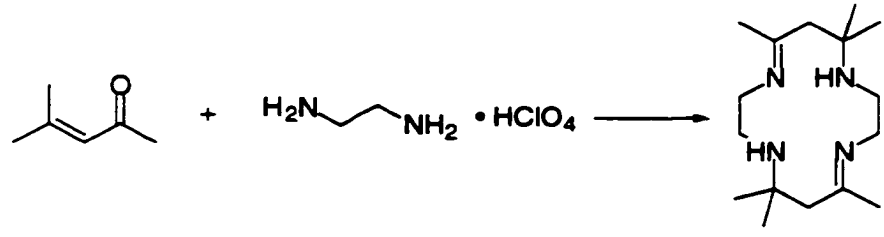
2.B.2. Direct Condensation

Other syntheses that negate the need for the metal templates, eliminating the decomplexation step in the production of the free tetraazamacrocyclic ligand, have been developed. Classic methods for macrocyclization involve high dilution conditions, and most of the direct condensations are run at higher dilutions than the template reactions. However, most of the following methods attempt to keep the reaction conditions as concentrated as possible to facilitate scale up of the cyclization reactions.

The first reported synthesis of a tetraazacyclotetradecane came in 1937 by Van Alphen[10] from the reaction of 1,3-dibromopropane and 1,2-ethylenediamine. Van Alphen isolated many polymeric products from this reaction and a small amount of what he described as a cyclam. No yield was

reported for the reaction and the product was also characterized by the methods of the day, derivatization and elemental analysis. Twenty five years later, the structure was unequivocally proven by Stetter and Meyer[11] following a lengthy synthesis.

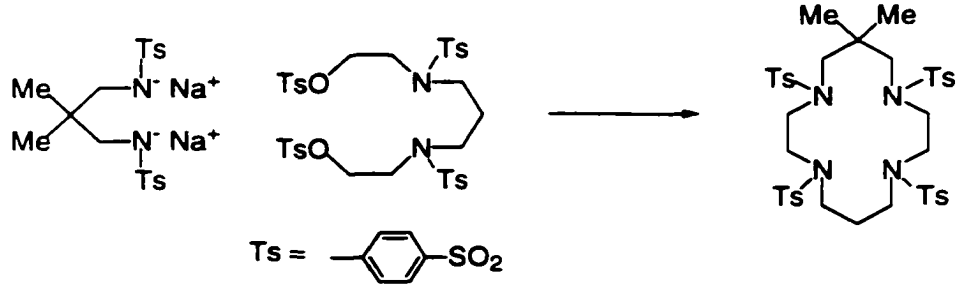
Curtis reported a second, more efficient, metal free method for the production of bisimine-cyclams using mesityl oxide and a diamine hydroperchlorate salt (Equation 2.6).[12] The insolubility of the perchlorate salt of the bisimine cyclam in the reaction solvent was thought to inhibit oligmerization by removing the product from the reaction.



(2.6)

This approach solves the problem of decomplexation seen in the earlier template assisted syntheses, allowing the synthesis of complexes of many different transition metals with this ligand.

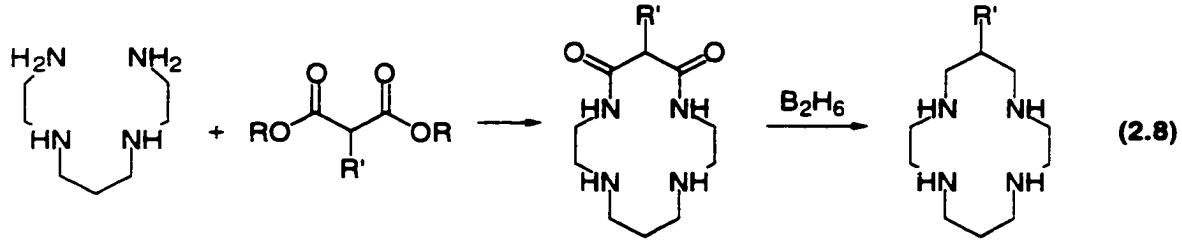
One very direct synthesis in which a tosyl-protected tetraazamacrocycle was condensed with a bis-sulfonamide sodium salt with a bis-sulfonate ester (Equation 2.7) was developed by Richman and Atkins[13] . This reaction did not



(2.7)

require high dilution, and the reasons for the efficiency of the reaction are not well understood. A template effect by sodium was ruled out, because the reaction proceeded with the same efficiency with tetramethyl-ammonium as the counter ion. This reaction also showed great flexibility as to ring sizes and substituents. One drawback was the harsh conditions needed to remove the tosyl protecting group.

Tabushi developed another route to cyclams that involved the reaction of a linear tetraamine with a malonate ester to form a dioxocyclam, which was then reduced to yield a cyclam (Equation **2.8**).[14] This method can accommodate many



(2.8)

different substituents on the malonate leading to many differently-substituted cyclams. It also does not require protection of the amines, thus removing the problematic protection/deprotection sequence seen in other syntheses.

An unusual method for the direct synthesis of macrocycles involves the dimerization of cyclic imines. The initial report of this unusual dimerization, in which a diazamacrocycle from the dimerization of 3,4-dihydro-5H-2-benzazepine was isolated was by Goldman 1969 (Figure **2.2**).[15] These studies were followed other groups who substituted oxygen[16] (Kluiber and Sasso), sulfur[17] and methyl arsine[18] (Wild) for one of the methylenes in the benzazepine. These imines also underwent the dimerization reaction to afford the differently-substituted macrocycles. Goldmann found that the monomer

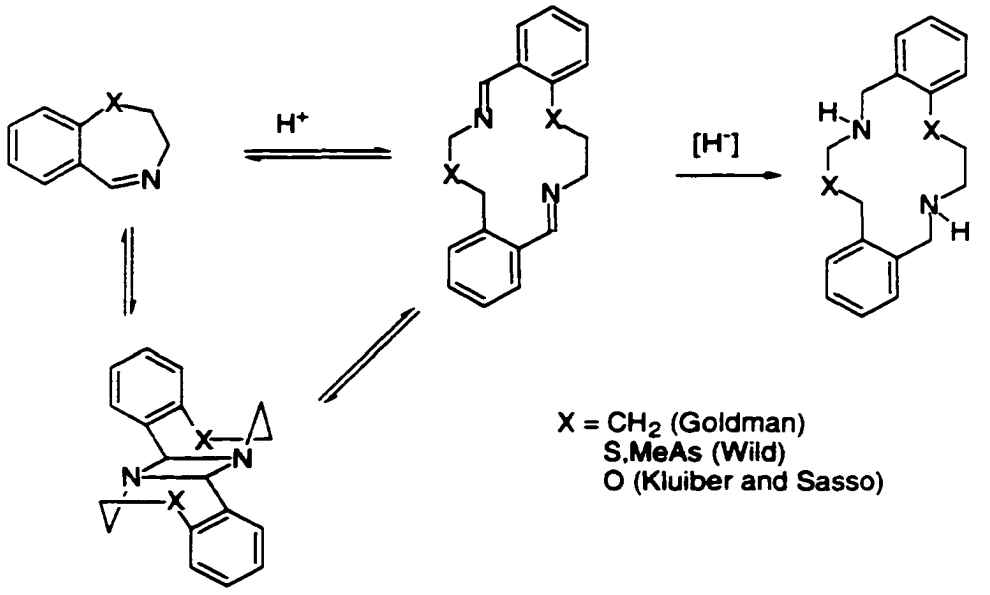
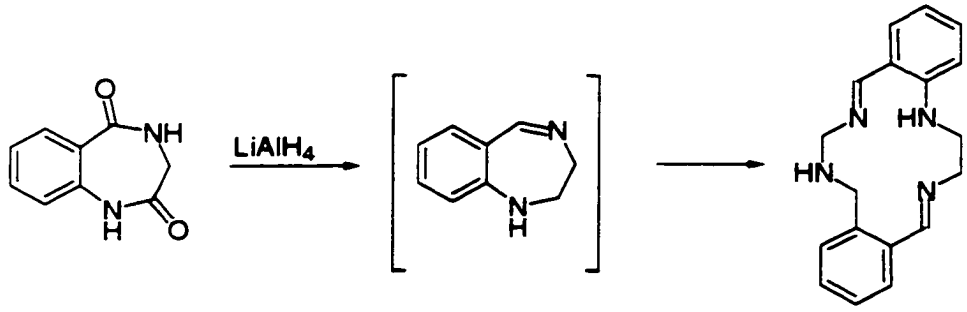


Figure 2.2 Goldmann's imine dimerization

dimerized upon standing and the dimer reverted to the monomer under acidic conditions. Reduction of the imines halted the interconversion of the two species. The dimerization is thought to proceed through an imine metathesis forming first a 1,3-diazetidine intermediate which then ring opens in the opposite direction to form the macrocycle (Equation **2.9**). This same process is thought to be involved in Wild and Sasso's systems. Jan Bergman also encountered this



(2.9)

dimerization in attempts to synthesize benzo-1,4-diazepine[19]. Reduction of benzo-1,4-diazepinedione did not yield the desired seven membered ring but rather spontaneously led to dimerization to the tetraazamacrocycle (Equation **2.9**).

2.B.3. Modifications of the Core Macrocycle[20].

Most of the proceeding syntheses are quite flexible, allowing for many different substitution patterns on the cyclam ring backbone. Varying the substituents can change the physical properties of the macrocycles. Long chain alkyl groups have been included to increase the solubility of metal complexes in organic solvents. Stereocenters can be included to produce chiral non-racemic complexes. Pendant arms with donor-atoms can add further sites for coordination to metal centers, thus changing the coordination geometry of the complex. Other ligand systems can be attached to the ring so that more than one metal can be coordinated to the molecule, producing heterobimetallic systems. The two main classes of modifications to cyclams consist of pendant groups attached to the carbon backbone and groups attached to the nitrogens.

2.B.3.a. Carbon Pendant Groups

One modification of cyclams that is often undertaken is the attachment of pendant groups containing a donor-atom which can coordinate to metal centers within the macrocycle (**Figure 2.3**).[21] Two main synthetic strategies lead to carbon substituted macrocycles: incorporation of the pendant group as part of the cyclization process, and attachment of the pendant group after the

macrocycle is formed. Of these two methods incorporation of the pendant group in the cyclization process is most often used.

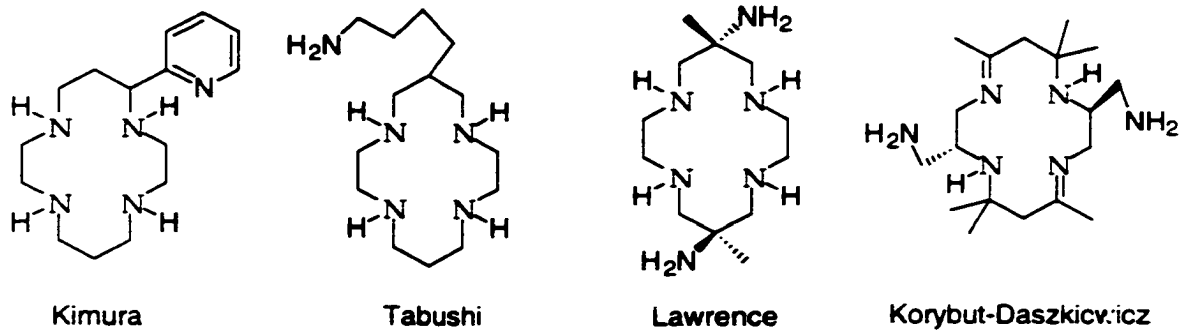


Figure 2.3 Examples of coordinating pendant arm cyclams: carbon based

Tabushi's macrocyclization (Equation **2.8**) was one of the first methods developed in which the pendant coordinating groups were introduced in the cyclization process. Kimura's synthesis (Figure **2.4**) of carbon-based pendant-arm cyclams is similar to Tabushi's method but instead of a substituted

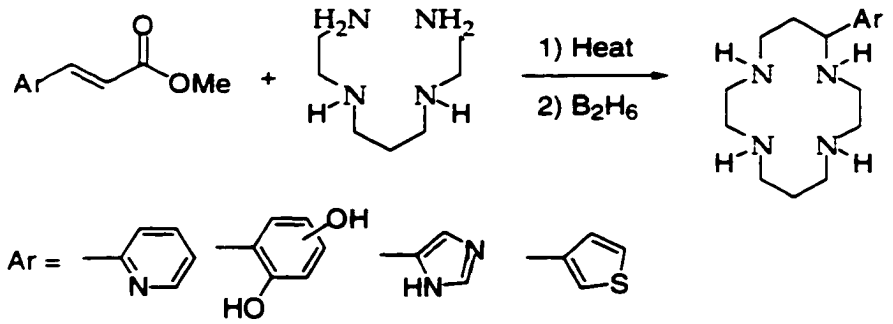
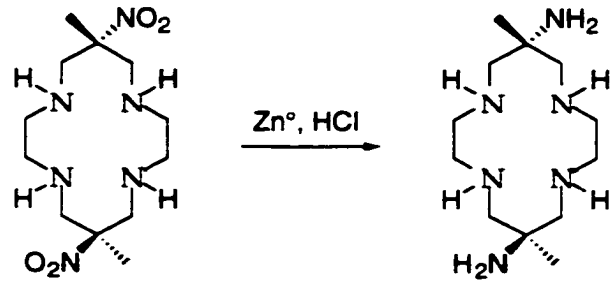


Figure 2.4 Kimura's synthesis of pendant arm cyclams

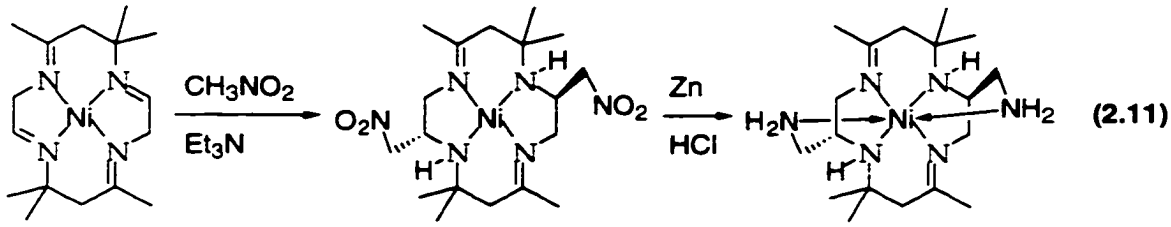
malonate, an aryl acrylate was condensed with a the linear tetraamine.[22] Lawrence reduced the nitro groups from Comba's bisnitro-cyclam (Figure **2.1**) to produce a bis amino cyclam (Equation **2.10**).[23]

There have been fewer examples of post cyclization methods to attach pendant arms on carbon. One modification was developed by Korybut-Daszkicwicz. His synthesis involved attack of nitromethane on a coordinated



(2.10)

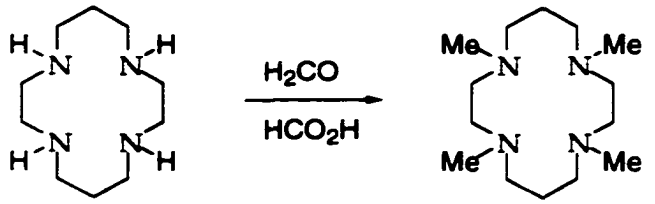
imine producing a hexa-coordinate ligand (Equation **2.11**).[24] It is thought that attack of the nitromethane is directed by steric considerations to produce the two pendant arms as shown.



(2.11)

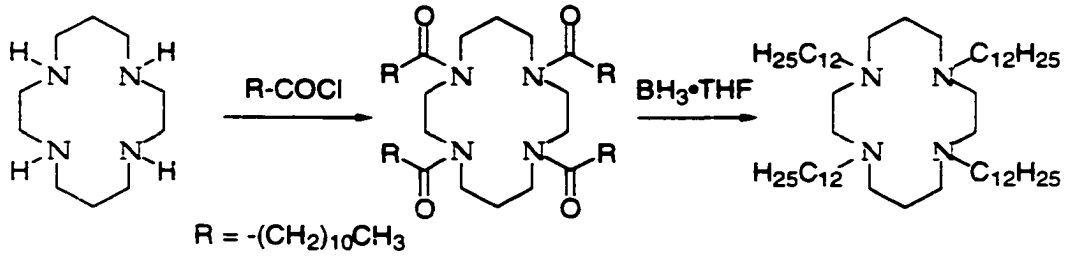
2.B.3.b. Nitrogen Pendant Groups

The other points of attachment for pendant groups are the secondary nitrogens on the ring. Due to the ease of modification of the ring nitrogens, there are many more examples of nitrogen-based pendant groups than of carbon-based pendant groups.[25] A drawback of alkylating the ring nitrogens is the decreased stability of the metal complexes due to steric requirements of the tertiary amines.[26] One of the first examples of nitrogen-based pendant groups was the N-tetramethyl cyclam synthesized by Barefield (Equation **2.12**)[27]



(2.12)

Long alkyl groups have been appended to the cyclam nitrogens to increases their solubility in non aqueous solvents.[28] Attempts to directly alkylate the cyclam nitrogens using simple aliphatic alkyl halides led to over alkylation of the ring nitrogens to quaternary amines (Equation **2.13**), so an acylation/reduction process was used to produce these substituted cyclams.



(2.13)

As with the carbon-linked pendant arms, much work has gone into attaching groups with additional coordination sites to the ring nitrogens (Figure **2.5**).[20,29]

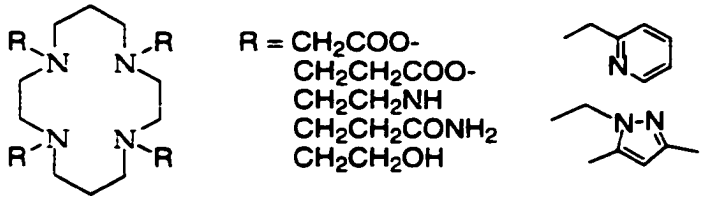


Figure 2.5 Coordinating pendant arm cyclams: nitrogen based.

All of the examples in Figure **2.5** take advantage of the nucleophilic character of the ring nitrogens either through Michael addition to α,β-unsaturated carbonyl

compounds or through the ring-opening of epoxides. These methods also place the same substituent on all of the ring nitrogens, which is not always desirable.

Differentiation of the ring nitrogens has proven to be difficult but many synthetic routes and even a solution phase combinatorial method[30] have been developed to produce cyclams with 2, 3, or 4 different groups attached to the ring nitrogens. Monoalkylated cyclams have proven to be the easiest to synthesize by reacting an excess of cyclam with the alkylating agent (Figure 2.6).

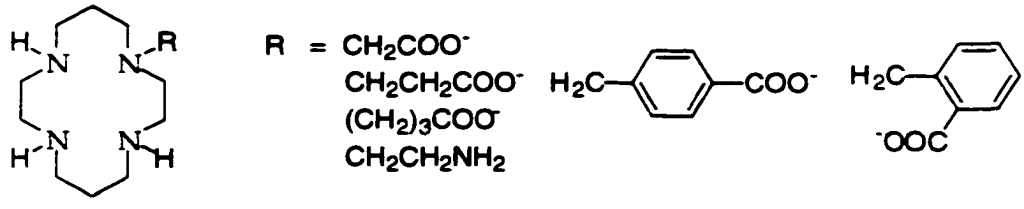
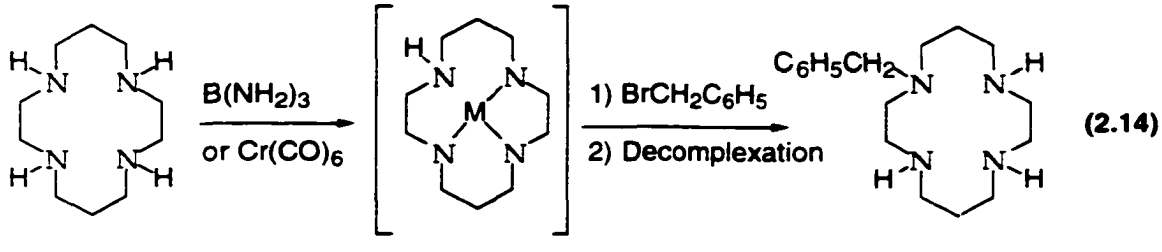


Figure 2.6 Examples of mono N-alkylated cyclams

Mono N-alkylated cyclams offer the benefits that the pendant group provide while having only one tertiary nitrogen to destabilize the cyclam metal complex. A drawback of this method is that an excess of cyclam is used and that excess can be difficult to remove after the reaction. Two protection schemes were developed to produce the monoalkylated product with the use of a triaminoborane[31] or chromium tricarbonyl[32] as the protecting groups (Equation 2.14).



(2.14)

M = B, $Cr(CO)_3$

Often cyclams with different N-substituents are desired. This generally requires several protection-deprotection sequences to produce the desired

substitution pattern. Several approaches to differently-substituted cyclams have been developed (Figure 2.7).[25]

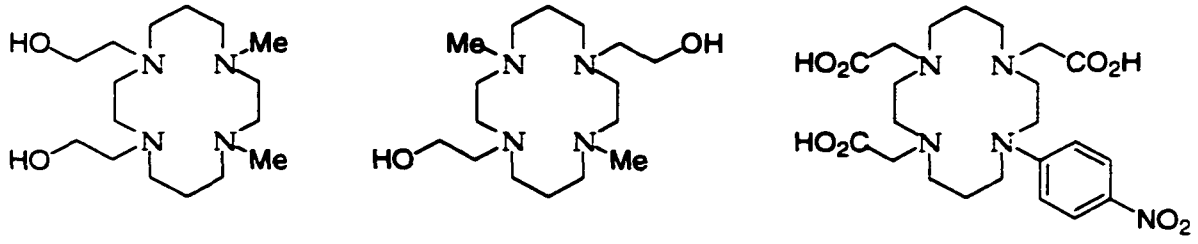


Figure 2.7 Examples of differently N-substituted cyclams substituted cyclams

1,8-Disubstituted cyclams have also been synthesized, because the octahedral complexes formed from 1,8-disubstituted cyclams experience less strain than those with 1,11-disubstituted (Figure 2.8).

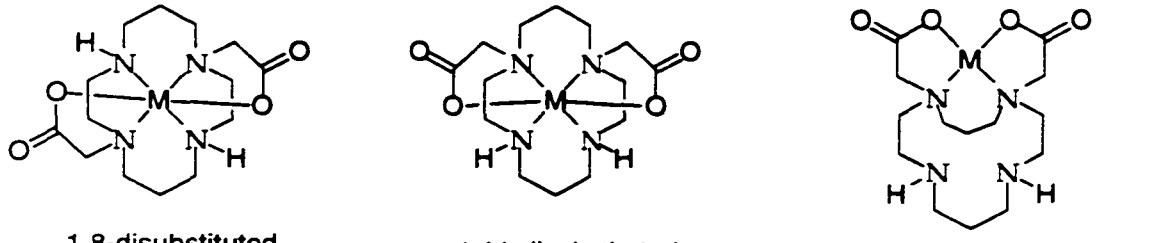
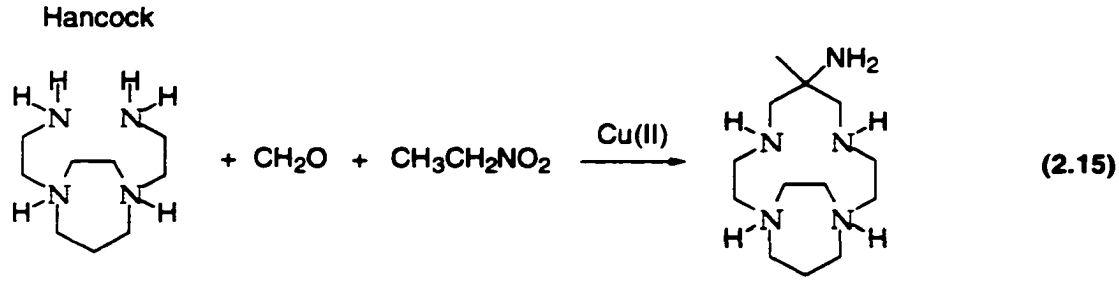


Figure 2.8 *Trans vs. cis* coordination complexes

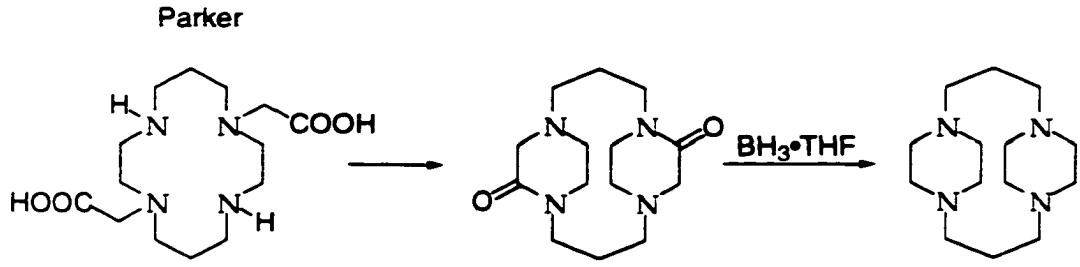
A further complication with 1,11-pendant arms is the likelihood of coordination of the metal outside the cyclam ring. This is rarely observed with 1,8-pendant arms.

Another substitution motif that has been developed connects two of the ring nitrogens, making a bicyclic system. Both *cis* and *trans* capped cyclams have been produced. Hancock has been working to reinforce the flexible cyclam

backbone by synthesizing 4,8-capped cyclams[33] and Parker has synthesized the isomeric 1,4 -capped cyclam (Equations **2.15, 2.16**).[34]

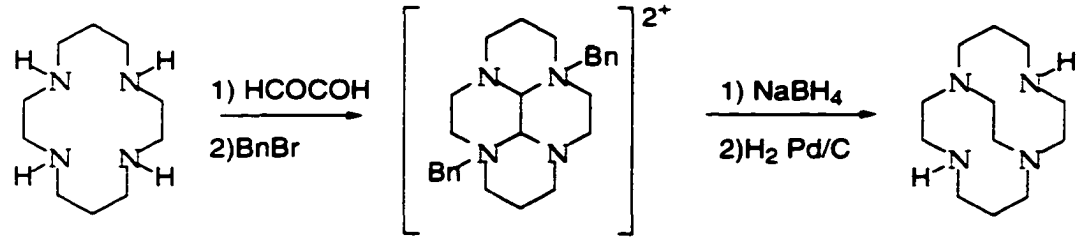


(2.15)



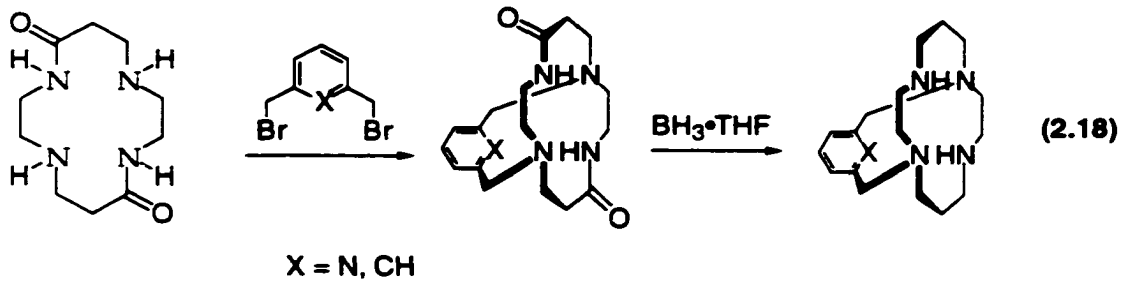
(2.16)

One of the first examples of 1,8-capped cyclams was developed by Weisman (Equation **2.17**)[35]



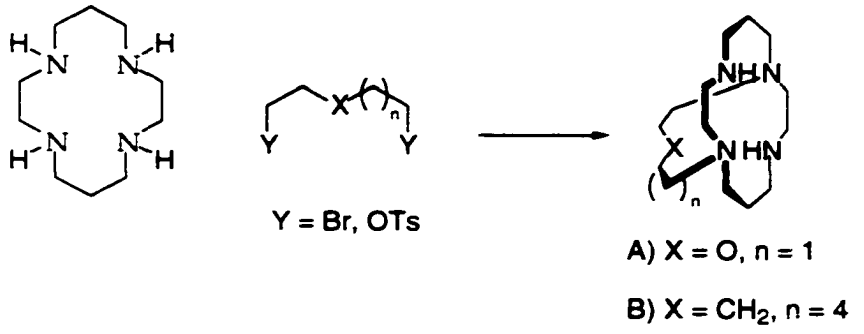
(2.17)

A limitation of this method is that only a two-carbon cap can be produced. Recently the crystal structure of a manganese(II) complex of this very rigid ligand was reported.[36] Guilard has also published several methods for the generation of differently-capped cyclams. Starting with the 5,12 dioxocyclam two different aryl-capped cyclams were produced (Equation **2.18**).



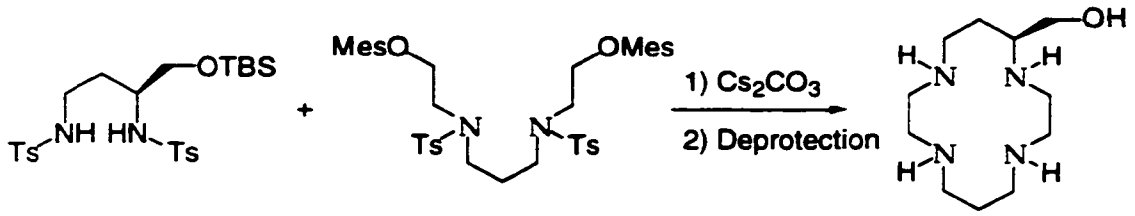
(2.18)

Dioxocyclams were used because the trans-disposed amides would not react with the aryl halide, in effect protecting two of the nitrogens. With reduction of the amide carbonyls, the 1,8-capped cyclam was produced. With simple aliphatic bis-electophiles, *trans*-capped cyclams could also be produced, albeit in lower yield (Equation **2.19**).[37]



(2.19)

Many of the cyclams that have been synthesized are racemic mixtures and a few studies resolving these racemates have been reported.[38] There have been surprisingly few reported syntheses of optically active cyclams.[39] Burrows has reported the synthesis of an optically active cyclam based on the Richard-Atkins method in which an optically active 1,3-propanediamine was used as the chiral subunit (Equation 2.20).[40]



(2.20)

TBS = *t*-butyldimethylsilyl
Mes = methane sulfonyl

2.C. METAL COMPLEXES OF TETRAAZAMACROCYCLES

To date, cyclam complexes of almost all transition metals and several lanthanides have been characterized. For most of these complexes, X-ray crystal structures have been reported (Table **2.1**). For nickel alone there are more than 130 different X-ray structures in the Cambridge Structural Database for 14-membered tetraazamacrocycles.[41]

Table 2.1 Metal complexes of cyclams

V(IV)[42]		
Cr(III)[43]	Mo(0),[44](III)[45]	
Mn(II)[46](III)[47]	Tc(V)[48]	Re(V)[49]
Fe(II)[50]	Ru(II),[51](III),[52](IV),[53]	Os(VI)[54]
Co(III)[55]	Rh(III)[56]	Ir(III)[57]
Ni(II),[58]Ni(III)[59]	Pd(II), (IV)[60]	Pt(II)[61]
Cu(II)[62]	Ag(II)[63]	Au(III)[64]
Zn(II)[65]	Cd(II)[66]	Hg(II)[67]
Tb(III)[68]	As(III)[69]	Pb(II)[70]

Groups 3 and 4 transition metals are too small to coordinate effectively to cyclams but from vanadium to mercury the literature is full of complexes of various substituted and unsubstituted cyclam complexes.

2.C.1. Coordination Geometry of Tetraazacyclotetradecanes

Cyclams generally complex to transition metals with all four nitrogens of the macrocycle but there are some examples for which only two or three of the ring nitrogens bind to a metal center. The coordination geometry of cyclams is generally square planar, leaving the two *trans* coordination sites unoccupied by the macrocyclic ligand (trans isomer). However, *cis* coordination is also possible (Figure **2.9**).

Figure 2.9 Possible coordination geometries of cyclams

The preference of these ligands for square planar coordination increases the selectivity of cyclams for metal centers that prefer square planar coordination, e.g., copper(II) and nickel(II); thus there are many more examples of complexes with these metals. The backbone of the cyclam ring is also quite flexible, allowing the nitrogens to move to accommodate metals with different ionic radii or metals that prefer coordination geometries other than square planar. With transition metals that prefer octahedral coordination, counter ions can coordinate to the two empty *trans* coordination sites, filling out the octahedral coordination. The flexibility of the cyclam backbone also allows the metal center to lift above

the plane of the four nitrogens to accommodate metal ions that are larger than the cavity of the cyclam. This is seen for most of the third row transition metals and the lanthanide complexes that have been reported. Generally, when the metal center rises out of the plane of the nitrogens, the metal complexes are less stable than the strictly square planar complexes (Figure **2.10**).

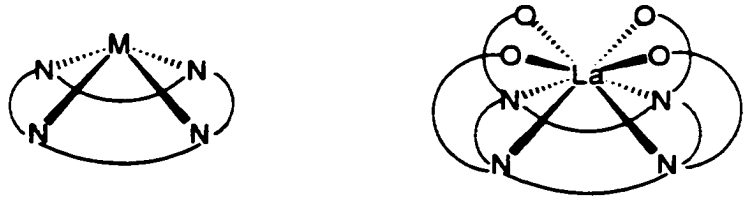


Figure 2.10 Possible coordination geometries of large ions

The instability of the "metal out" complexes is one of the driving forces behind the development of pendant arm cyclams with further donor groups, for use as magnetic resonance imaging agents.[71]

2.C.2. Stereochemistry of Metal Complexes

The flexibility of the cyclam backbone allows the macrocyclic ring to adopt several different ring isomers when coordinating a metal. Bosnich developed a system for classifying the five different isomers that are observed with cyclam metal complexes.[72] Two major stereochemical aspects develop upon metal complexation: the secondary amines are no longer free to invert and thus become stereocenters, and the fourteen membered ring is divided into two five-membered rings and two six-membered rings. These two aspects are taken into account in order to identify the different ring isomers.

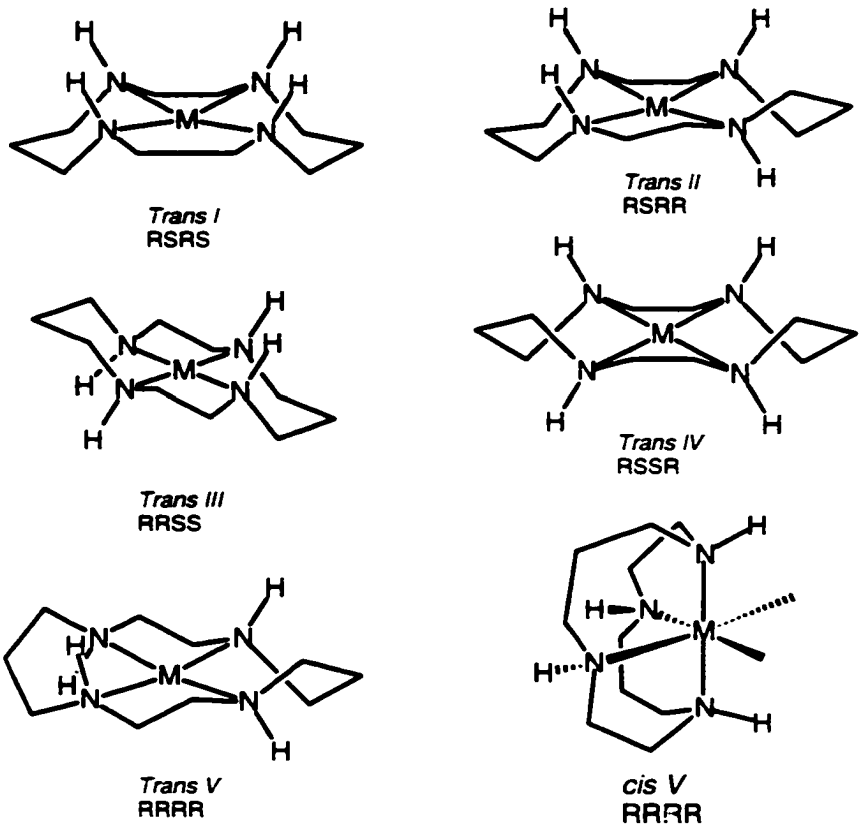


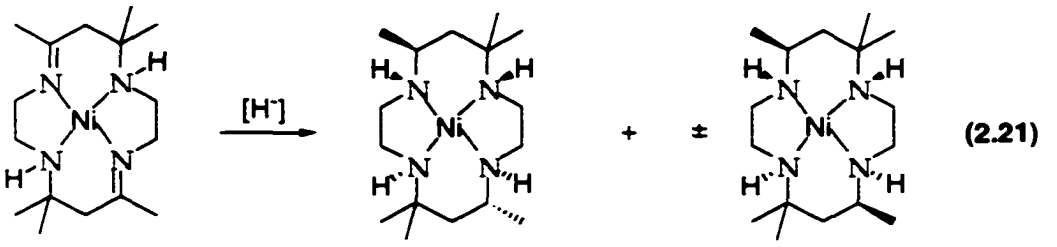
Figure 2.11 Possible cyclam configurations. *Trans/cis* refers to the coordination geometry. R/S refers to the absolute configuration about the nitrogens

The coordination geometry about the metal center is established by the *cis* and *trans* designations. The Roman numerals are arbitrary descriptors that differentiate five different ring isomers that are commonly observed. What makes the ring isomers different is a combination of the ring conformations of the five- and six- membered rings and the absolute configuration at the nitrogens. For example, the *trans I* isomer has the two 6-membered rings in chair conformations and the two five-membered rings are in matching envelope conformations. Also, the absolute configurations at the nitrogens alternate around the ring. With *trans II* one of the six-membered rings is in a chair with the second in a twist boat conformation. The absolute configurations of the nitrogens are now RSRR. *Trans III* is the most often observed ring isomer and

from calculations[73] it is the lowest energy ring isomer, with both of the six-membered rings in chair conformations and the two five-membered rings in twisted envelopes. The *trans V* and *cis V* isomers have the same absolute configurations at the nitrogens and can be interconverted by folding the macrocyclic ring on a diagonal. The *cis V* ring isomer is more rare than the *trans* isomers, but bidentate counterions such as oxalate can force the ring into a *cis*. The various ring isomers can also be differentiated simply by assigning the absolute configurations at the nitrogens and complexes are often named using either or both of the classification systems (e.g. *trans III*, or RRSS, or *trans III* (RRSS)).

Groups attached to the ring can affect which ring isomer is most stable and all 5 ring isomers along with several intermediate structures have been observed in complexes with many different substitution patterns. For example, *trans I* is the predominant configuration for metal complexes of tetra-N-methyl cyclams. Also, configurations are not necessarily static, with the *trans I* and *trans III* configurations readily equilibrating in donor solvents.[74] Often the different configurations of a metal complex have different colors, indicating a difference in the coordination around the metal center.

The configuration of the cyclam is not only affected by the identity of substituent groups but also by the stereochemistry of those groups. Curtis[75] found that, upon reduction of the of a bis-imine nickel cyclam complex, two isomers, tet-a and tet-b, that had different solubilities were produced (Equation **2.21**). This shows that different stereoisomers on the carbon backbone can produce different ring configurations.



(2.21)

tet-a

C *meso trans* [14]tetramine

tet-b

C *rac trans* [14]tetramine

X-ray crystal analysis established the relative orientations of the methyl groups at the asymmetric carbon center and the *meso* and *rac* designations were applied to the two diastereomers. These two types of stereoisomers are often seen with chiral cyclams and the generally accepted nomenclature for the isomers generated by carbon centered stereocenters in cyclams uses the *meso* / *rac* designations.

2.C.3. Properties of Metal Complexes

The spectroscopic properties of cyclam metal complexes are quite variable, because of the dependence on the identity of the metal and its oxidation state along with the identity of the cyclam. This variability results from differences in the electronic environment of the metals The geometric configuration, conformation, substituents, and nitrogen oxidation state of the coordinating cyclam can all affect the electronic environment around the metal center. This wide variety of electronic environments is one of the very attractive features of cyclams as coordination ligands. Analysis of all the data collected on the many different complexes that have been generated is beyond the scope of this dissertation but a few examples can show the general trends of metal complexes of cyclams.

Most transition metal-cyclam complexes are colored. The colors that are observed are quite variable. Even with the same metal in the same oxidation state, the color of the complex can vary through the entire visible spectrum. The color of cyclam metal complexes is mainly a result of d-d absorption bands. For unsaturated cyclams (those containing imines) there is also a metal to ligand charge transfer band that is observed, but these generally fall in the UV region and do not contribute to the observed color of the complex. Ligand field splitting forces can greatly effect d-d transition bands, so with the large number of ligand configurations, conformations, and geometries available it is not surprising that so many differently-colored cyclam complexes are observed.

The large number of X-ray structures (more than 130) that have been solved for nickel(II) cyclam complexes is an indication of how well these complexes have been studied. Nickel(II) is d^8 and can form either high or low spin complexes. High spin complexes can have six coordinate (octahedral), five coordinate (square pyramidal and trigional bipyramidial) and four coordinate (tetrahedral) geometries. Low spin complexes form with five coordinate systems (square pyramidal and trigional bipyramidal) and four coordinate (square planar) systems. For low spin nickel(II) complexes the ideal Ni-N bond distance is 2.89Å, while for high spin complexes it is 2.10Å. In an analysis of all of the crystal structures of nickel(II) cyclam complexes in the Cambridge Structure Database it was found that there were 64 low spin complexes and 75 high spin complexes. The spin states were grouped by those with Ni-N distances less than 2.02Å (low spin) and those with Ni-N bond distances greater than 2.05Å (high spin). The low spin systems were square planar and most of the high spin complexes were octahedral.[41] The octahedral complexes are generally high spin because the six of the eight d-electrons are in the three degenerate t_{2g} orbitals the final two electrons are divided between the two degenerate e_g orbitals. Because

the two electrons are in separate orbitals the spins do not pair, thus the overall spin of the octahedral complexes is 2. For the square planar complexes there is a single, non-degenerate HOMO that the final two electrons occupy. When two electrons are in the same orbital the spins must be paired, thus the overall spin of the square planar nickel(II) complexes is 0. The flexibility of the cyclam ring helps in stabilizing both spin states of nickel by being able to expand slightly to accommodate the larger high spin nickel(II) ion. In water both the yellow planar low spin *trans III* and blue octahedral high spin trans-*trans III*- diaquo complexes are present (Figure **2.12**).[76]

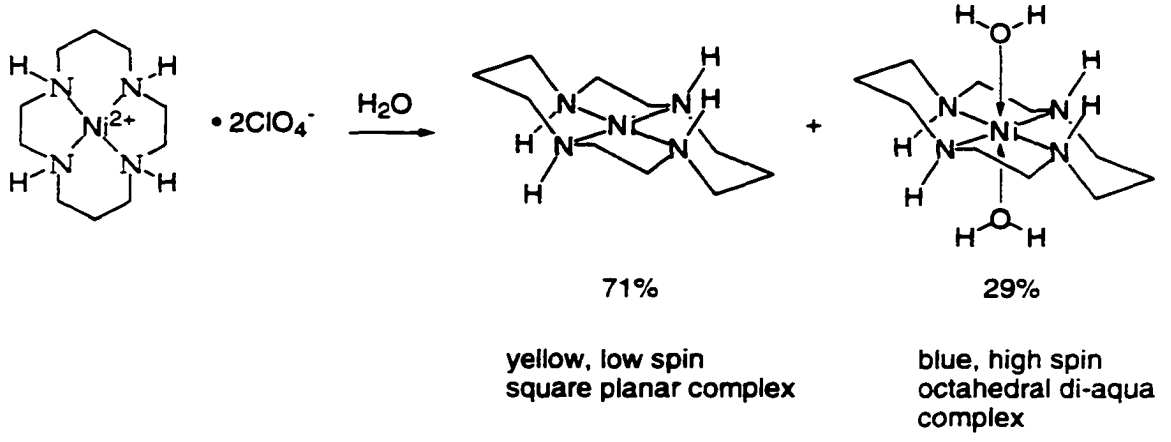


Figure 2.12 Mixture of high and low spin Ni^{2+} complexes

A similar conformational analysis of X-ray crystal structures of copper (II)[77] and cobalt (III)[78] complexes has been made.

2.D. APPLICATIONS OF CYCLAMS AND CYCLAM METAL COMPLEXES

2.D.1. Biological Systems

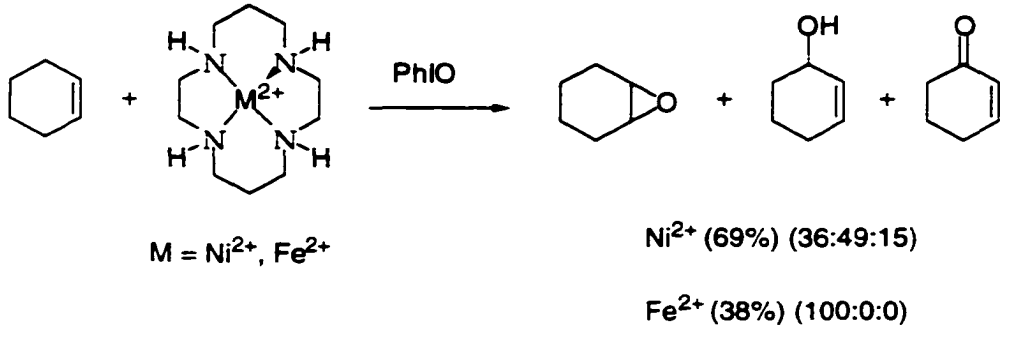
Many biological systems contain metal centers in the active site of the system, and the complexity of these systems greatly complicates their study. One way to study the environment around the metal center that is required for a specific transformation is to model the system with simpler coordination complexes. Cyclams are an attractive choice for modeling biological systems because of the flexibility of synthesis and fine control of the electronic environment around the metal center of interest.[79] An example of this is Nashida's study of an iron(II) cyclam complex for the peroxidation of linolenic acid.[80] This cyclam complex was used as a model to study Lipoxygenase (linoleate oxygen oxidoreductase), a non-heme iron dioxygenase which catalyzes the dioxygenation of polyunsaturated fatty acids[81] and it is also thought to have a role in inflammation.[82]

Along with studying the mode of action of biological systems, many cyclams and cyclam complexes themselves have biological activity. A 1,4,8,11-tetrakis(2-pyridylmethyl)-1,4,8,11-tetraazatetradecane exhibited some biological activity against several microorganisms (E. coli, Staphylococcus, Bacillus, and Pseudomonas).[83] A tetra-N-substituted cyclam has activity towards HIV-1 replication.[84] A copper(II) cyclam has some activity towards phytopathogenic fungi.[85] The kinetic inertness of many cyclam metal complexes has attracted the attention of many researchers in the study different types of complexes either as radiopharmaceuticals[86] or as Magnetic Resonance Imaging (MRI) agents.[87] Cyclams are exceptional ligands for technetium-99m and these complexes provide a new class of renal imaging agents.[88] A copper-62 cyclam tetraacetate

complex was used in positron-emission tomography.[89] These techniques introduce a toxic metal center into the patient's body, so it is of utmost importance that the metal center is retained by the ligand, to be excreted after the imaging/treatment is concluded.

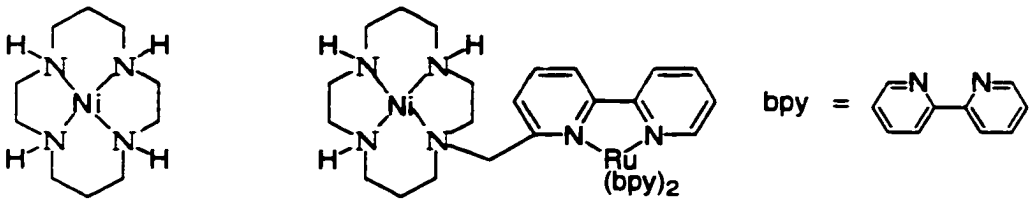
2.D.2. Cyclam Complex Mediated Oxidations/Reductions

Metal cyclam complexes have also been studied as catalysts for various oxidation/reduction reactions. Both nickel(II)[90] and iron(II)[91] cyclam complexes have been used as catalysts for the epoxidation of olefins (Equation **2.22**).



(2.22)

Cyclam complexes are also catalysts for the electrochemical reduction of CO_2 (Figure **2.13**).[92] A stable nickel(II) cyclam catalyst that raised the reduction potential of CO_2 to CO from -2.0V (uncatalyzed) to -2.0V (catalyzed) vs. natural hydrogen electrode (NHE) has been developed. Photochemical reduction of CO_2 was also accomplished with a mixed nickel(II), ruthenium(II) cyclam complex, in which the nickel was coordinated by the cyclam, and the photosensitizer (ruthenium(II) tripy) moiety was attached covalently to the cyclam ring nitrogen.[93] Upon irradiation of the bimetallic complex in a saturated CO_2 ascorbate buffer solution, CO evolved from the solution.

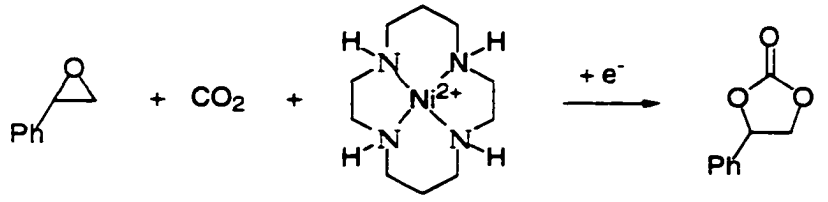


Electrochemical Catalyst

Photochemical catalyst

Figure 2.13 Catalyst systems for the reduction of CO_2 to CO

Electrochemical reduction of dioxygen to hydrogen peroxide was accomplished using a cobalt(III) cyclam complex.[94] The catalyzed reduction potential was -0.2 V vs. standard saturated calomel electrode (SSCE) compared to the uncatalyzed reduction of dioxygen which is -0.9 V vs (SSCE). Another process that was catalyzed by nickel (II) cyclam complexes was the insertion of CO_2 into terminal epoxides to form cyclic carbonates (Equation **2.23**).[95] The process was thought to proceed through an electrochemically generated nickel(I) complex which then affects the cyclization.



(2.23)

Several other cyclam complexes have seen use in areas other than catalysis. Cyclams have also been used in the extraction of heavy metal ions from solutions.[96] A nickel cyclam complex has been used as a fluorescent molecular thermometer.[97] As the temperature changes the fluorescence of the appended naphthalene increases (Figure **2.14**).

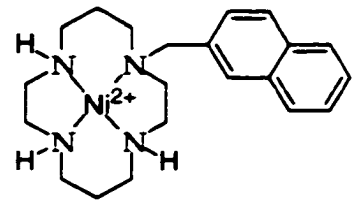
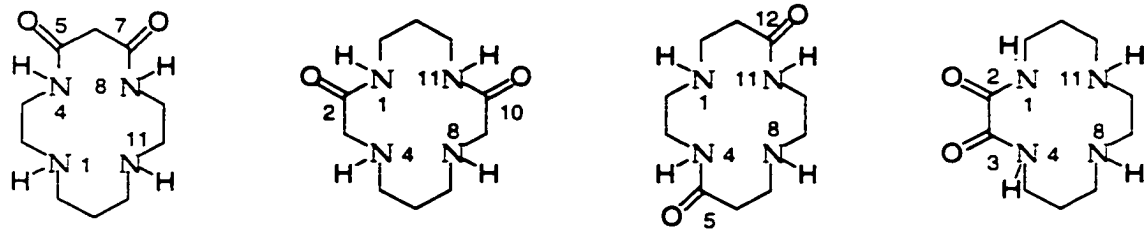


Figure 2.14 Fluorescent molecular thermometer

2.E. DIOXOCYCLAMS

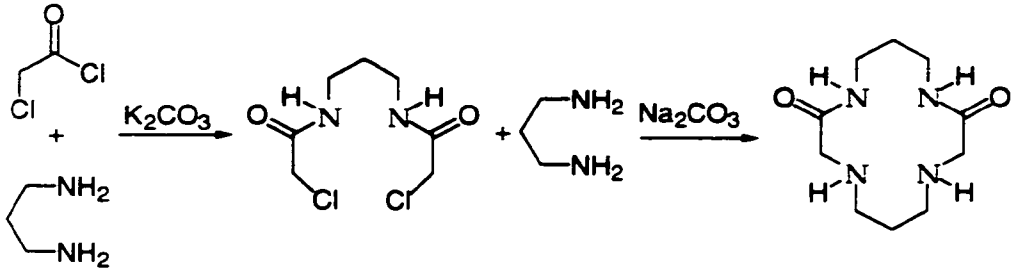
Dioxocyclams are a subset of tetraazamacrocycles which contain two amides and two amines and are considered intermediate between cyclams and cyclic peptides (Figure 2.15). The first examples of dioxocyclams were developed by Tabushi, but the amides were reduced to produce the fully saturated cyclam and the properties of the dioxocyclam were not studied. Kimura saw the potential of these tetraazamacrocycles and has extensively studied various dioxocyclams and their metal complexes. The carbonyl groups have been placed in various positions on the cyclam ring, positioning the amides either *cis* or *trans* to each other.



5,7-dione 2,10-dione 5,12-dione 2,3-dione

Figure 2.15 Dioxocyclam isomers

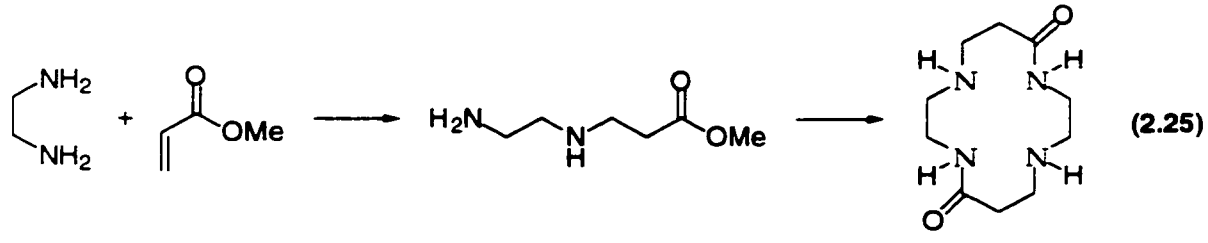
The methods of synthesis of these dioxocyclams are for the most part similar to each other. Tabushi's method (Equation **2.8**) is often used for the synthesis of the 12,14-dioxocyclam. 2,10-Dioxocyclams[98] are less common and are synthesized by the condensation of 1,3 diaminopropane and chloroacetyl chloride followed by cyclization with another equivalent of 1,3-diaminopropane to produce the dioxocyclam (Equation **2.24**).



(2.24)

The yield of this synthesis is generally poor but the starting materials are very inexpensive and the sequence is amenable to large scale reactions.

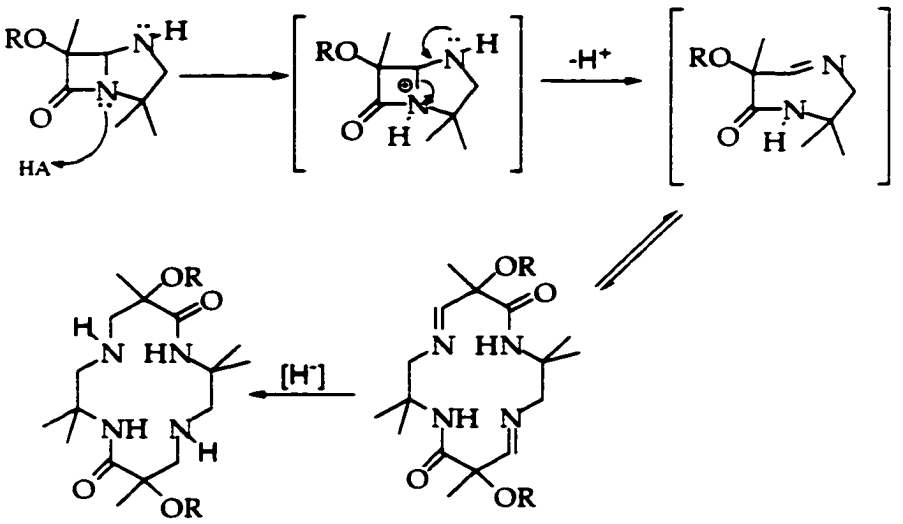
Two methods have been developed to synthesize 5,12-diones. The first method involves the condensation of methyl acrylate and ethylene diamine followed by cyclization to produce the dioxocyclam in 10% yield (Equation **2.25**).[99]



(2.25)

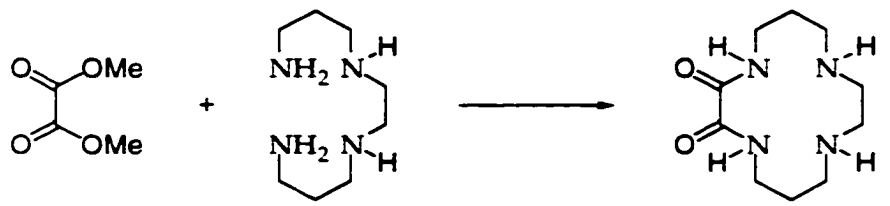
Hegedus discovered a second method for the synthesis of 5,12 diones.[100] In the attempt to synthesize azapenams (penicillin analogs) an acid-catalyzed ring opening occurred to form a seven membered imine, which cleanly

underwent a dimerization/metathesis reaction similar to Goldman's systems (Figure 2.5).[15] Reduction of the bisimine-dioxocylam produced a stable, saturated dioxocyclam (Scheme 2.1).



Scheme 2.1 Hegedus' synthesis of 5,12 dioxocyclams

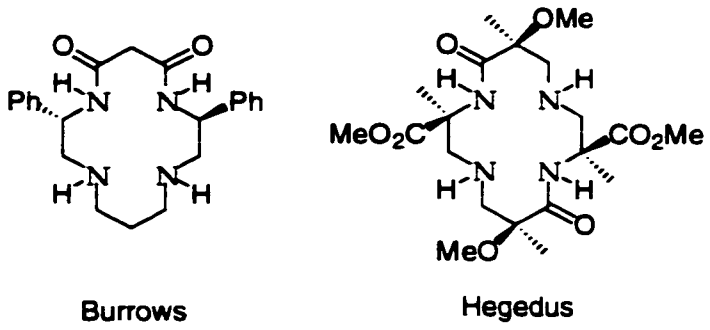
Finally there has been only one reported synthesis of the 2,3-dioxocyclam.[101] This cyclam was produced in reasonable yield from the condensation of the tetraamine and dimethyloxalate. (Equation. 2.26)



(2.26)

There are a limited number of syntheses of optically active dioxocyclams. Burrows has produced several optically active C_2 symmetric tetraazacyclo-tetradecanes derived from amino acids.[102] This synthesis follows Tabushi's method but is hampered by low yields. Hegedus has recently synthesized a

highly functionalized C_2 symmetric tetraazacyclotetradecane from dimerization of optically active azapenams (Figure 2.16).[103]

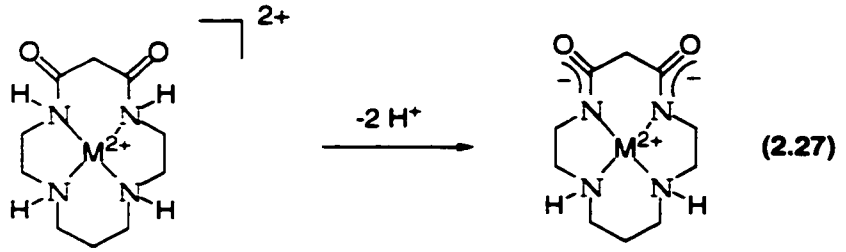


Burrows Hegedus

Figure 2.16 Examples of optically active dioxocyclams

2.E.1. Metal Complexes of Dioxocyclams

Dioxocyclams also form stable transition metal complexes. One of the main differences between cyclams and dioxocyclams is that upon complexation of a divalent metal the secondary amides protons become acidic. Once the coordinated amides are deprotonated a neutral complex is produced (Equation 2.27).



(2.27)

As is expected, the stretching frequency of the amide carbonyls typically diminishes 80 cm^{-1} upon complexation. The stretching frequency for the amide carbon nitrogen bond increases, indicating an increase in the double bond character of the carbonyl carbon-nitrogen bond This shows the weakening of the carbon oxygen double bond and concomitant increase of the bond order of

the amide carbon nitrogen bond and a flattening of the ring by these 4 sp^2 centers. The dissociation of the two amide protons can be followed by potentiometric titration, and Kimura has used this technique to study the kinetics of complex formation in water.[104] Dioxocyclam metal complexes undergo demetalation when exposed to strong acid, presumably by reprotanation of the amides and metal decomplexation.[105] Dioxocyclams show a greater selectivity in transition metal complexation than do cyclams, with Cu(II)[103], Ni(II)[103] and Co(II),[106] Pt(II)[103], and Pd(II)[103] forming stable complexes. X-ray crystallographic studies show, as is expected, that the N-M distance is shorter for the amide nitrogens than for the amine nitrogens.

The number of possible stereoisomers is less for dioxocyclams than for cyclams because of the amide sp^2 centers within the ring (Figure **2.17**). There are fewer X-ray structures of dioxocyclam metal complexes than of cyclam metal complexes, but there are representative examples of each class of dioxocyclam. For the 5,7 dione, the *trans syn* has appeared most often[107] but there is also a report of a *trans anti* isomer .[108] For the 5,12 dione both isomers have also reported. With the 5,12 dioxocyclams, the stereochemistry and substitution pattern on the carbon backbone affected which N-H epimer was seen.[103,109]

Electrochemical studies have shown that dioxocyclams stabilize the +3 oxidation states for nickel and copper.[110] Pendant coordinating groups also help to stabilize the Ni(III) oxidation state, as seen by the lowered oxidation potential (Figure **2.18**). This is of interest in studying copper(III) and nickel(III) intermediates in biological systems

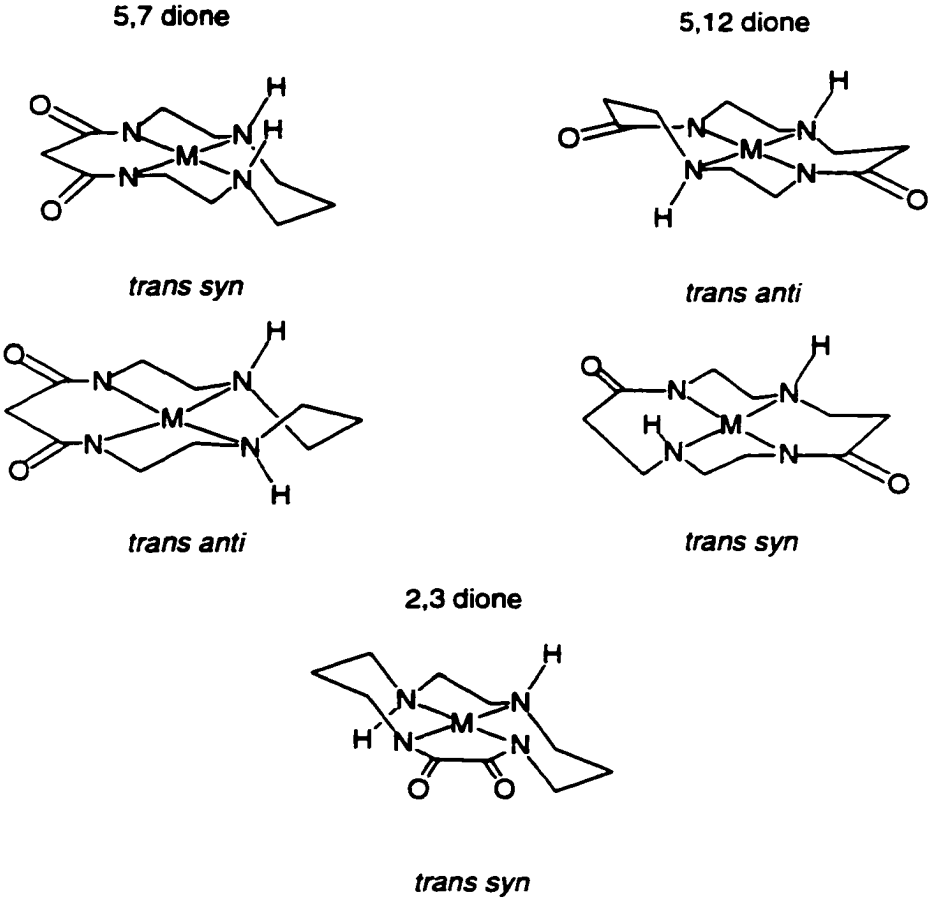


Figure 2.17 N-H isomers for dioxocyclams. *Trans* refers to the coordination geometry *syn/anti* refers to the N-H positions.

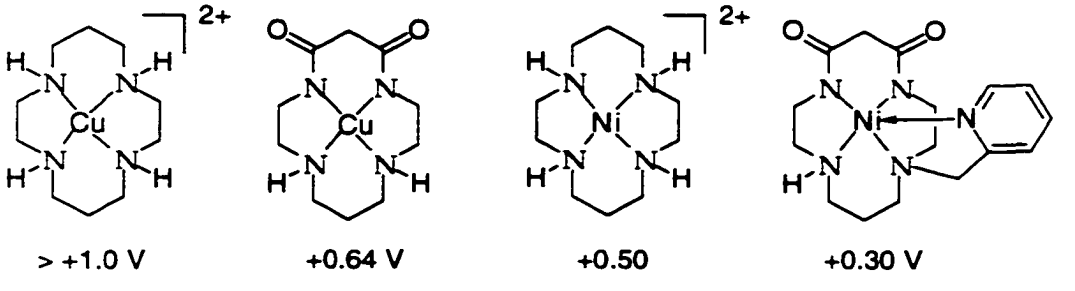


Figure 2.18 Redox potentials *vs.* SCE in aqueous solution at 25° C, I=0.2

2.E.2. Applications of Dioxocyclams

Dioxocyclams mirror cyclams in the types of application that have been developed. Dioxocyclam metal complexes have been used to model some biological systems; notably nickel(II) and copper(II) dioxocyclam complexes show superoxide dismutase activity.[111] To date there have been no examples of biologically active dioxocyclams or dioxocyclam metal complexes. One aspect that effects the applications of dioxocyclams is the selectivity of dioxocyclam for copper (II), nickel (II), cobalt (II), and palladium (II). An application was developed by Kimura that takes advantage of the selectivity and the reversibility of metal uptake controlled by pH. Kimura designed a dioxocyclam that selectively extracted copper(II) through a liquid membrane (Figure **2.19**).[112]

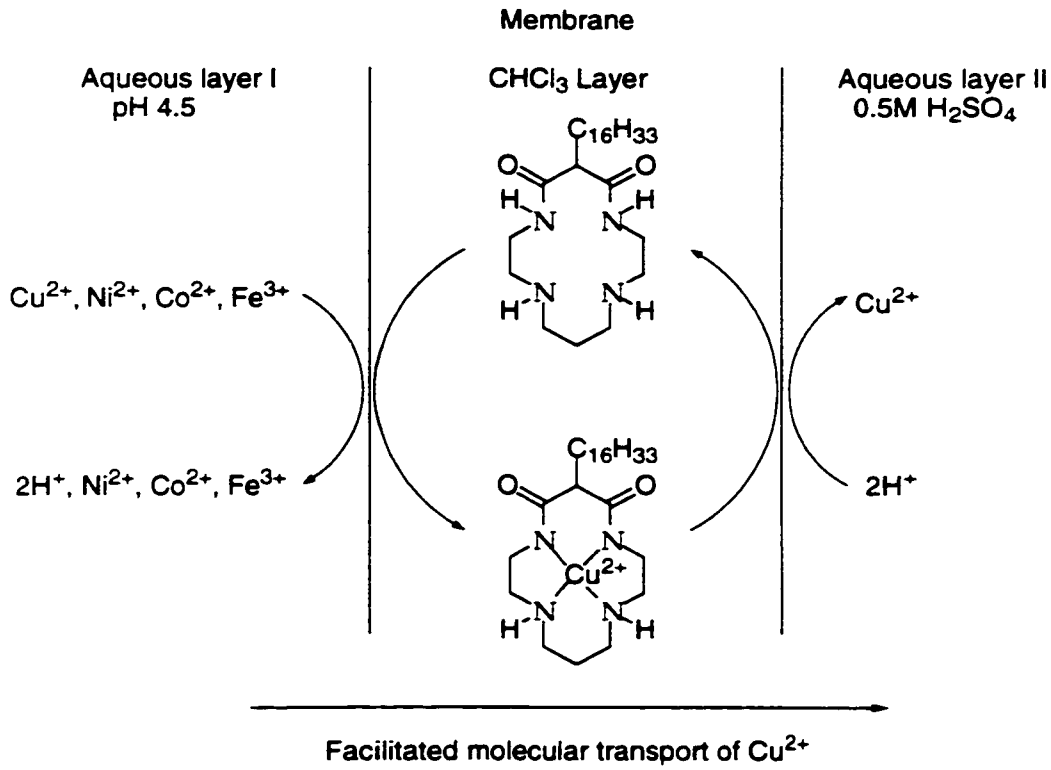
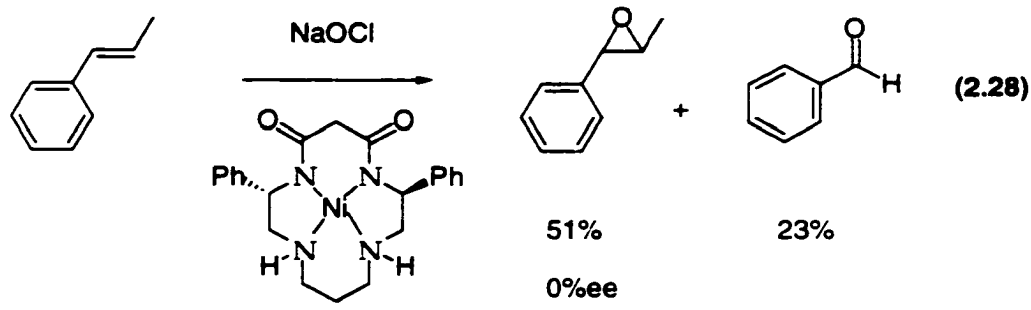


Figure 2.19 Proton driven copper(II) ion pump.

In aqueous layer I, the cyclam selectively complexed copper (II); then when the copper complex transversed the organic membrane and was exposed to the strong acid conditions of aqueous layer II, the cyclam was protonated. Once protonated the copper decomplexed and remained in the aqueous II layer. Burrows has used an optically active nickel(II) dioxocyclam complex as an epoxidation catalyst (Equation **2.28**).[102] Even though a modest amount of the epoxide was produced in the reaction, no stereoinduction was seen.

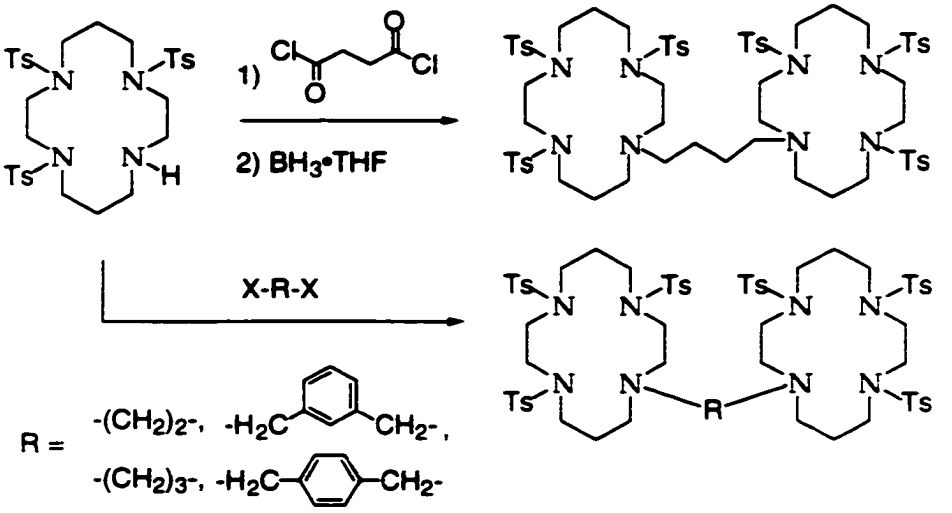


(2.28)

2.F. BIS-CYCLAMS AND BIS-DIOXOCYCLAMS

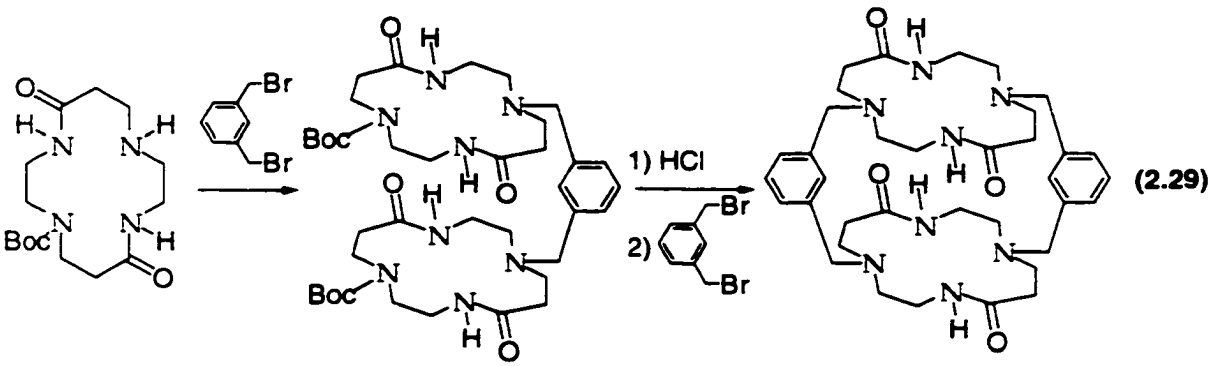
2.F.1. Synthesis of Bis-cyclams and Bis-Dioxocyclams

Bis-cyclams, in which two cyclam rings are covalently joined, are another class of cyclams that has been investigated.[113] Bis-cyclams are of interest because when two complexed metals are held in close proximity the properties of the two metal centers can change. The methods for synthesis of biscyclams are extensions of cyclam synthesis. One of the simplest methods for the linking of two cyclams together is through the ring nitrogens (Scheme **2.2**).[114]

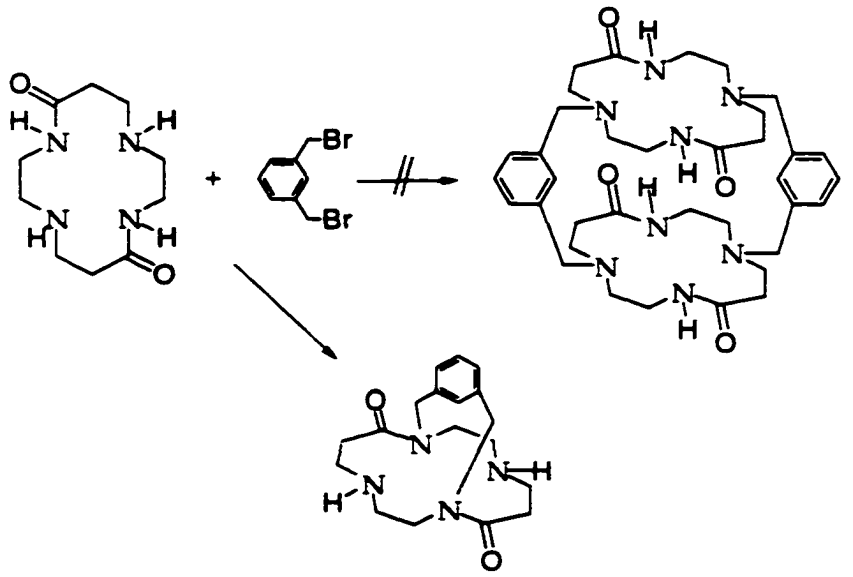


Scheme 2.2 N-linked biscyclams

Along with biscyclams that are linked once, macro*tri*cyclic compounds, in which two linkers join the cyclams, placing the two rings in a face to face orientation have also been developed (Equation **2.29**).[115]

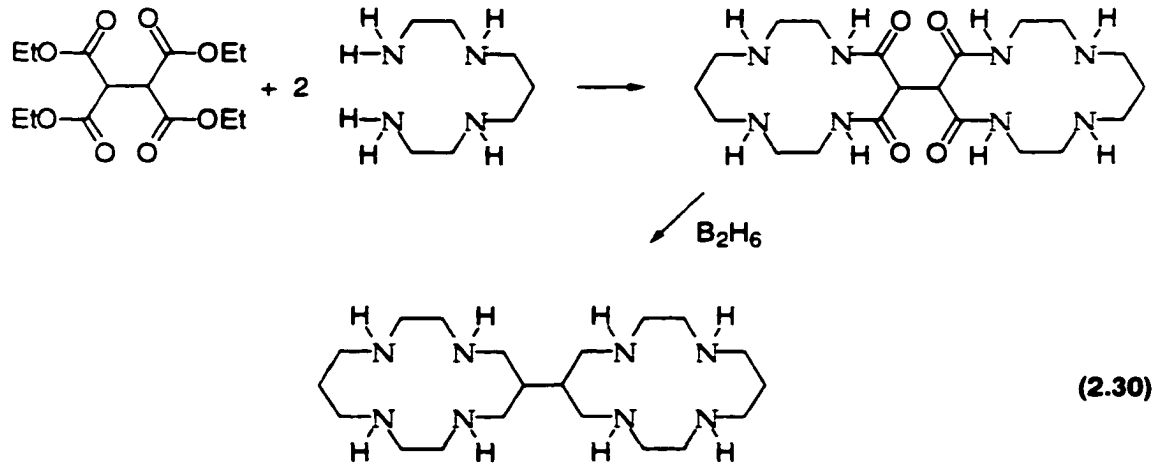


The stepwise synthesis in Equation **2.29** was required to affect the macrocyclization, since capping occurred with a 1:1 mixture of unprotected cyclam and dibromoxylene (Scheme **2.3**)



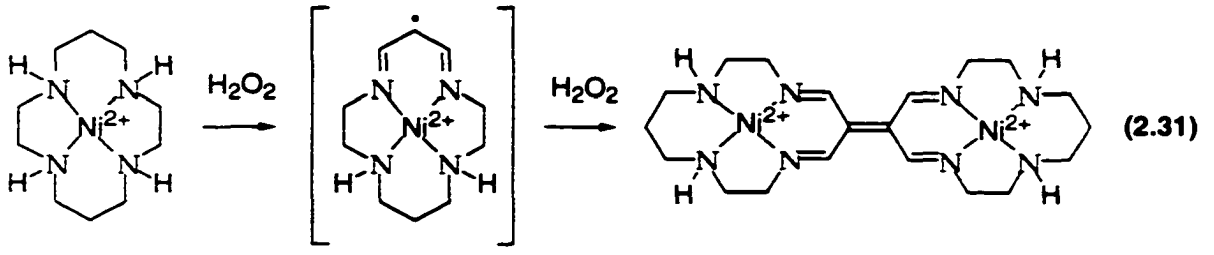
Scheme 2.3 Capping of unprotected dioxocyclam

Several different methods that link two cyclams through the carbon backbone of the cyclam have also been developed. This is advantageous because metal complexes of N-substituted cyclams are generally less stable than cyclams with only secondary amines. Fabbrizzi developed and studied the metal complexes of a carbon linked biscyclams and bis-dioxocyclams using an extension of Tabushi's dioxocyclam synthesis (Equation **2.30**).[116]



(2.30)

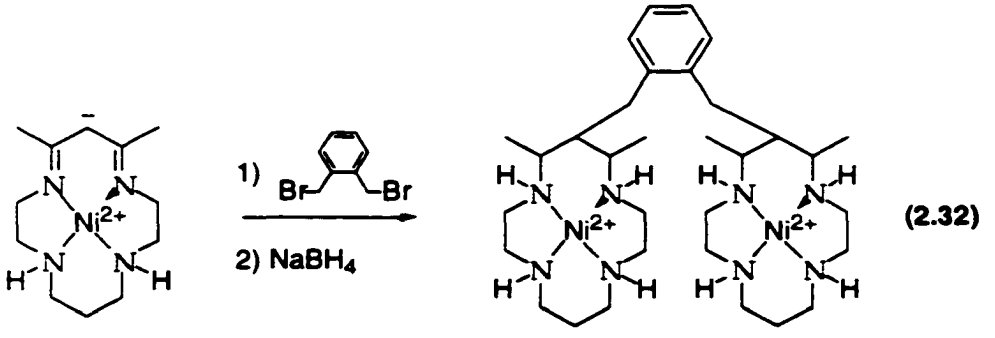
A novel approach to a bis-cyclam bis-nickel complex was developed by McAuley when he oxidatatively coupled two nickel cyclam complexes (Equation **2.31**) .[117]



(2.31)

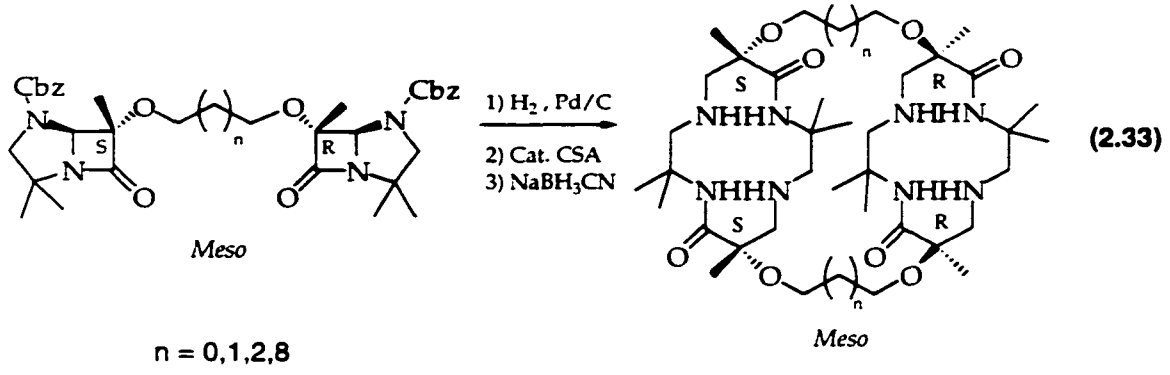
It was postulated that several oxidation steps were required to produce the bis-cyclam. The hydrogen peroxide is thought to oxidize the nickel (II) to nickel(III); then one of the coordinated amines is oxidized to an imine. This process is then repeated to form the second *cis* imine. Once the bis-imine cyclam is formed yet another oxidation produces a radical cation which can couple with a second radical cation to form an intermediate that is oxidized to the bis-copper(II)-bis-cyclam. The same process occurs by aerobic oxidation of a similar iron(II) complex.[118]

A face to face bis-cyclam complex was synthesized using a single *o*-xylyl bridging group linking the two cyclams through the carbon backbone (Equation **2.32**).[119]

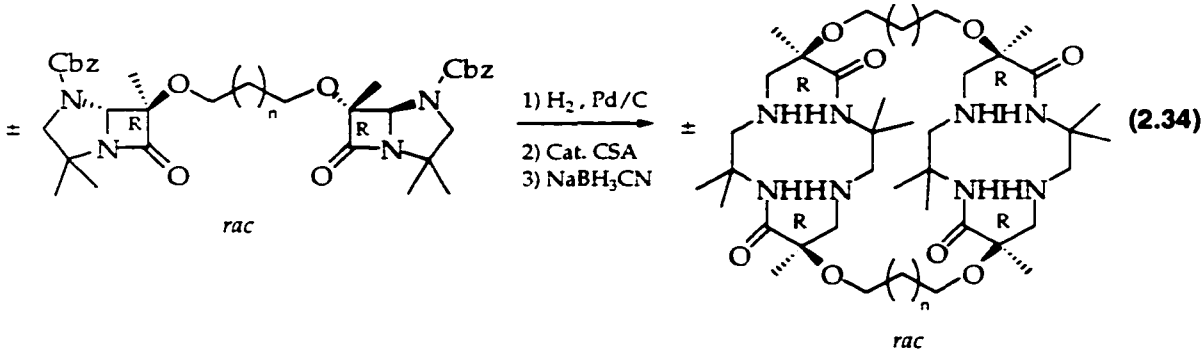


(2.32)

An X-ray crystal structure was solved for this complex and the cyclam rings were indeed found to be face-to-face with a bromide bridging the two nickel centers. Hegedus has also generated several face-to-face carbon bridged dioxocyclam complexes, for which the bridge length of the bis-dioxocyclam was varied (Equations **2.33, 2.34**).[108]

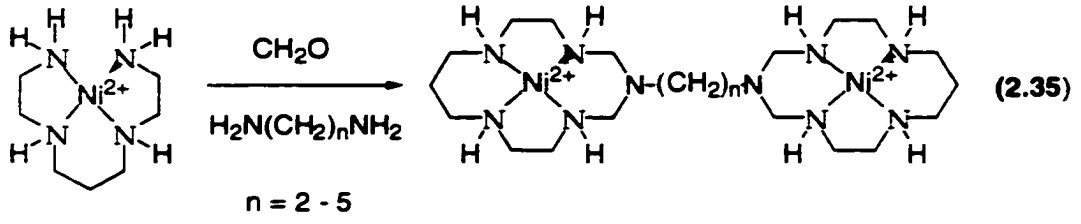


(2.33)



(2.34)

The synthesis produced a mixture of the *meso* and the *rac* diastereomers, which differ by the absolute configuration at the apical ether. Yet another type of bis-cyclam in which the two cyclam rings were linked through a nitrogen in the backbone of the ring was developed by Lampeka (Equation **2.35**).[120]



(2.35)

2.F.2. Applications of Biscyclams

The most successful application of a bis-cylam is as an inhibitor of HIV-1 and HIV-2, for which several structural activity relationship studies have been performed to find the ideal linker for activity. Bis-cyclams with an aromatic linker have the highest activity and are currently in clinical studies as an HIV therapeutic. It is thought that the bis cyclams interfere at an early stage in the HIV replicative cycle, which could be either viral uncoating or virus-cell fusion (Figure **2.20**).[121]

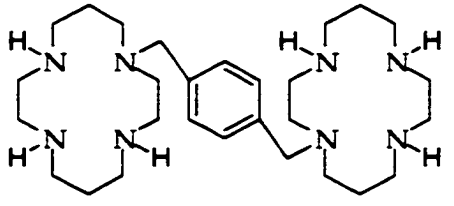
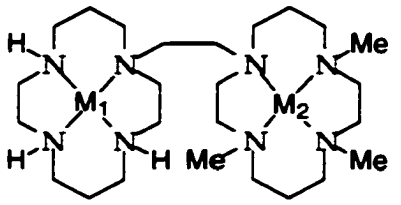


Figure 2.20 Biscyclam HIV-1,2 inhibitor.

Biscyclams have also been used to design heterobimetallic complexes which are used to study the communication between the two metal centers.[122] In this system, the methylated ring underwent complexation more slowly than the non-methylated ring, allowing the introduction of two different metals sequentially (Figure **2.21**).



$M_1 = Cu^{2+}, Ni^{2+}, Zn^{2+}$
$M_2 = Cu^{2+}, Ni^{2+}, Co^{2+}, Zn^{2+}$

Figure 2.21 Heterobimetallic biscyclam systems

2.G. SUMMARY

The shear volume of work published on tetraazamacrocycles demonstrates the utility of these compounds. They are able to isolate transition metals in a well-defined environment which can affect the physical properties of the metal center. Also, many different groups can be appended to the core macrocycle, adding functionality to the complex. Many researchers have developed applications ranging from medicine to waste water treatment for there ligands. The research area has matured in the 35 years since the first usable synthesis of cyclams and the pace of development of new cyclam architectures and applications shows no sign of slowing.

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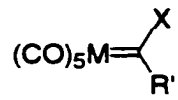
CHAPTER THREE

SYNTHESIS OF CAPPED DIOXOCYCLAMS

3.A. INTRODUCTION AND BACKGROUND

3.A.1. Synthesis of Fischer Carbene Complexes

Fischer carbene complexes were first synthesized by Fischer and Maasböl in 1964.[1] These carbene complexes contain a formal metal-to-carbon double bond that is stabilized by the presence of a heteroatom α to the carbene carbon (Figure **3.1**). The formally zero valent metal center is typically coordinated by electron withdrawing ligands such as carbon monoxide (CO).



M= Cr, Mo, W X = NR_2, OR, SR

Fig. 3.1 Fischer carbene complexes

The heteroatom substituent on the carbene carbon stabilizes the complex by donating electron density to the metal center which is then delocalized into the CO ligands (Figure **3.2**). This polarizes the complex resulting in electrophilic character at the carbene carbon so that the carbene carbon is likened to the

carbon of a carbonyl group. The presence of the heteroatom also stabilizes the Fischer carbene complex to air and water which greatly facilitates their use in organic synthesis.

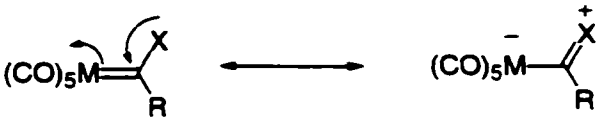
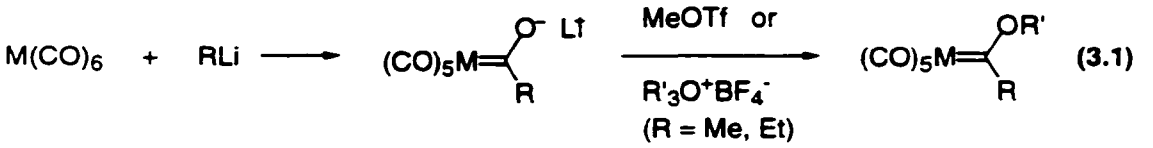


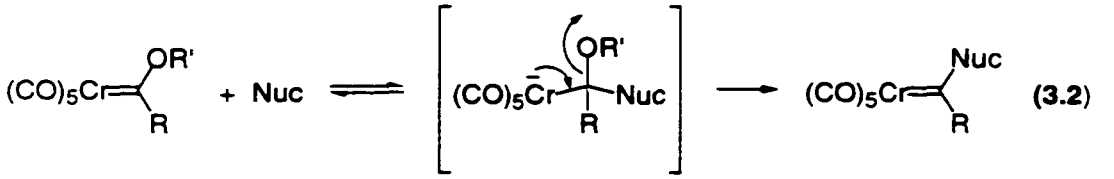
Figure 3.2 Resonance stabilization in carbene complexes

Fischer carbene complexes can be generated by several methods,[2] the most common being nucleophilic attack of an alkyl lithium reagent on a metal hexacarbonyl followed by O-alkylation by a hard alkylating agent (Equation **3.1**).



(3.1)

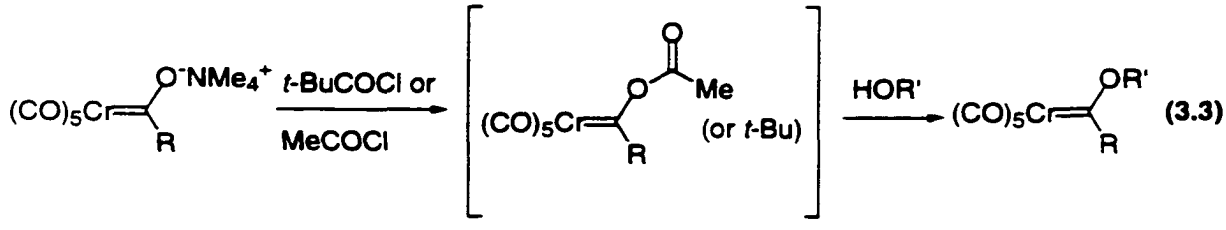
Nucleophiles can be substituted into the carbene complex, similar to nucleophilic attack on an ester, to place different heteroatom substituents on the carbene carbon. For example, an amino group can be exchanged for an alkoxy group, if the amino group is not sterically demanding (Equation **3.2**). This exchange reaction relies on the greater stability of aminocarbene complexes compared to that of



(3.2)

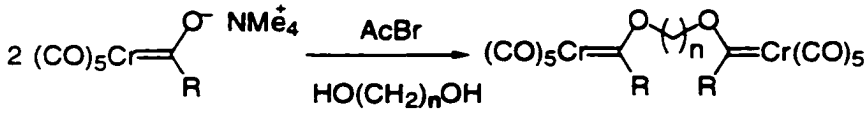
Nuc = RNH_2, small R_2NH

alkoxycarbene complexes. To generate alkoxycarbene complexes with substituents on oxygen that are not available as hard electrophiles, an activated carbene complex must be used. This is done by the *in situ* generation of an acyloxy-carbene complex from the stable tetramethylammonium "ate" complex to which an alcohol with desired functionality is added (Equation **3.3**). Using this method two



(3.3)

carbene complexes can be linked to form a bis-carbene complex, if an α–ω diol is used in the exchange reaction (Equation **3.4**).



(3.4)

3.A.2. Photoreactions of Chromium Carbene Complexes

Fischer carbene complexes also show synthetically useful photochemistry.[3] It is proposed that when chromium carbene complexes are irradiated with visible light, carbon monoxide is reversibly inserted into the chromium-carbene π-bond. The intermediate has never been observed, but it shows reactivity similar to ketenes. The possibility of a metal-bound ketene being produced during photolysis is demonstrated by the consumption of the carbene complex in the presence of ketene trapping agents. In the absence of a trapping agent, the chromium-bound carbene complex can be photolized for extended periods with recovery of the complex. The synthetic applications of

chromium-bound carbene complexes have been extensively studied by the Hegedus group over the past fifteen years. These studies have produced a number of classes of organic compounds including β-lactams,[4] cyclobutanones,[5] allenes,[6] amino acids[7], and peptides (Figure 3.3).[8].

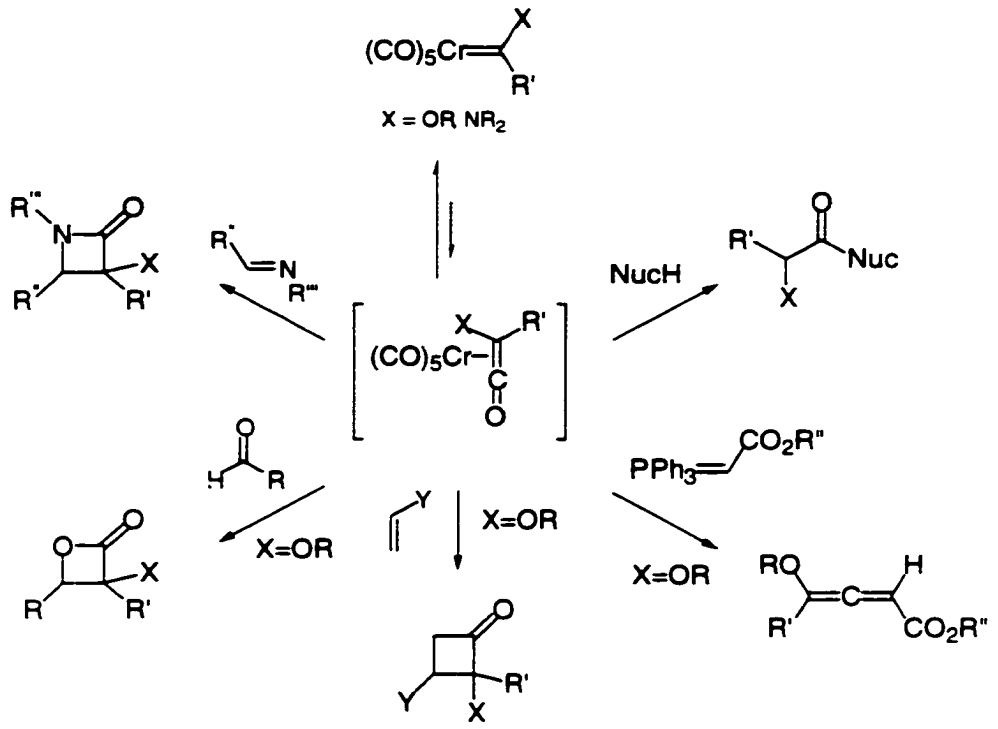


Figure 3.3 Synthetic photochemistry of chromium carbene complexes.

Chromium carbene complexes are generally yellow to red in color corresponding to an absorption in the 350-460 nm range. This adsorption has been assigned to an allowed metal to ligand charge transfer (MLCT).[9] This MLCT promotes an electron from a metal-centered HOMO to a carbene-centered LUMO, a process which can be viewed as a reversible, formal, one electron oxidation of the metal. This oxidation is thought to be the driving force behind the CO insertion. The recovery of unreacted complex after photolysis in the absence of a trapping agent suggests that the CO insertion process is reversible. The exact structure of the photogenerated intermediate is not know

but it can be represented either as a metallocyclopropanone or a metal-bound ketene (Figure 3.4). The photogenerated intermediates from carbene complexes

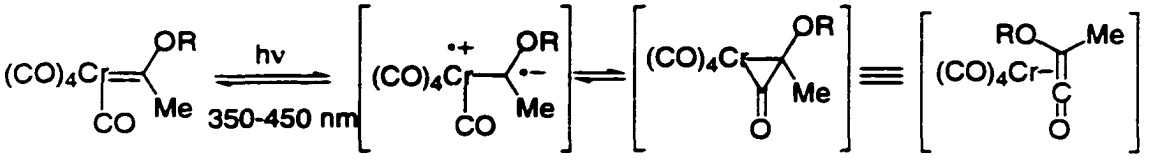


Figure 3.4 Photolytically driven CO insertion.

do not suffer from side reactions which often plague reactions with free ketenes. These side reactions include dimerization of the ketene or multiple addition of the ketene to the substrate.

3.A.3. Synthesis of Dioxocyclams

The classic method for the synthesis of β-lactams is the Staudinger ketene-imine cycloaddition. The photolysis of alkoxycarbene complexes in the presence of an imine also results in a cycloaddition to form β-lactams with high diastereoselectivity. An example of the selectivity of the photoreaction is the photolysis of an alkoxycarbene complex in the presence of a protected imidazoline to produce a protected azapenam (Figure 3.5). In this reaction two

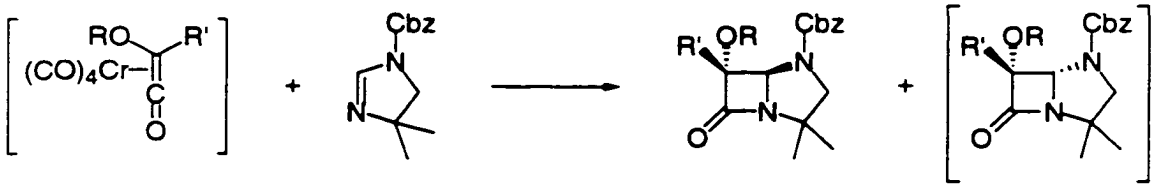
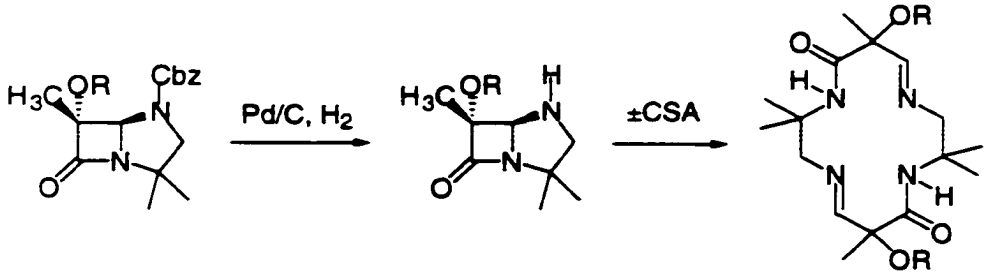


Figure 3.5 Observed diastereoselectivity in N-protected azapenam formation

stereocenters are produced but only the azapenam with the two heteroatoms *anti* is observed. Thus, with a racemic imidazoline only a racemic mixture of *anti* azapenams is produced.

It was discovered in the course of studying azapenams that when deprotected (Equation **3.5**), the azapenam was not stable under acidic conditions



(3.5)

undergoing a very efficient dimerization to give bis-imine dioxocyclams.[10] The mechanism of this reaction appears to be an acid catalyzed ring scission followed by dimerization/metathesis of the resulting cyclic imine (Figure **3.6**).

When a racemic mixture of the azapenam is used, two diastereomers of the bis-imine dioxocyclam are produced. The cycloaddition/cycloreversion reaction is reversible and the two diastereomers are in equilibrium in solution (Figure **3.7**). This equilibrium was demonstrated by a series of exchange studies.[11] This equilibrium was also suggested by the observation that recrystallization of the diastereomeric mixture gave only the centrosymmetric isomer in 85% yield in spite of the fact that it was present to an extent of only 50% in the solution.

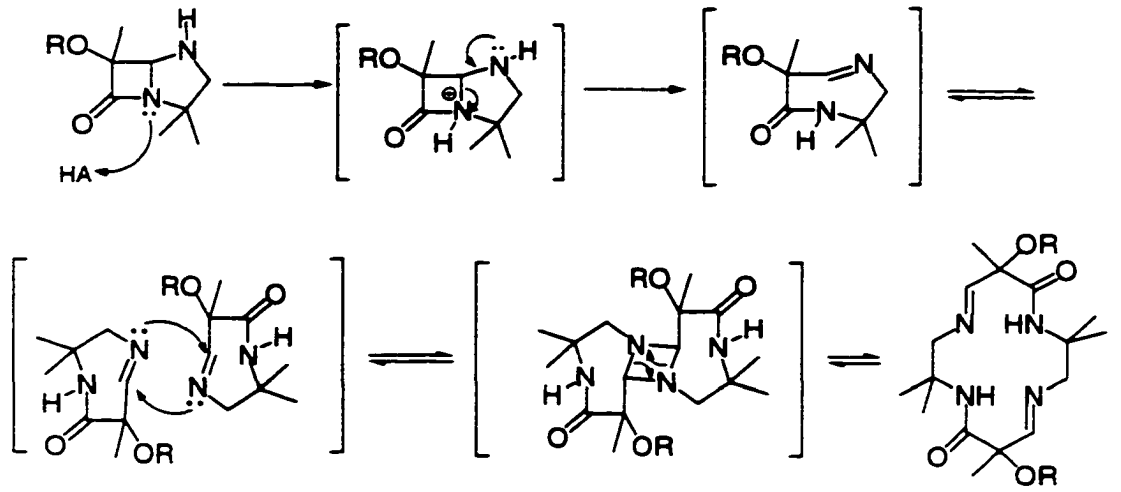


Figure 3.6 Mechanism of azapenam dimerization to dioxocyclams

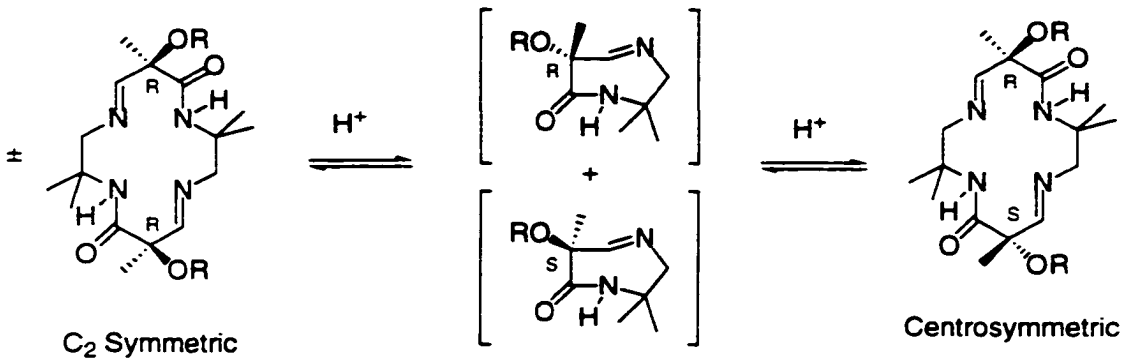
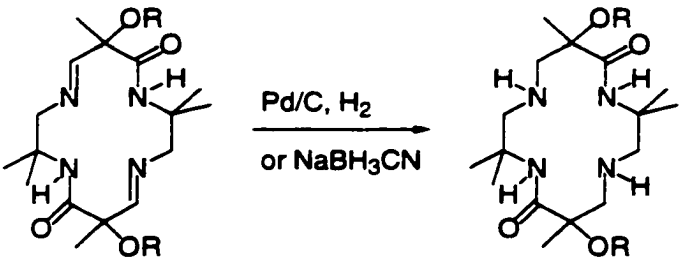


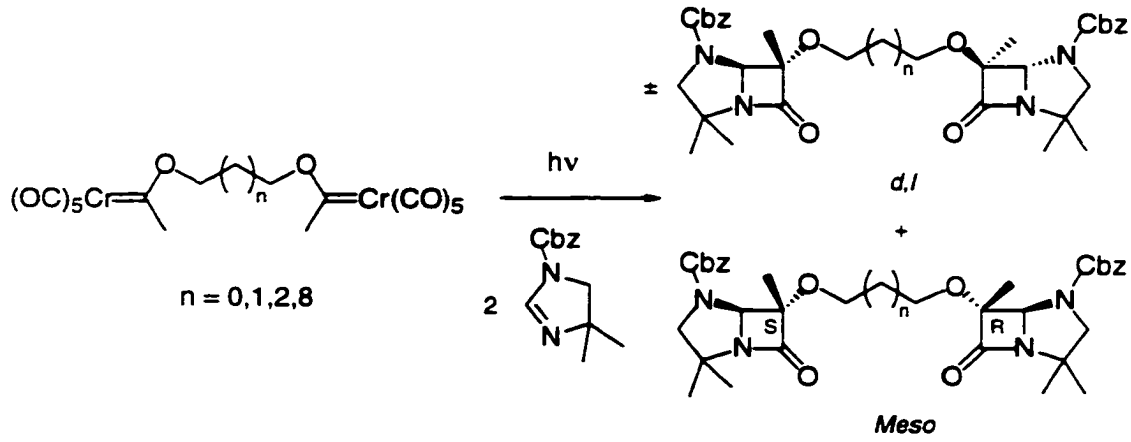
Figure 3.7 Bis-imine dioxocyclam diastereomers

During crystallization the less soluble centrosymmetric isomer selectively crystallized, shifting the equilibrium mixture over to the centrosymmetric isomer. This equilibrium was halted when the imines were reduced to the secondary amines (Equation **3.6**).



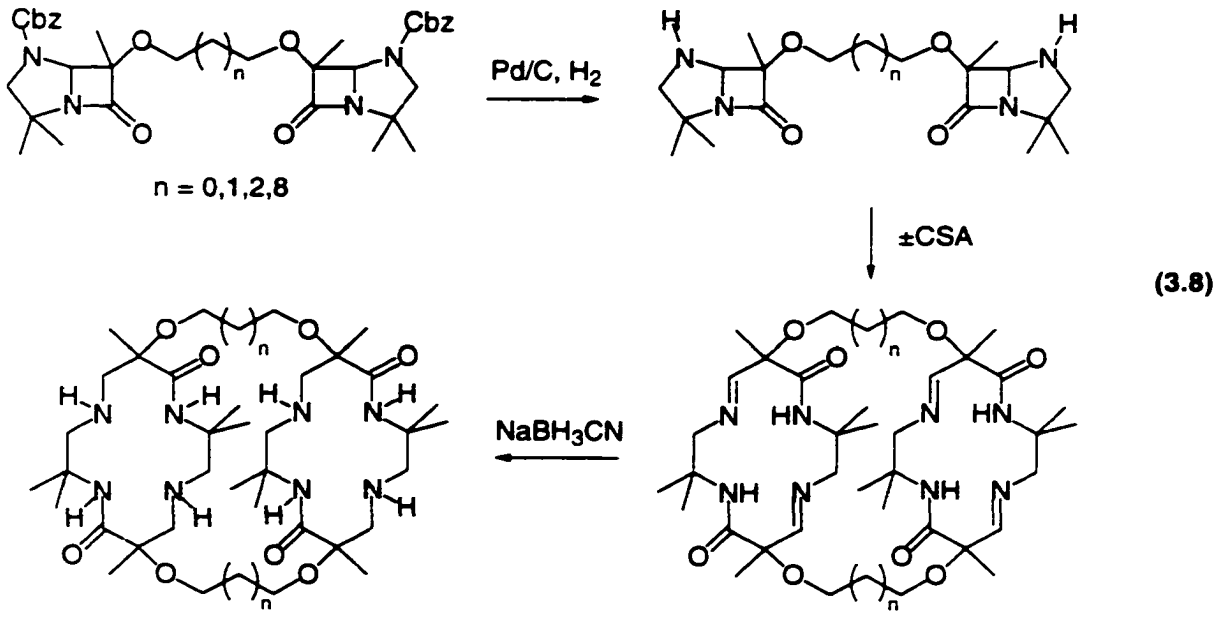
(3.6)

As an extension of this work, the synthesis of bis-dioxocyclams was developed.[12] When bis-carbenes were photolyzed in the presence of a protected imidazoline, bis-azapenams were produced (Equation 3.7). Two diastereomers



(3.7)

that differ by the absolute configuration of the alkoxy bearing carbon on the β-lactam were produced in this reaction. The racemic, *d,l* diastereomer had the same absolute configuration at the alkoxy bearing carbons, either R,R or S,S. The achiral *meso* diastereomer had opposite configurations at the alkoxy carbons. These diastereomers were separable for some bis-azapenams, especially when the alkyl bridge between the two azapenams was relatively short. When the protecting groups were removed the bis-azapenams underwent the imine cycloaddition /cycloreversion seen in the mono-dioxocyclam cases (Equation 3.8). This



(3.8)

dimerization process showed remarkable diastereoselectivity. Both the *meso* and the racemic *d,l* diastereomers showed a strong preference for formation of "homo" dimers, in which two cyclic imines of like configuration (R=R, S=S, R≠S) came together to give cyclams in which the chiral centers had the same configuration. Formation of the first cyclam ring by "homo" dimerization places the two remaining cyclic imines on the same face, in perfect alignment to undergo reaction. In contrast, an initial "hetero" cyclization would place the cyclic imines on opposite faces, making subsequent cyclization more difficult. Because dioxocyclam formation is reversible, the less favored heterodimer precursor can reopen, then homodimerize (Figure 3.8).

The photolysis of chromium carbene complexes with optically active imidazolines proved to be not only diastereoselective but also highly enantioselective. Two different classes of optically active imidazolines were developed to produce optically active azapenams. The first class of imidazolines contained a tertiary stereocenter derived from various amino acids (Equation 3.9).

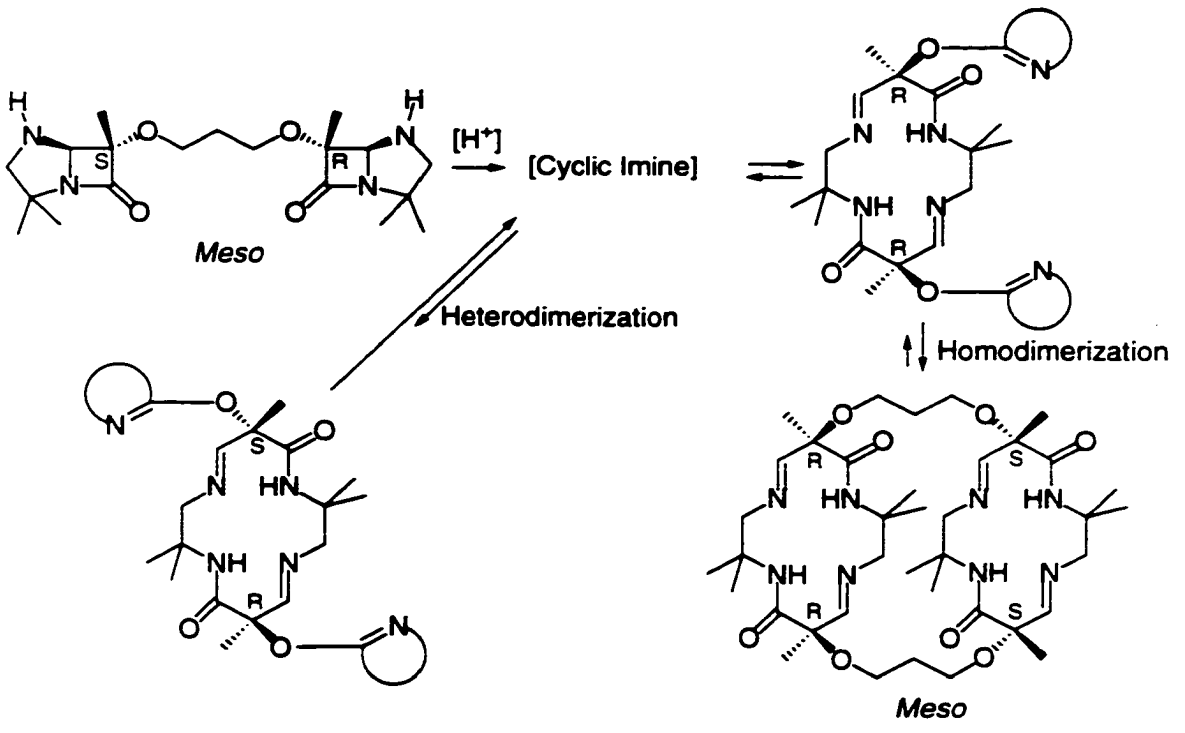
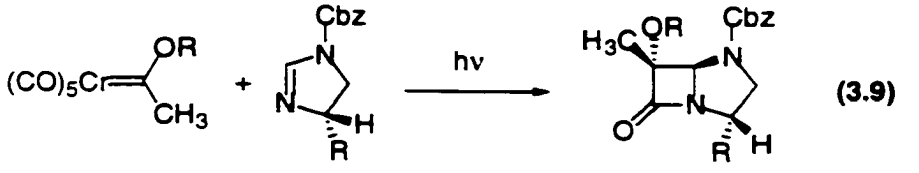
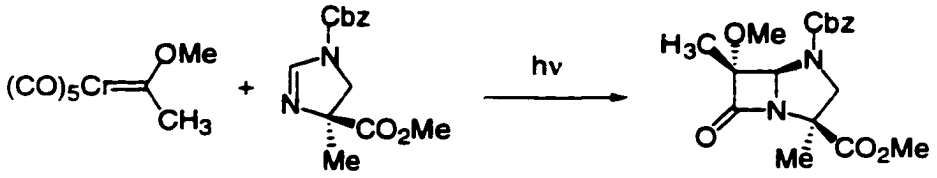


Figure 3.8 Dimerization of bis-azapenams



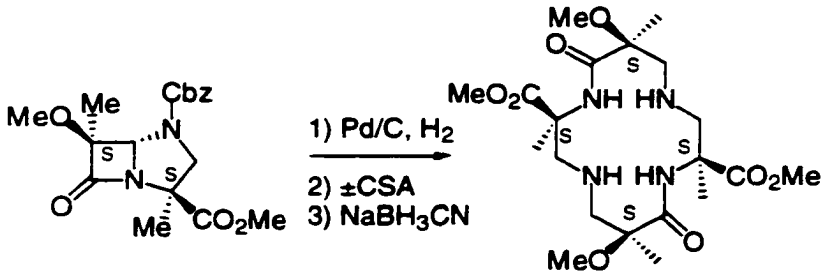
R = iPr, Me, Ph

The efficiency of the photoreaction with these imidazolines was low, due to the surprising instability of the monosubstituted imidazolines. Geminal substitution greatly enhanced imidazoline stability, and the yields improved when the second class of imidazolines, which had a quaternary stereocenter, was used (Equation **3.10**).[13]

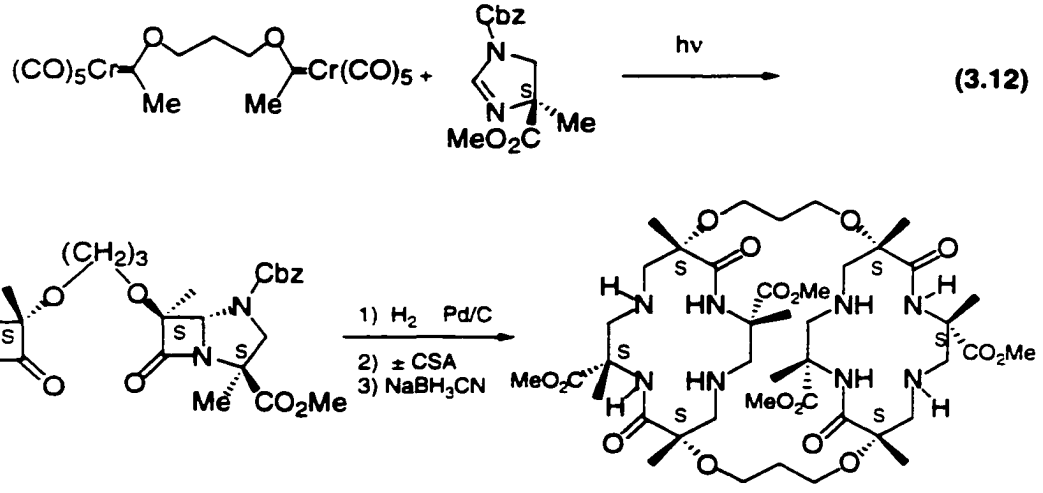


(3.10)

The single enantiomer of the azapenam then underwent the cyclization reaction to produce an optically active C_2 symmetric dioxocyclam (Equation **3.11**). The use of optically active imidazolines was extended to produce optically active bis-dioxoxyclams (Equation **3.12**) . This is a very efficient use of chirality, in that in



(3.11)

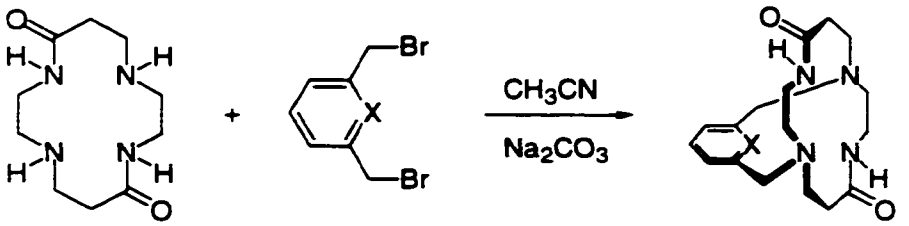


(3.12)

just three steps and from a single stereocenter a chiral molecule with eight stereocenters can be produced.

The above chemistry provided ready access to a range of 5,12 dioxocyclams. Recently, Guilard has developed a method for the modification of

5,12-dioxocyclams. Guilard's modification placed a "cap" across a 5,12-dioxocyclam by alkylating the two amine nitrogens with a bis-electrophile.[14] In the capping reaction, the two *trans* amide nitrogens were non-nucleophilic, and were not alkylated, leaving the 1,8 amines to react with the bis-electrophile thus capping the dioxocyclam ring with an phenyl, or pyridyl ring (Equation 3.13).



(3.13)

Guilard used simple, unsubstituted 5,12 dioxocyclam in his capping studies. Hegedus' methodology produces, highly functionalized and even optically active 5,12 dioxocyclam. Merging the two chemistries could produce highly functionalized dioxocyclams that have one face blocked. Also if a pyridyl group is used as the capping agent, a fifth coordination site is attached, thus changing the coordination geometry presented by the dioxocyclam from square planar to square pyramidal..

3.B. RATIONALE

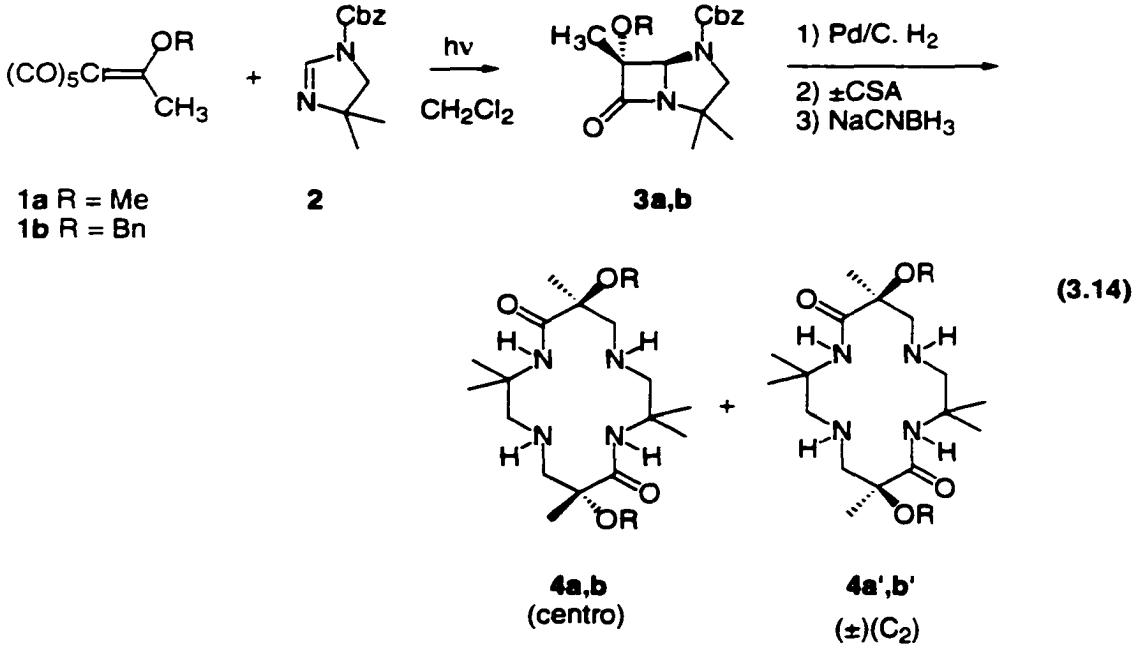
With acid catalyzed azapenam dimerization as a source for 5,12-dioxocyclams of novel substitution patterns, capping of 5,12,-dioxocyclams opens up a new class of pentacoordinate ligands. The following section describes the synthesis of capped and bridged 5,12-dioxocyclams and discusses the novel

molecular structures that were produced. Also a copper(II) complex of a capped dioxocyclam was synthesized that had a variable ligand conformation.

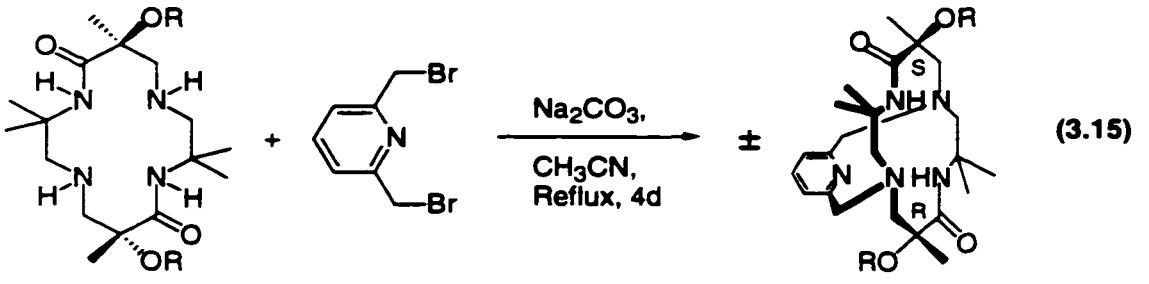
3.C. RESULTS AND DISCUSSION

3.C.1. Capping Studies

The synthesis of (methyl) (methoxy) (**4a, 4a'**), and (methyl) (benzyloxy) (**4b, 4b'**) dioxocyclams was previously reported.[10] From the photolysis of achiral imidazoline **2**, and either (methyl) (methoxy) **1a** or (methyl) (benzyloxy) **1b** chromium carbene complexes, an easily separated mixture of centrosymmetric (**4a,b**) and C_2 symmetric (**4a',b'**) diastereomers was obtained (Equation **3.14**). When the centrosymmetric isomers **4a,b** were subjected to the capping conditions with 2,6-bis-bromomethyl pyridine, racemic mixtures of the respective capped dioxocyclams were produced (Equation **3.15**). Once capped



(3.14)



the amine nitrogens were not free to invert, and thus became stereocenters. The pyridyl cap destroyed the center of symmetry in the dioxocyclam, producing a pair of enantiomers that differed by the absolute configuration at the amine nitrogens. The two faces of the dioxocyclam ring were differentiated as either the R or the S depending on the absolute configuration at the amines (Figure **3.9**)

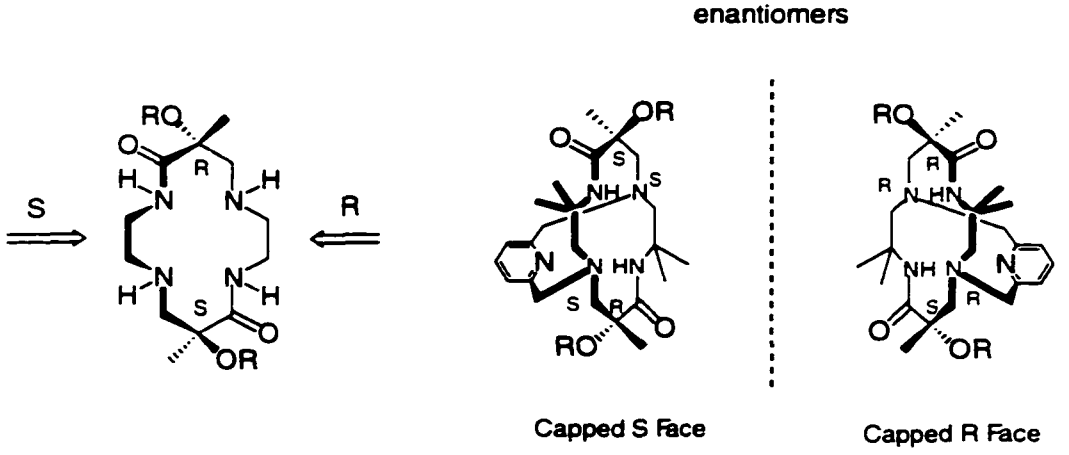
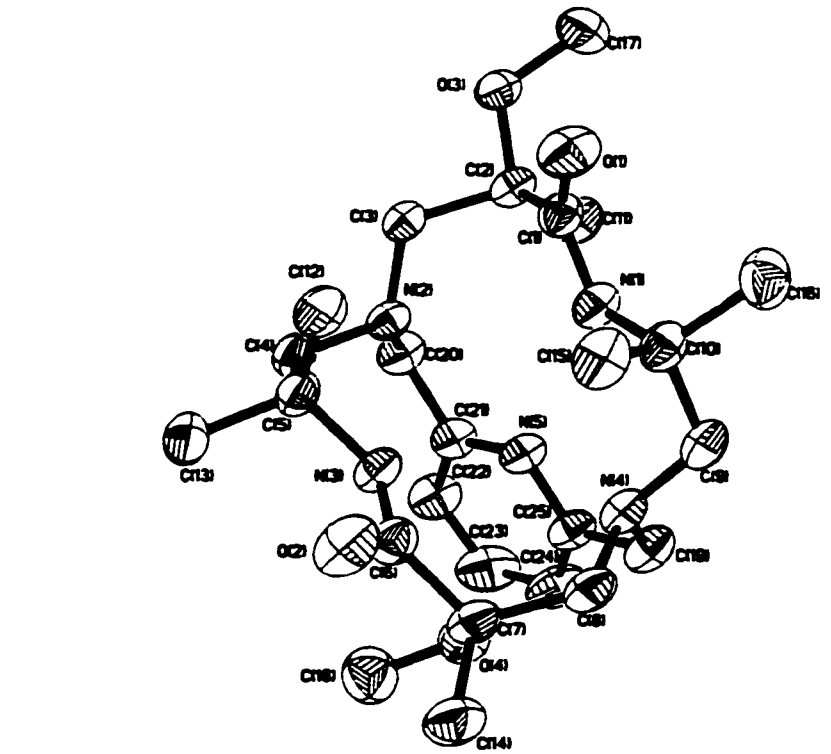


Figure 3.9 Stereochemistry of capped centrosymmetric dioxocyclams

Two distinguishing features were seen in the ^1H NMR spectrum of the capped centrosymmetric dioxocyclam **6a**. First, the two apical methoxy groups in **6a** appeared at different chemical shifts, with one appearing at a typical shift of δ 3.50 while the other is shifted upfield 1 ppm to δ 2.52. Compound **6a** places one

of the methoxy groups in the shielding cone of the pyridyl ring, accounting for the upfield shift. Capping of the dioxocyclam also resulted in the amide protons becoming diastereotopic as evidenced by the 1 ppm difference for their signals in the ^{1}H NMR spectrum. An X-ray crystal structure was solved for **6a** (Figure **3.10**), confirming that the dioxocyclam was capped across the amine nitrogens. The resulting capped dioxocyclam has five possible sites for coordination with two amine nitrogens, two amide nitrogens and a pyridine nitrogen. The 14 membered ring in the capped dioxocyclam is not planar, a feature observed with other dioxocyclams.[12] The amine and pyridine nitrogen lone pairs all pointed into the cavity of the cyclam, with the amide groups bent away from what would have been the plane of the ring. The crystal structure also confirms that one of the methoxy groups (C (18)) is over the aromatic ring which accounts for the shielding if one methoxy group that is observed in the ^{1}H NMR spectrum.

When the C_2 symmetric (methyl) (methoxy) dioxocyclam **4a'** was capped two diastereomers were produced (Equation **3.16**). In the ^{1}H NMR spectrum of the major diastereomer the signal for the two methoxy groups appeared at δ 3.36, and for the minor diastereomer the signal for the two methoxy groups appeared at δ 2.72. Based on the shielding arguments discussed above, the structures of the two diastereomers were assigned. The major diastereomer was capped on the face opposite the methoxy groups and the minor isomer was capped on the face with the methoxy groups. When capped, the C_2 symmetric dioxocyclam retains its C_2 symmetry which accounts for the single signal for the two methoxy groups seen in the ^{1}H NMR spectrum. Also, the starting dioxocyclam was racemic so the capped products are also racemic. From the observed product ratio the ring face containing the methoxy groups is more hindered than the face containing the two methyl groups, thus limiting the capping of that face.



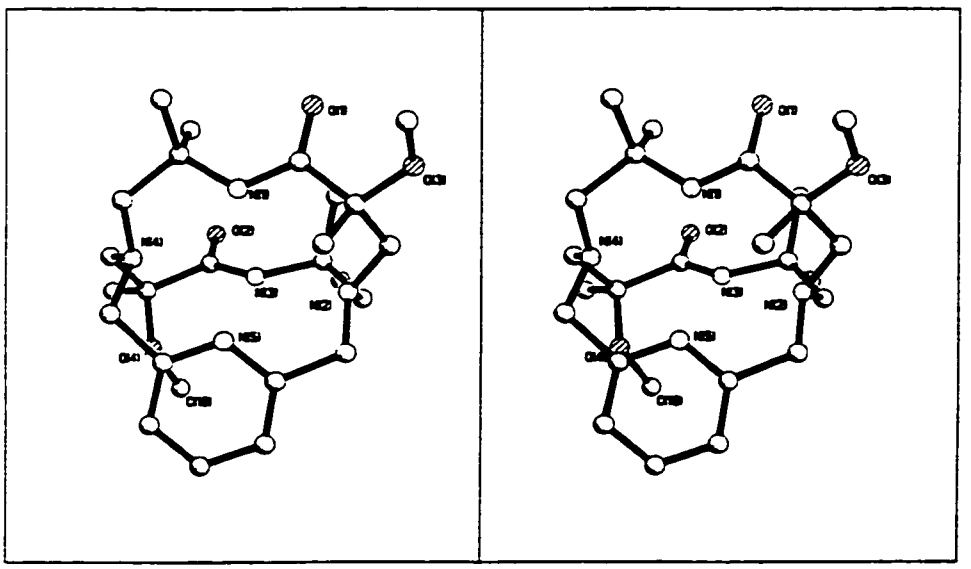
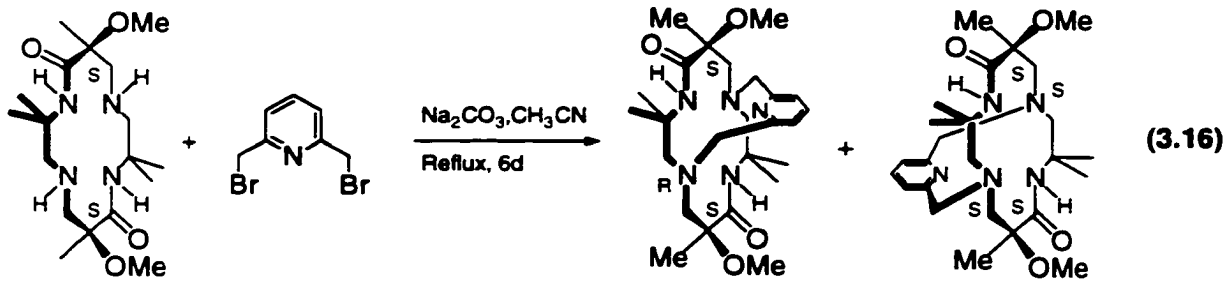


Figure 3.10 X-ray structure and stereo view of **6a**



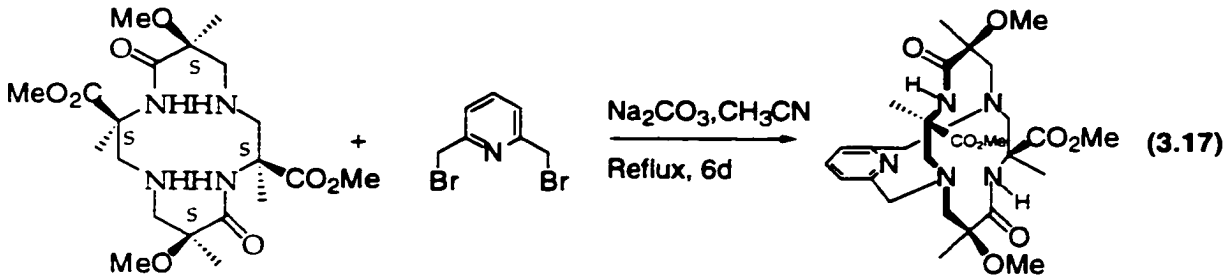
(±)4a'

(±) 7
25%

(±) 8
56%

(3.16)

When optically active (+)-(methyl)(methoxy) dioxocyclam **+9** was subjected to the capping conditions the reaction proceeded sluggishly, with 45% of the capped product isolated after 6 days at reflux in acetonitrile (Equation **3.17**).



+9

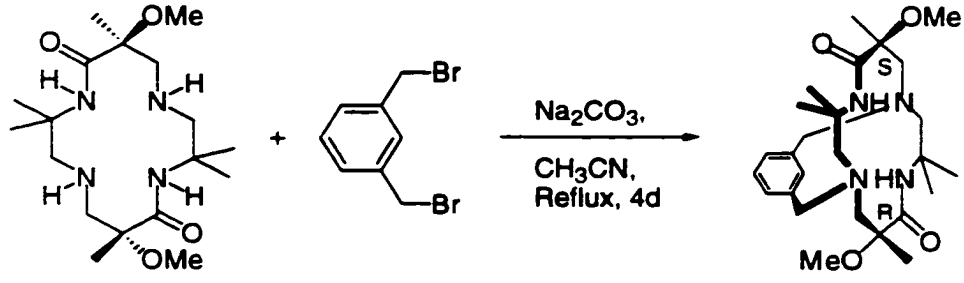
+10

(3.17)

A single isomer was obtained from this reaction, and, based on the ^{1}H NMR spectrum, capping occurred exclusively on the face opposite the methoxy and methyl ester groups. This assignment was based on signal for the methoxy groups which was virtually unchanged from that of **+9** at δ 3.35. The signal for the apical methyl groups was shifted upfield slightly (≈ 0.2 ppm) from that of the starting material indicating that the methoxy group was not over the aromatic ring. The single product indicated, once again, that the face *syn* to the methoxy

and methyl esters was more congested than the face containing the methyl groups.

Finally centrosymmetric (methyl) (methoxy) dioxocyclam **4a** was capped with α–α'-dibromo-*m*-xylene (Equation **3.18**), producing, in low yield, a xylyl capped dioxocyclam that showed a similar upfield shift of the one of the methoxy signals in the ^1H NMR spectrum. The signal for the isolated aromatic proton is shifted significantly up field (δ 5.90) which can be rationalized by its position within the circle of nitrogens of the dioxocyclam ring.



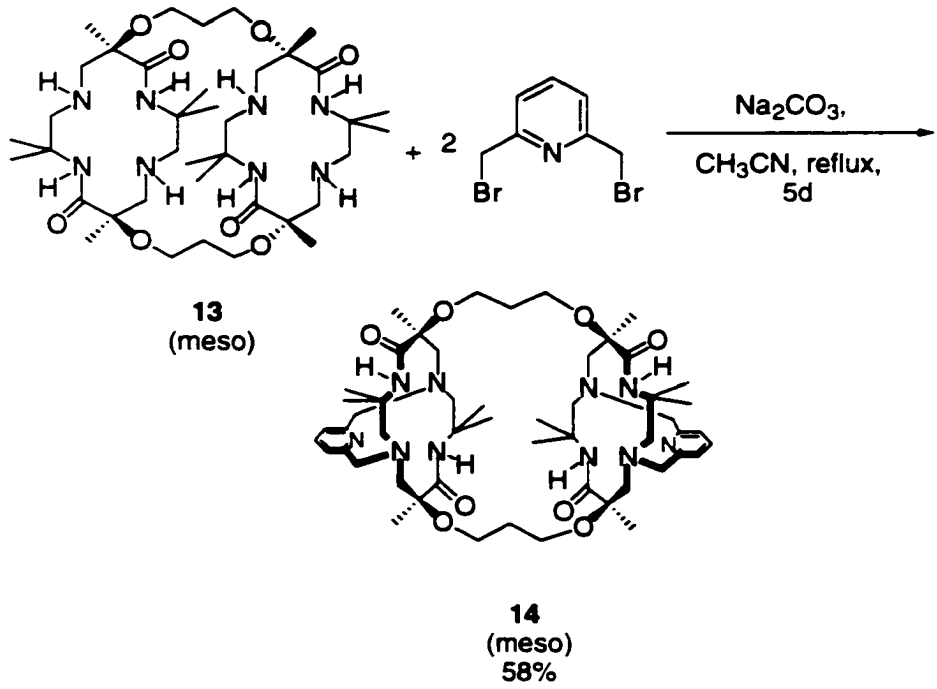
4a **11** **±12** 30%

(3.18)

Bis-dioxocyclams also underwent the capping reaction with 2,6-bis-bromomethyl pyridine, and produced biscapped-bis-dioxocyclams (Equations **3.19**, and **3.20**). These unusual compounds had two, potentially five coordinate ligands that surrounded a well-defined central cavity. The dimensions of the central cavity could be easily controlled by the chain length of the alkyl bridge between the two rings which could be set by the choice of bis-carbene complex used in the photoreaction (Equation **3.7**). The two diastereomers of the bis-dioxocyclams that were available differ in the orientation of the two macrocyclic rings. The meso bis-dioxocyclam **13** had the two macrocyclic rings face to face and the D_2 symmetric bis-dioxocyclam **(±)15** had the two rings at an angle to

each other, analogous to the pages of an open book.[12] Therefore, two different cavities between the two rings are available by choice of diastereomer.

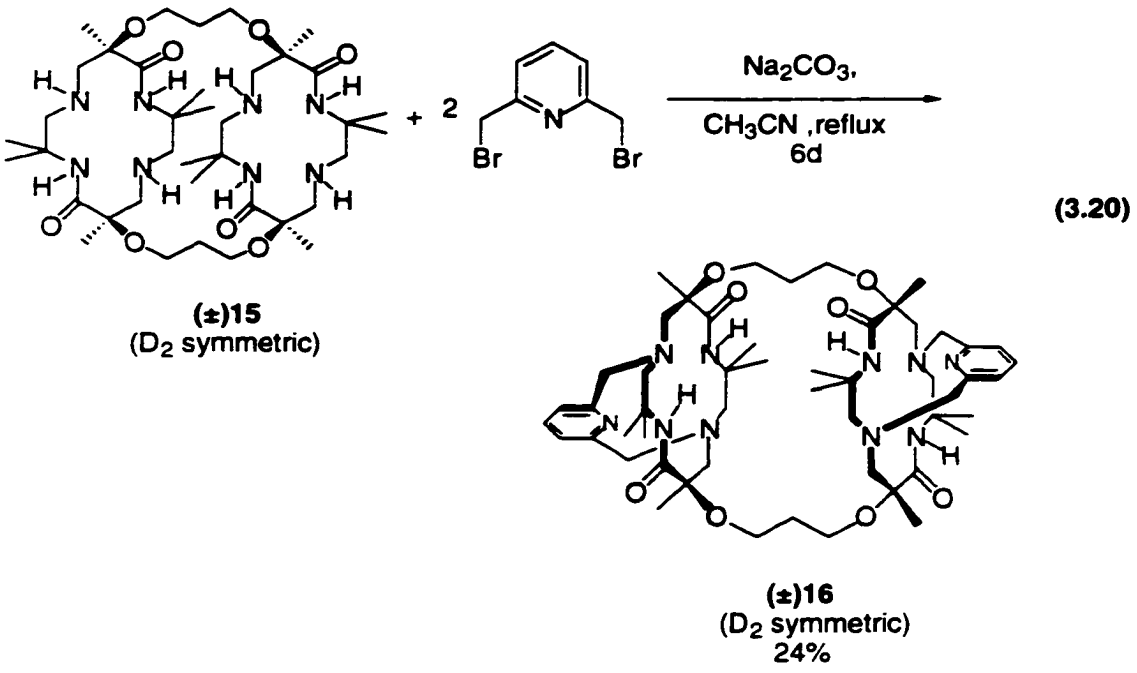
Capping was anticipated to occur on the external face of the rings because of the limited space between the two rings. This was found to be the case. The bridging OCH_2- signals in the ^1H NMR were the same in starting material and capped product. There was a small up field shift (≈0.2 ppm) in the signals of the apical methyl groups, which was consistent with capping occurring on the external faces of the rings. The D_2 symmetric bis-dioxocyclam was also capped in low yield and showed characteristics similar to the meso diastereomer (Equation **3.20**).



13
(meso)

14
(meso)
58%

(3.19)



(3.20)

(±)15
(D_2 symmetric)

(±)16
(D_2 symmetric)
24%

3.C.2. Bridging Studies

A new class of bis-dioxocyclams was generated when two dioxocyclam rings were bridged with a tetramethyl pyrazine ring (Figure **3.11**). When two equivalents of the optically active dioxocyclam **+9** were allowed to react with an equivalent of 2,3,5,6-tetrakis-(bromomethyl) pyrazine, bridged bis-dioxocyclam **+18** was produced. This reaction was very sluggish and after 6 days in acetonitrile at reflux only 10% of the bridged dioxocyclam was isolated and over 60% of the starting dioxocyclam **+8** was recovered. An X-ray crystal structure of **+18** was solved and revealed several interesting features of this compound (Figure **3.12**). As was expected, the face opposite the methoxy and methyl ester groups was bridged. This corroborated the analysis outlined above in the capping studies of **+8**.

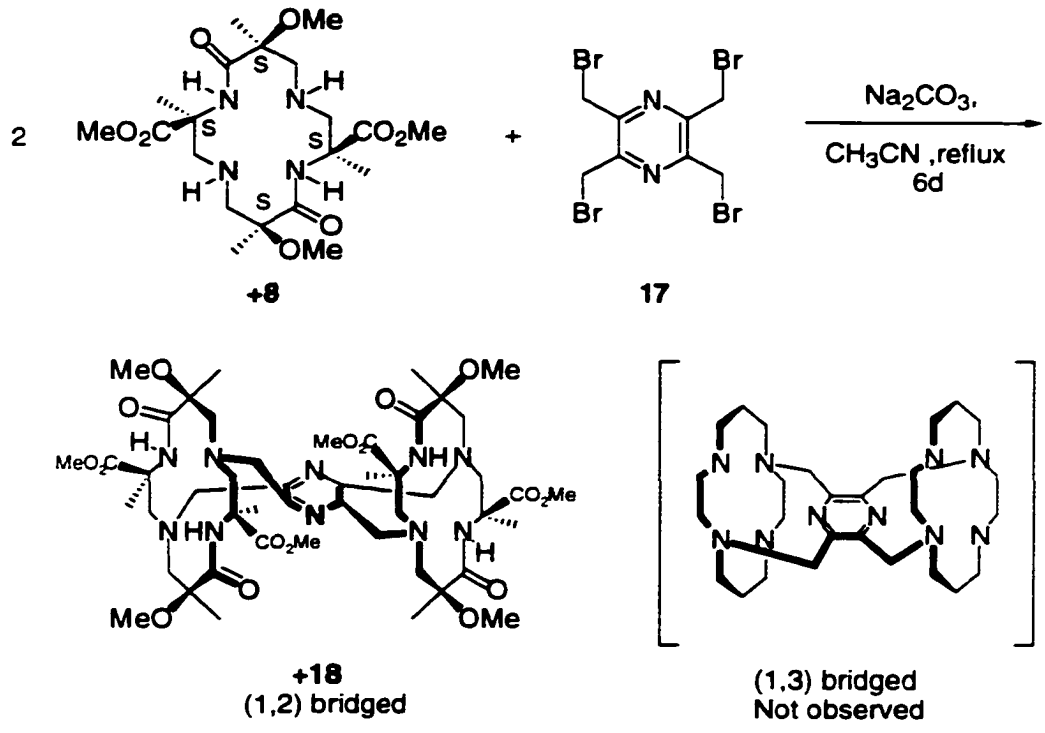


Figure 3.11 Bridging of **+8** dioxocyclam

Tetrakis(bromomethyl)pyrazine can alkylate the dioxocyclam either ortho or meta. With meta alkylation the pyrazine nitrogens are directed into the dioxocyclam ring as seen in the previous capping studies. Ortho alkylation directs the pyrazine nitrogens 90° away from the plane of the dioxocyclam ring.

Unfortunately, when **+8** was bridged only the ortho alkylation was observed. The ortho alkylation directed the pyrazine nitrogens orthogonal to the two dioxocyclam rings The crystal structure of **+18** also showed that, with ortho capping, the amine nitrogens of the dioxocyclam were closer together than were the amines of meta capped dioxocyclam **6a** (N-N distance: 3.62 Å for **+18** vs. 4.49 Å for **6a**). Another apparent effect of ortho capping is that the amine-nitrogen lone pairs no longer point directly at each other as was seen in the crystal structure of capped dioxocyclam **6a**. The bridged dioxocyclam **+18** was modeled with a dummy atom to illustrate the angle between the two lone pairs

(Figure **3.13**). The ortho bridged dioxocyclam also adopts a conformation similar to the *cis V* isomer seen in cyclam complexes.

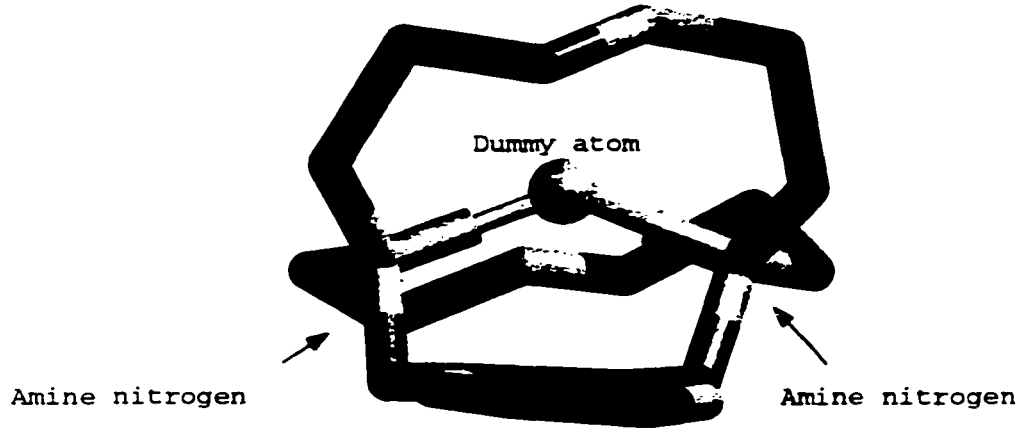


Figure 3.13 Modeling of **+18**, to illustrate the angle between the two amine lone pairs. For clarity only one 14 membered ring is shown

There is also a twist between the two dioxocyclam rings when viewed down the axis through the two rings (Figure **3.14**).

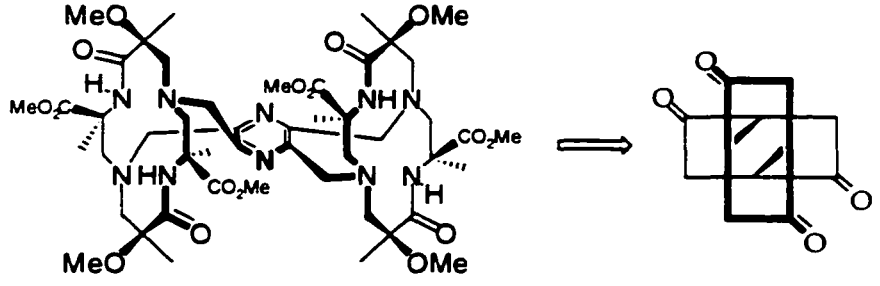
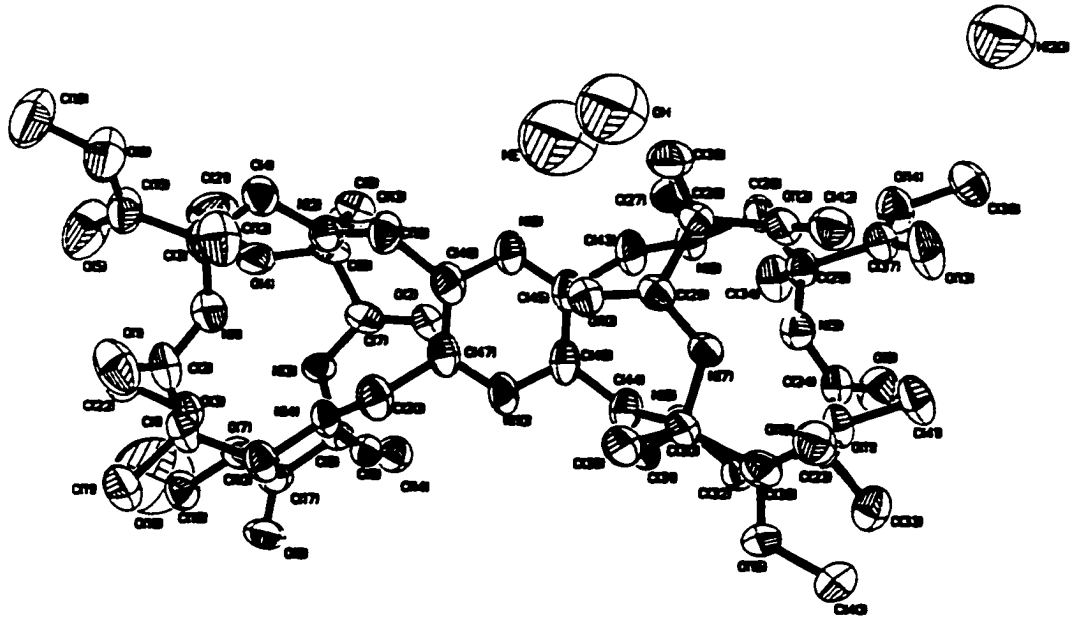


Figure 3.14 Cartoon representation of the twist in **+18**.



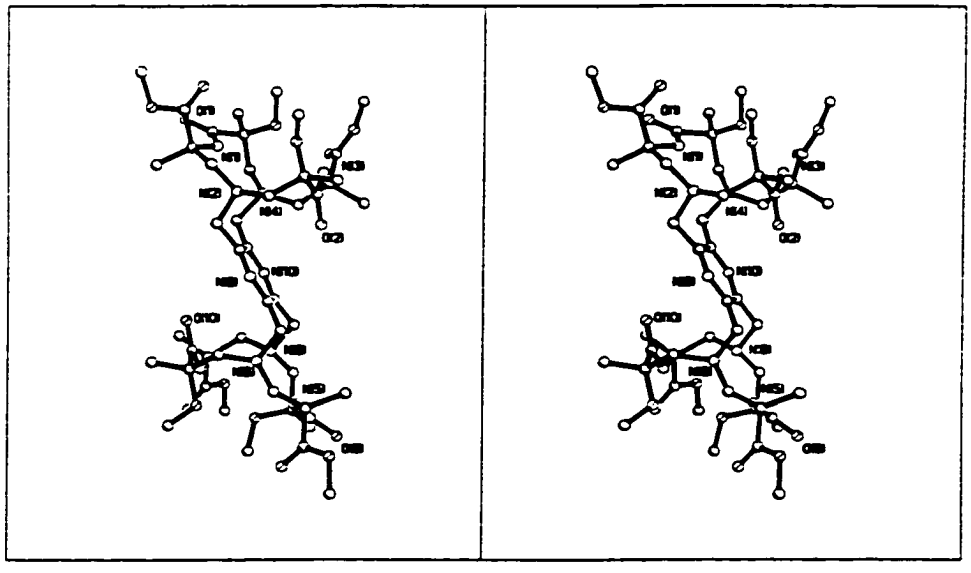


Figure 3.12 X-ray crystal structure and stereo view of bridged bis-dioxocyclam +18

This twist is a result of the bridge linking the amine nitrogens. If the two dioxocyclams are lined up back to back, the amine nitrogens line up on opposite corners (Figure **3.15**). In order to be bridged the two dioxocyclam rings must twist with respect to each other so that the amines line up.

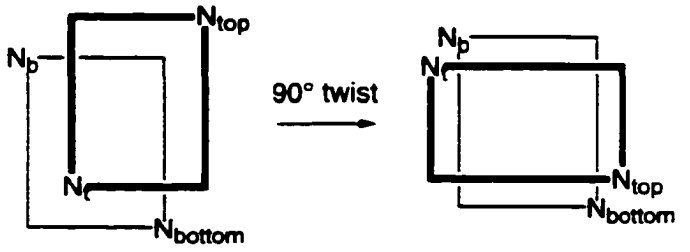
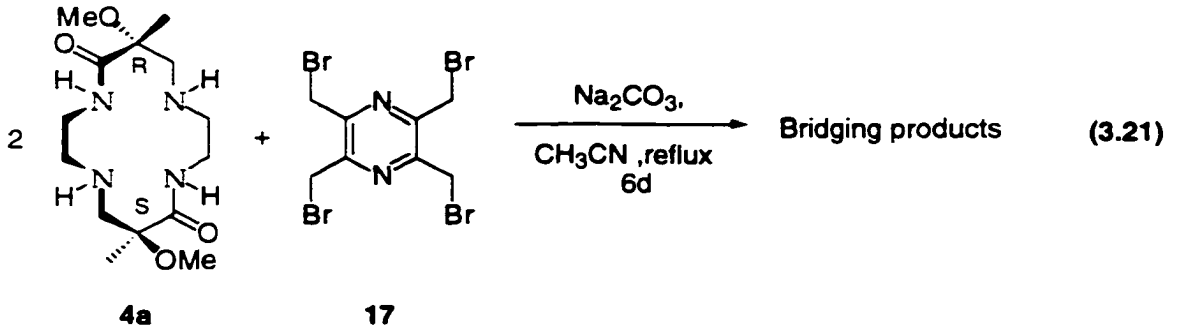


Figure 3.15 Cartoon of back to back orientation of dioxocyclam.

The bridging reaction proved to be much more complex when centrosymmetric **4a** was used (Equation **3.21**). There were two main stereochemical aspects that were considered when the products of the bridging



of centrosymmetric **4a** were analyzed. First, the dioxocyclam ring had two enantiotopic faces that could be bridged. When two faces of like configuration were joined a homodimer was produced, while a heterodimer was formed when two faces of opposite configuration were joined. Second, the absolute configuration at the apical methoxy group was either matched or mismatched with its partner across the bridging pyrazine (Figure **3.16**). Thus, from achiral

starting material, six stereoisomers can be produced. Also, ortho and meta bridging of the pyrazine could have occurred doubling the possible number of compounds to 12. Careful fractional crystallization of the reaction mixture produced a 61% yield of a mixture of just two isomers. X-ray crystal structures of these two isomers were partially solved. Unfortunately, the X-ray data was not able to be refined to a publishable quality, but the structure did show the connectivity. The crystal structures showed that the achiral centrosymmetric **20** and achiral meso **22** isomers were isolated.

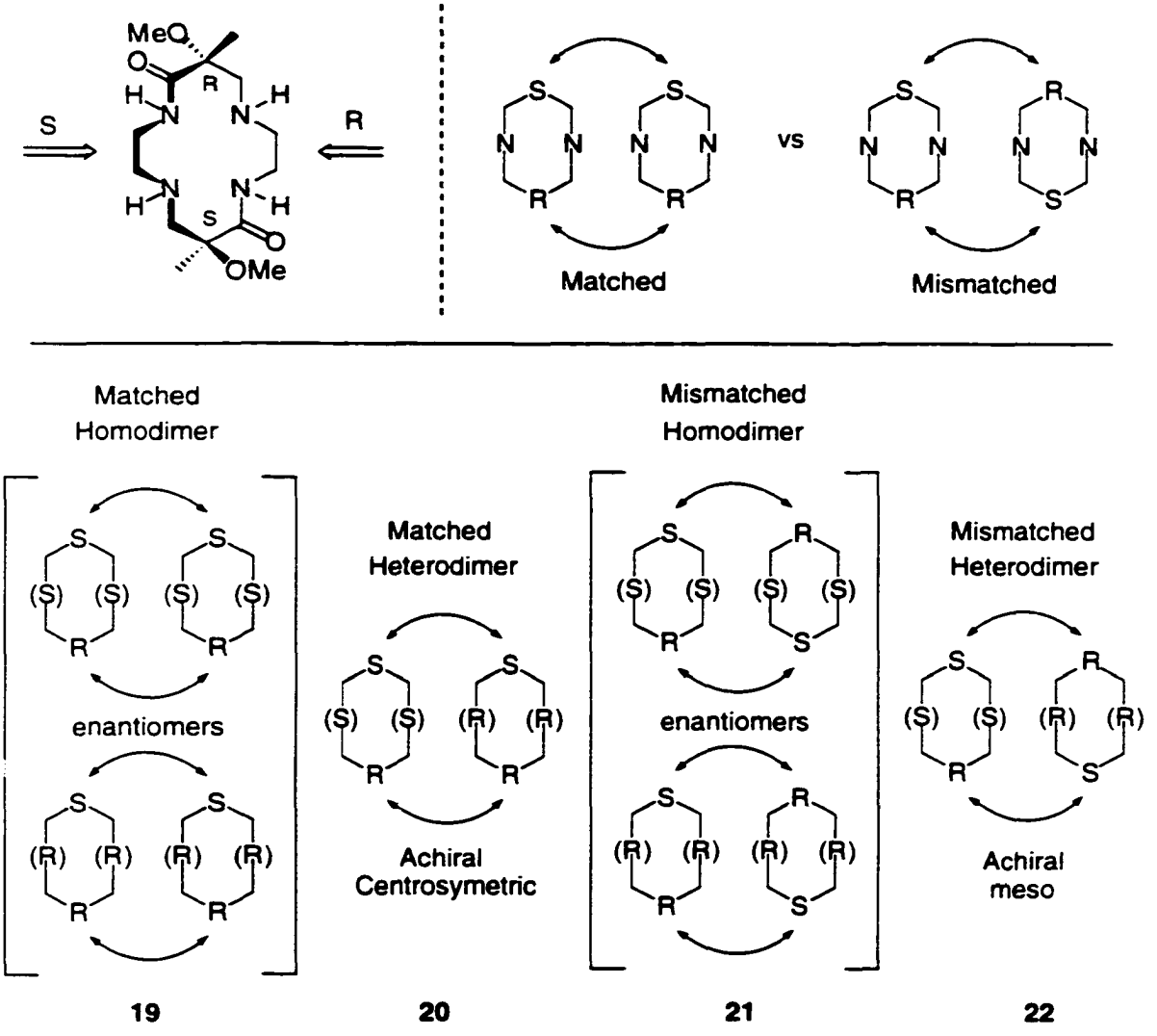
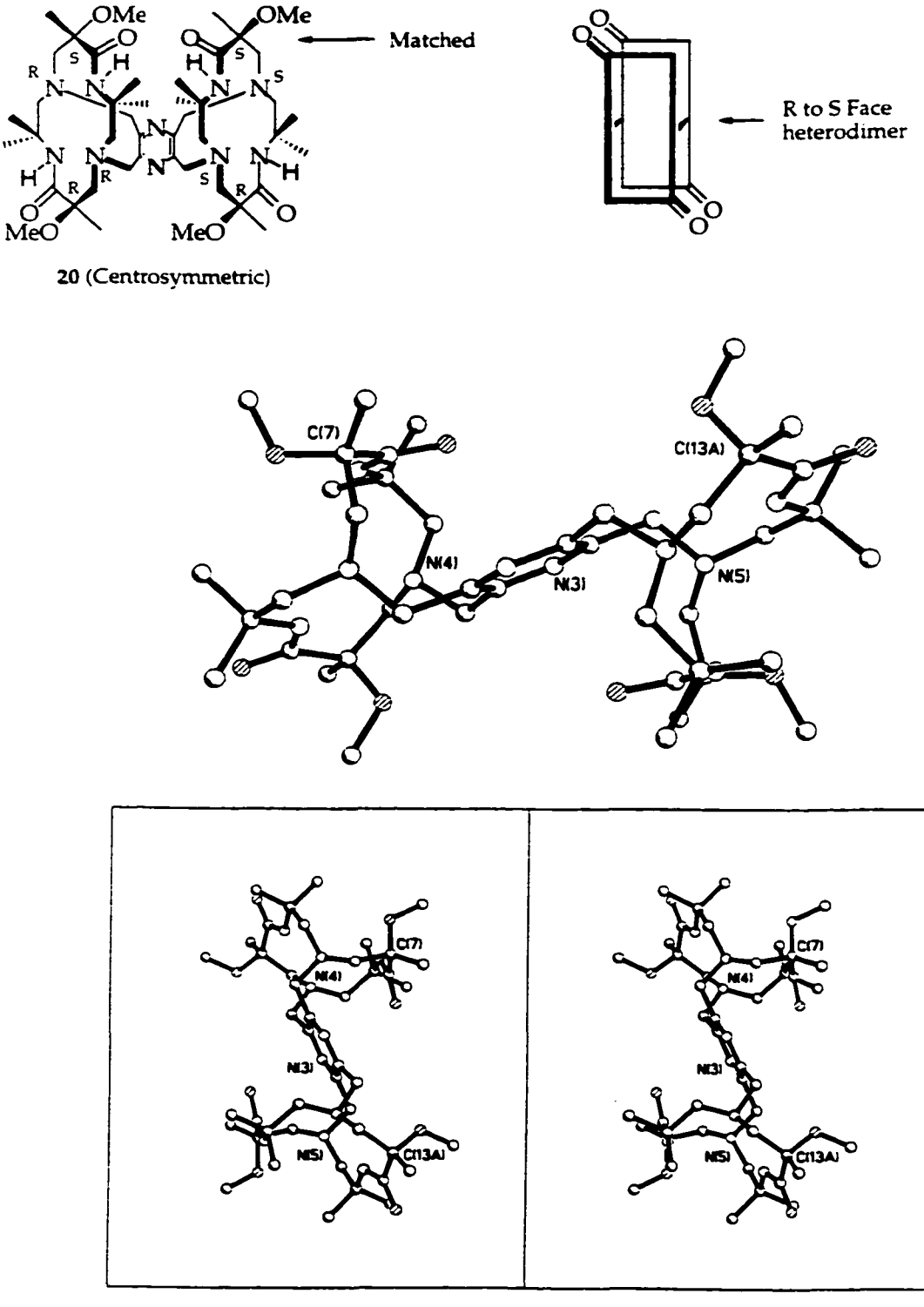


Figure 3.16 Possible bridging products from of centrosymmetric **4a**

From the crystal structure of **20**, the different stereochemical aspects that defined the isomer as centrosymmetric could be seen (Figure **3.17**). The absolute configuration at the apical methoxy groups *matched* (C(7) and C(13A) in Figure **3.17**), and the absolute configuration at the amine nitrogens differed (N(4) and N(5)). The center of symmetry was retained, even with dioxocyclam rings forced into a saddle shape. From the crystal structure of **22** the aspects that defined the isomer as meso could also be seen (Figure **3.18**). The absolute configuration of the apical methoxy groups *did not* match (C(28) and C(49) from Figure **3.18**), and the absolute configuration at the amine nitrogens also differed (N(3) and N(7)). The central pyrazine ring was slightly twisted, which was presumably due to crystal packing forces. The twist of the pyrazine ring destroyed the plane of symmetry between the two dioxocyclam rings.

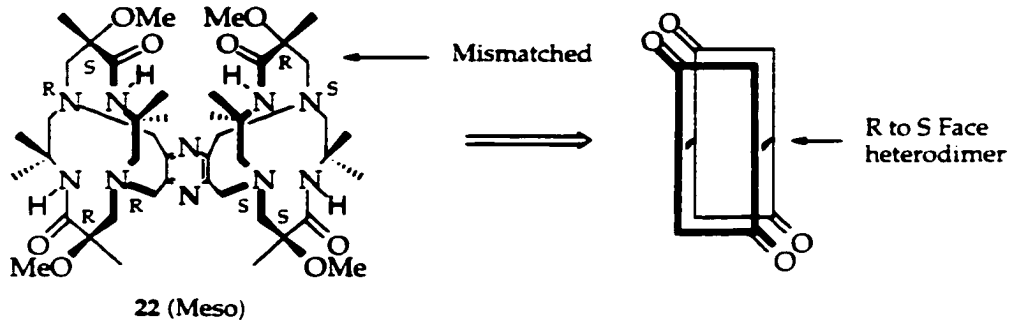
Neither of the racemic bridging products **19, 21** were observed. This could be due to the strain involved in homodimerization, (the yield of the analogous bridged **+18** was very low). Also, no meta alkylation products were observed corroborating what was seen in the synthesis of **+18**. In the ortho alkylated dioxocyclams the two amine nitrogens are much closer together (3.62 Å) than meta capped dioxocyclams (4.17 Å). Thus, once one amine is alkylated by the tetrabromomethyl pyrazine ring closure to the smaller 12-membered ring from ortho capping seems to be favored over ring closure to the larger 13-membered ring from meta capping (Figure **3.19**).



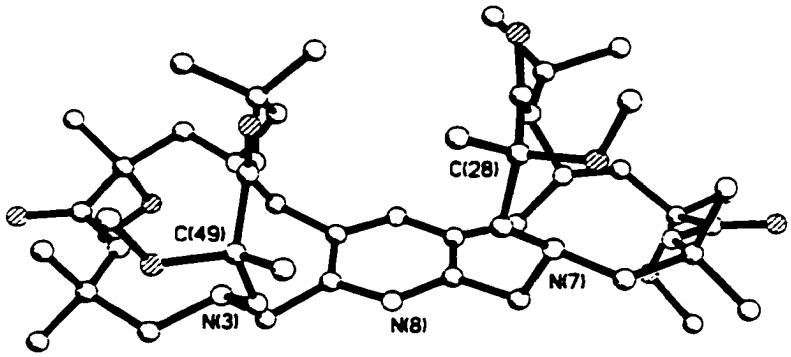
20 (Centrosymmetric)

Figure 3.17 X-ray structure and stereo view of centrosymmetric heterodimer **20**

Hydrogens and included solvent molecules have been removed for clarity



22 (Meso)



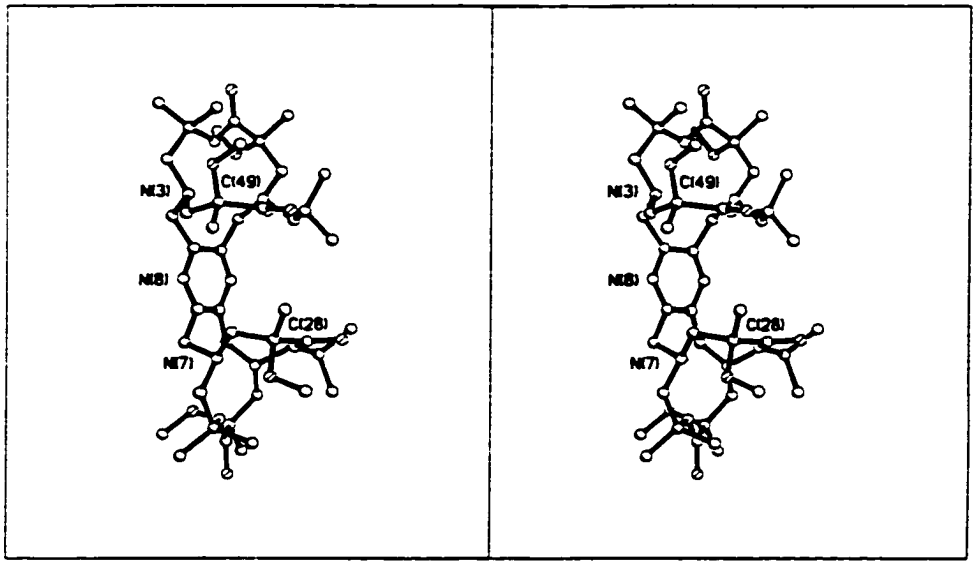


Figure 3.18 X-ray structure and stereo view of meso heterodimer **22**

Hydrogens and included solvent molecules have been removed for clarity

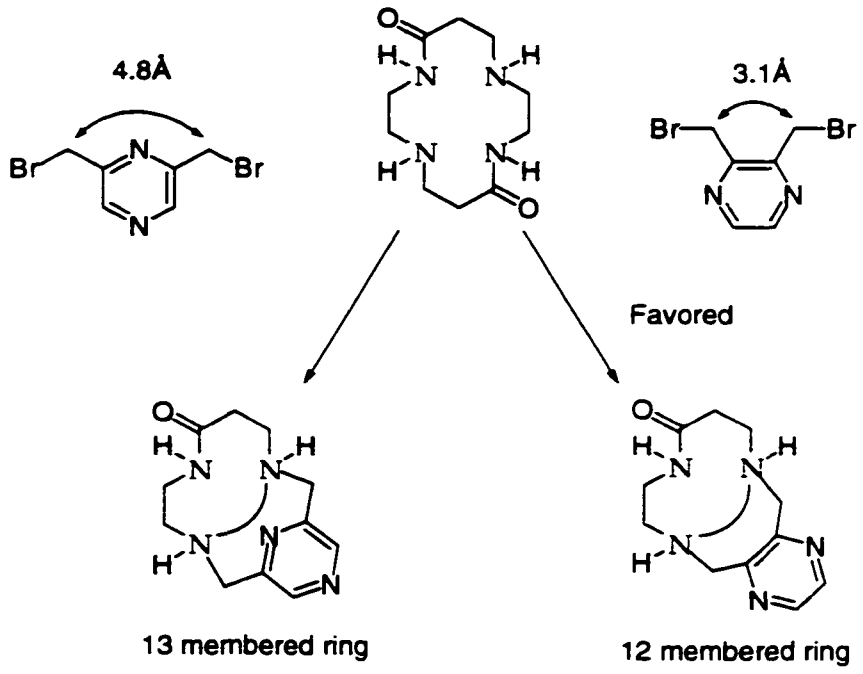


Figure 3.19 ortho vs meta capping by tetrabromomethyl pyrazine

3.C.3. Copper (II) Coordination Complexes

2,6-dimethyl pyridine was chosen as the cap because it added a fifth donor atom to the dioxocyclam ring, thus producing a ligand that could potentially achieve a square pyramidal coordination geometry. There are several examples of copper(II) dioxocyclam complexes with pendant donor atoms that form square pyramidal complexes. Bu has solved X-ray crystal structures of two 11,13-dioxo[13]aneN_4 copper complexes with 1 or 2 pendant quinoline groups.[15] With both complexes, only one quinoline coordinates to the copper(II) center, producing distorted square planar complexes (Figure **3.20**). When two quinoline groups are attached to the larger 12,14-dioxocyclam, both quinoline groups coordinated to the copper center, producing an octahedral complex (Figure **3.21**).[16]

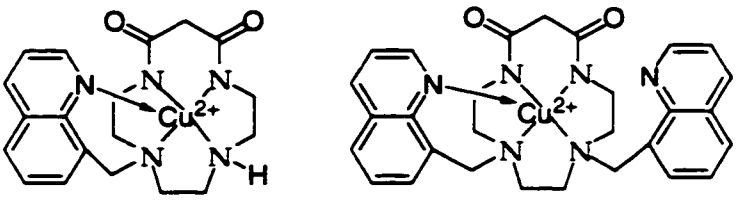


Figure 3.20 Square pyramidal 11,13-dioxo[13]aneN_4 copper(II) complexes

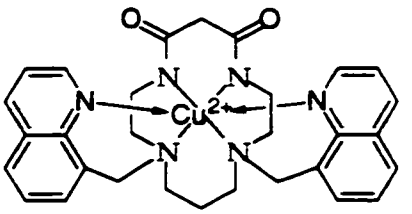
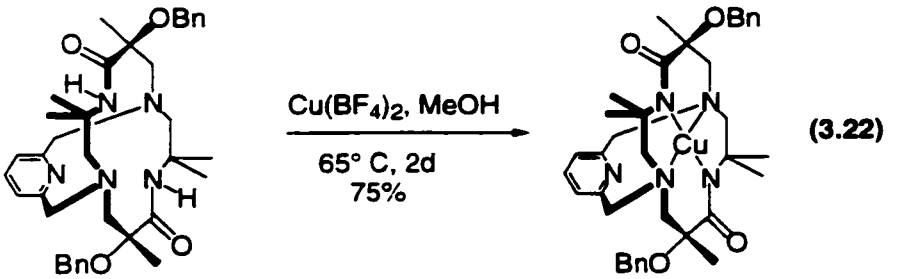


Figure 3.21 Bu's octahedral 12,14-dioxocyclam copper(II) complex

The copper(II) complex of (methyl)(benzyloxy)dioxocyclam **6b** was synthesized using copper bis-tetrafluoroborate as the copper(II) source (Equation **3.22**). Interestingly, the color of the complex in solution was solvent dependent. When the complex was dissolved in water or methanol the solution was blue, and when dissolved in dichloromethane the solution was green. To



6b **23**

test if the color change was the result of solvent coordination to the copper center, pyridine, which coordinates readily to copper (II), was added to the green dichloromethane solution. The pyridine solution showed no color change. The

electronic absorption data for the complex in dichloromethane showed two main absorptions; a very broad and weak absorption at 659 nm (d-d transition) and a stronger absorption at 368 nm (MLCT). In methanol there was also a very broad and weak absorption at 658 nm (d-d transition) and a stronger absorption at 339 nm (MLCT). The d-d transitions occurred at longer wavelength than in other square planar copper (II) dioxocyclam complexes.[12-17] Also, the d-d transition was expected to change if the coordination number at the copper center changed (from 5 with square planar to 6 with octahedral).

Help in the analysis of the solvent-dependent color change came when the complex was crystallized from a mixture of dichloromethane/hexanes. The dichloro-methane solution was green, but *both* blue and green crystals came out of solution. X-ray crystal structures were solved for both the blue **23a** (Figure **3.22**) and green crystals **23b** (Figure **3.23**) of **23**.

Both complexes were five coordinate, with the copper-nitrogen bond lengths virtually identical in both complexes (Table **3.1**). The bond distances were too similar to account for the differences in color of the two complexes.

Table 3.1 Cu-N bond distances in **23a** and **23b**

	Cu-amine distance	Cu-amide distance	Cu-pyridine dist.
23a (blue)	1.95 Å	2.12 Å	2.12 Å
(SP)	1.96 Å	2.14 Å	
23b (green)	1.94 Å	2.10 Å	2.13 Å
(TBP)	1.95 Å	2.10 Å	

What was different was the relative distortions from square pyramidal coordination around the copper center. For the blue complex **23a**, the copper-nitrogen bond angles more closely resembled a distorted square pyramid (SP),

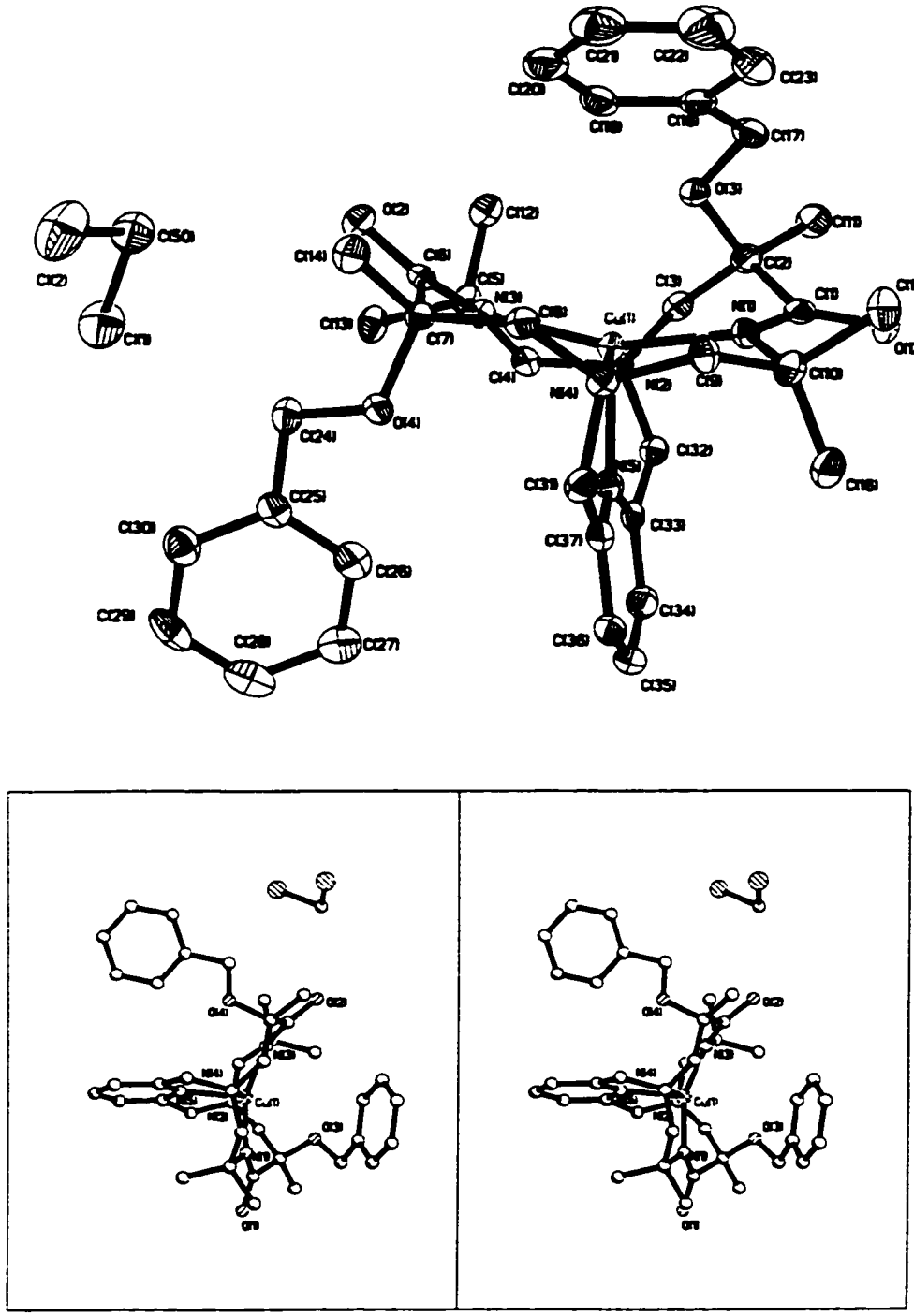


Figure 3.22 X-ray Crystal structure and stereo view of the blue complex **23a**

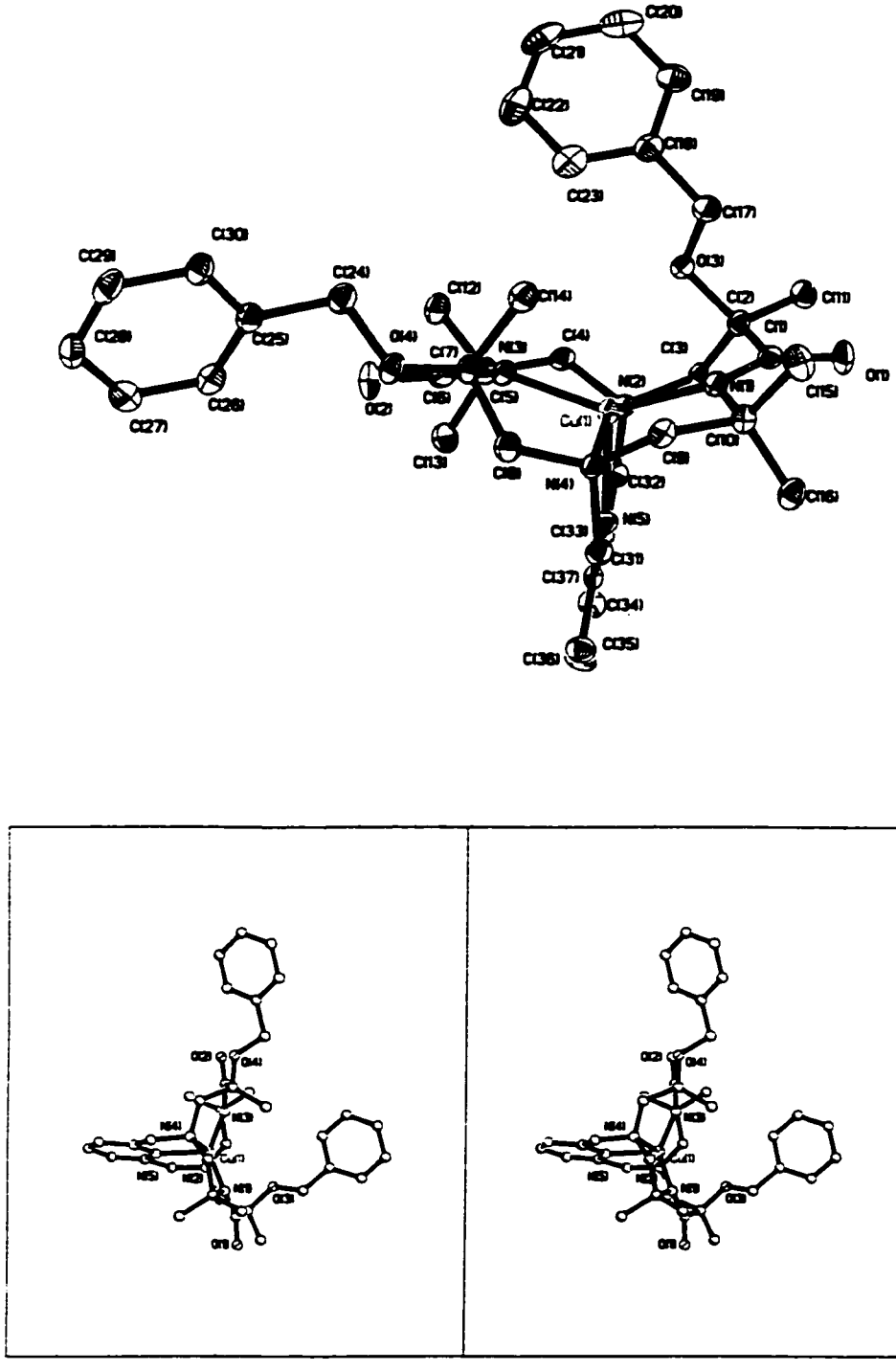


Figure 3.23 X-ray Crystal structure and stereo view of the green complex **23b**

than a distorted trigional bipyramid (TBP) complex (Table **3.2**, Figure **3.24**), and for the green complex **23b**, the copper-nitrogen bond angles more closely resembled a distorted trigional bipyramid (TBP) than a square pyramidal (SP) complex (Table **3.3**, Figure **3.25**).

Table 3.2 Cu-N bond angles for blue complex **23a** compared to ideal angles. The difference between observed and ideal are in parenthesis

	Observed	**Ideal (SP)**	Ideal (TBP)
N(1)-Cu(1)-N(3)	158.0°	**180° (22°)**	120° (38°)
N(1)-Cu(1)-N(5)	96.9°	**90° (6.9°)**	120° (23.1°)
N(5)-Cu(1)-N(3)	105.0°	**90° (15°)**	120° (15°)
N(2)-Cu(1)-N(4)	157.4°	**180° (22.6°)**	180° (22.6°)

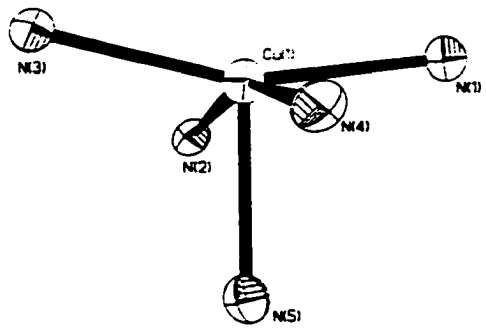


Figure 3.24 Coordination geometry for the blue **23a**

Table 3.3 Cu-N bond angles for green complex **23b** compared to ideal angles. The difference between observed and ideal are in parenthesis

	Observed	Ideal (SP)	**Ideal (TBP)**
N(1)-Cu(1)-N(3)	142.0°	180° (38°)	**120° (22°)**
N(1)-Cu(1)-N(5)	110.3°	90° (20.3°)	**120° (9.7°)**
N(5)-Cu(1)-N(3)	106.8°	90° (16.8°)	**120° (13.2°)**
N(2)-Cu(1)-N(4)	156.8°	180° (23.2°)	**180° (23.2°)**

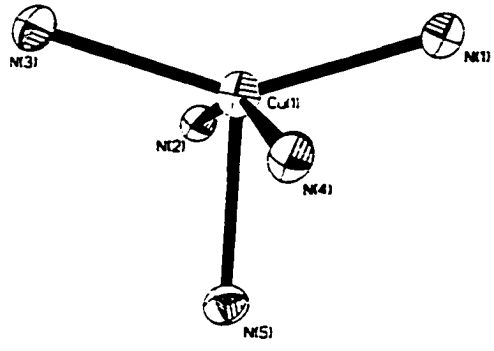


Figure 3.25 Coordination geometry for the green **23b**

What governed the distortions toward either trigional bipyramidal or square pyramidal coordination appears to be the conformation of the metallacyclohexanes formed by the copper center, one amine nitrogen, one amide nitrogen, and a propylene bridged that contains the benzyloxy group (Figure **3.26**). The metallacyclohexane conformations were, in turn, affected by the orientation of the benzyloxy group. In the blue complex **23a**, the metallacyclohexane was in a pseudo chair conformation with the benzyloxy group in a pseudo axial orientation (Figure **3.27**). In the green complex **23b**, the metallacyclohexane was in

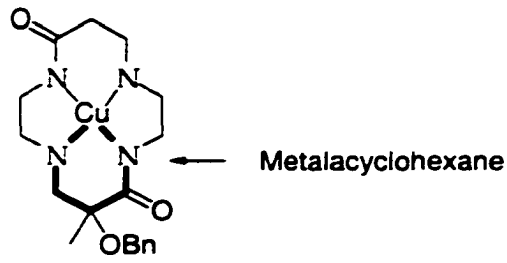


Figure 3.26 Structure of metallacyclohexane

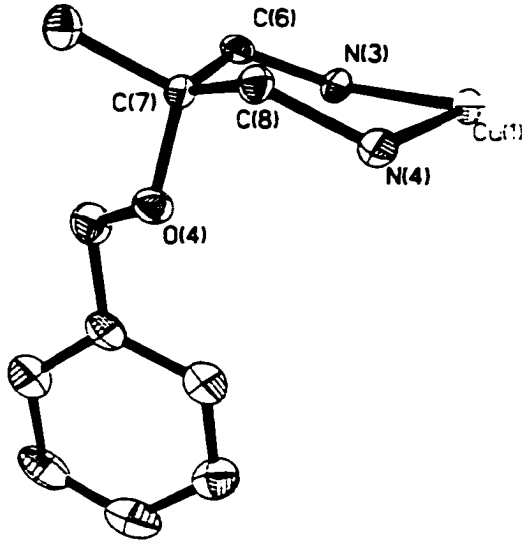


Figure 3.27 Metallacyclohexane conformation for the *blue* complex **23a**

in a pseudo boat conformation with the benzyloxy group in a pseudoequatorial orientation (Figure **3.28**). In the crystal structure of the blue complex **23a**, (Figure 3.22) a molecule of dichloromethane was included within the crystal lattice.

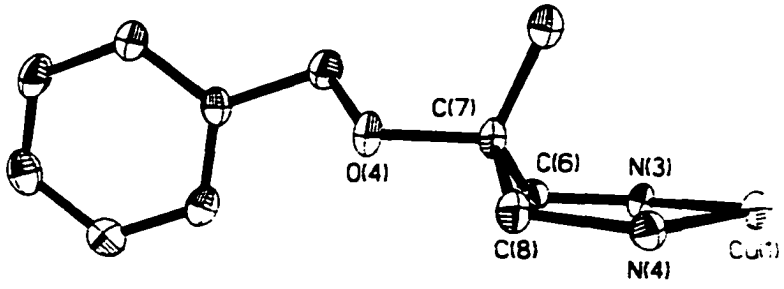


Figure 3.28 Metallacyclohexane conformation for the *green* complex **23b**

Relating solid state structures to solution structures is always risky, but some conjecture can be proposed relating the two. The blue structure **23a**, appears more compact than the green structure of **23b**, with the hydrophobic benzyloxy group tucking closer to the rest of the molecule. In the green structure **23b**, the benzyloxy group is further away from the rest of the complex. For the green structure **23b**, the calculated Connolly surface[18] area is 50Å^2 larger than the surface area calculated for the blue structure. Connolly surfaces are calculations that give a qualitative measure of the surface area of a molecule that is exposed to solvent. The calculated surface areas lend some support to the idea that the blue configuration is slightly more compact than the green. If these structures are present in solution it would stand to reason that in more polar solvents the hydrophobic benzyloxy group would retract thus exposing the benzyl group to less of the polar solvent. When the benzyl group retracts, the structure becomes more compact. In less polar solvents the benzyloxy group is better solvated and so it can move away from the rest of the molecule expanding

the structure. This could explain why the solution is blue when the complex is dissolved in more polar solvents (methanol and water). The blue color would indicate a more compact structure. In a less polar solvent (dichloromethane) the structure can expand, adopting the green conformation. More experiments need to be performed to demonstrate the correlation between the solid state structure and the solution state to explain the color change in different solvents. The color change does show that there is a solvent dependence to the electronic environment of the copper centers, giving strength to the idea that the electronics of the metal can be "tuned" by choice of ligand and, also, choice of solvent.

3.D. SUMMARY

Capping of dioxocyclams produces a new class of pentacoordinate ligands. These new ligand are highly functionalized, and many complex stereochemical issues are inherent to these ligand systems. The complexity of these stereochemical issues is demonstrated by the six stereoisomers that can be produced by the dimerization of achiral dioxocyclams. Further, metal complexes of these pentacoordinate ligands have some unexpected properties. A copper complex of one capped isomer shows that differences in ligand conformation can effect the electronic absorption spectrum (color) of the complex. These results demonstrate the utility of these five coordinate complexes and show the promise for the development of more complex ligand systems based on capping and bridging of dioxocyclams.

3.E. FUTURE DIRECTIONS

Several directions can be envisioned for the study of capped and bridged dioxocyclams. Capping agents other than pyridine and xylene could be used to produce many different effects. For example if 2,6 dibromomethyl pyrazine were to be used as a cap, a site for coordination *opposite* the dioxocyclam complexed metal center is produced . This external coordination site could be used to link two capped dioxocyclams through a second metal center, or allow the capped metal complexes to self assemble in solution (Figure **3.29**). If there is communication between the metal centers through the pyrazine aromatic systems, these supramolecular assemblies begin to resemble molecular wires[19].

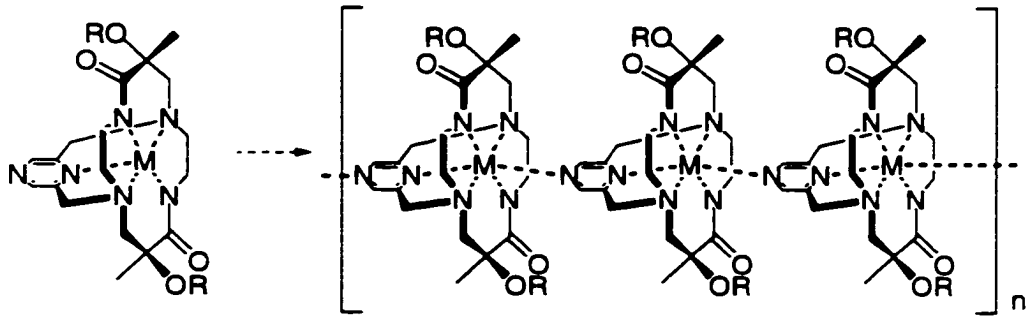


Figure 3.29 Possible self assembly for pyrazine capped dioxocyclams

Several interesting structures can also be devised by bridging the dioxocyclam rings with different groups. First the distance between the two dioxocyclam rings can be controlled, and if aromatic bridges are used, communication between two metal centers coordinated by the dioxocyclam rings through the bridge could be possible. Also, bent bridges can be used to study the effects of the orientation on electronic communication between two coordinated metals (Figure **3.30**). The problem of ortho vs. meta capping should not arise with longer bridges also simplifying matters.

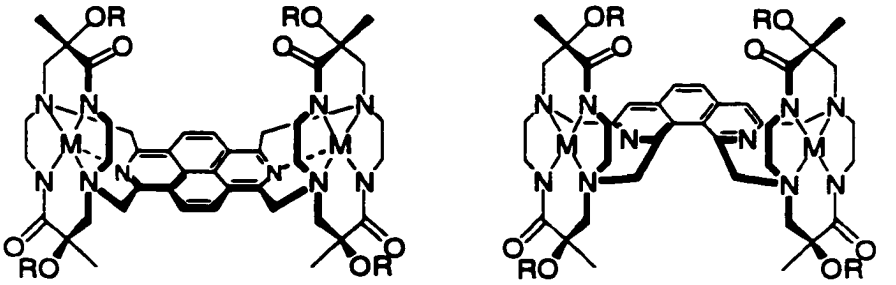


Figure 3.30 Possible long and bent bridged metal complexes .

If bipyridine is used to bridge to dioxocyclam an interesting structure in which the two rings are free to rotate with respect to each other is produced. If an isomer of pyrimidine is used to bridge the two rings a third coordination pocket can be formed. If a metal such as ruthenium were coordinated by the pyrimidine the rotation of the two rings would no longer be possible, thus locking them into one orientation (Figure **3.31**).

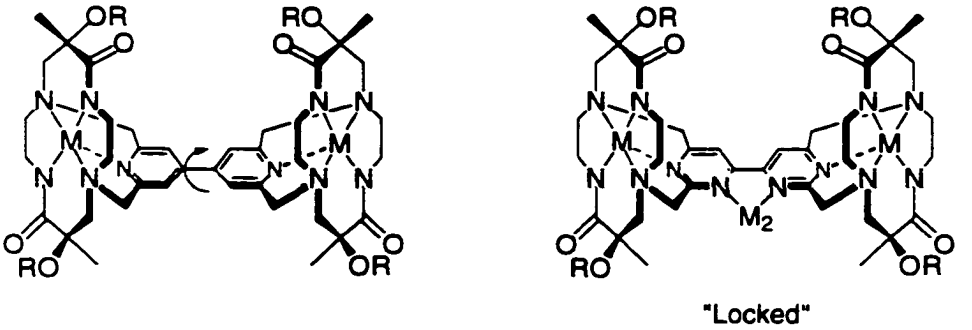


Figure 3.31 Rotating and "locked" bridged metal complexes

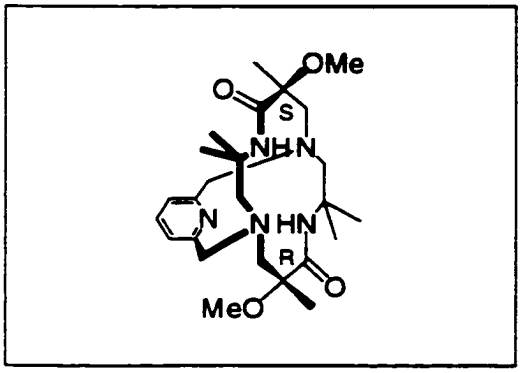
3.F. EXPERIMENTAL

General Procedures. Melting points were taken on a Mel-Temp apparatus and are uncorrected. 300 ^{1}H NMR and 75.5-MHz ^{13}C NMR were taken on a Varian Inova-300 spectrometer and 400-MHz ^{1}H NMR and 100.6-MHz ^{13}C NMR were taken on a Varian Inova-500 spectrometers. Chemical shifts are given in ppm relative to $(CH_3)_4Si$, (0 ppm, ^{1}H), or $CDCl_3$, (77.23 ppm, ^{13}C) unless otherwise noted. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR. UV/VIS spectra were recorded on a Beckmann Du 640 spectrophotometer. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. FAB Mass spectra were recorded on a Fisons Instruments VG autospec. X-ray crystallographic studies were performed on a Bruker Smart CCD diffractometer and the intenisty of the data set was integrated using Bruker SAINT software. The structures were solved using Bruker SHELXTL version 5.03 software. Column chromatography was performed on silica gel (Silicycle 230-400 Mesh). Radial chromatography was performed on silica gel (E M Science Silica Gel 60 PF_{254} containing gypsum) plates 1-2 mm in thickness.

Acetonitrile (Fisher Certified ACS grade), was used without further purification. Methanol (Fisher, ACS grade) was dried over 3Å molecular sieves. CH_2Cl_2 (technical grade) was distilled from CaH_2. $CHCl_3$ (Fisher), Et_3N (Fisher stored over KOH), Et_2O (Fisher) were used without further purification. Hexanes for crystallization purposes was distilled at ambient pressure. Distilled water was used for crystallization purposes.

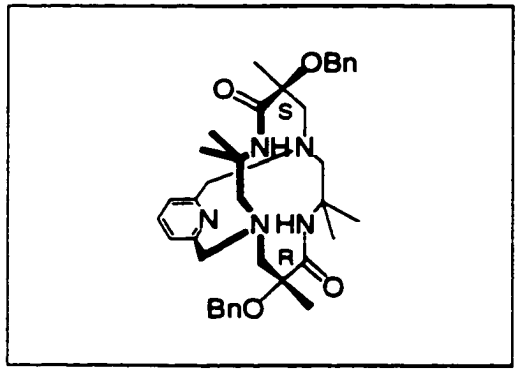
2,6-bis-(bromomethyl)pyridine and α,α′-dibromo-*m*-xylene were purchased from Aldrich and used without further purification. $Cu(BF_4)_2$ was purchased from Stem chemicals and was dried under high vacuum at room temperature for 2 days and then stored in a desiccator. The following chemicals

were prepared according to literature procedures: centrosymmetric (methyl) (methoxy) dioxocyclam **(4a)**,[10] centrosymmetric (methyl) (benzyloxy) dioxocyclam **(4b)**,[10] C_2 (methyl) (methoxy) dioxocyclam **(4a')**,[10] (S,+)-(methyl) (methoxy) dioxocyclam **(8)**,[13] *meso*-(C3) bis-dioxocyclam **(10)**,[12] D_2 (C3) bis-dioxocyclam **(12)**,[12] tetrakis-bromomethyl pyrazine **(17)**.[20]



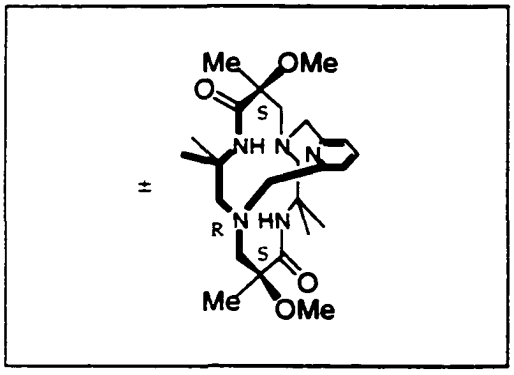
Pyridine Capped *centro* (Methyl) (Methoxy) Dioxocyclam 6a. In a 250 mL three neck flask equipped with a condenser 190 mg (0.51 mmol) of centrosymmetric (methyl) (methoxy) dioxocyclam **(4a)** was dissolved in 100 mL of CH_3CN. To this solution 216 mg (2.04 mmol, 4.0 eq.) of Na_2CO_3 was added and the turbid solution was heated to reflux. Then 135 mg (0.51 mmol) of 2,6-bis-(bromomethyl)pyridine in 5 mL of CH_3CN was added over 20 min. via syringe pump. The solution was then allowed to stir at reflux for 4 days, after which the reaction mixture was filtered through a pad of Celite and the solvent was removed *in vacuuo*. The resulting yellow oil was purified by radial chromatography on a 1 mm silica gel plate ($CHCl_3$ to 1:9 MeOH/$CHCl_3$) to yield 195 mg (0.41 mmol 80%) of a white solid. X-ray quality crystals were generated by slow evaporation of CH_2Cl_2. m.p.. >250° ^{1}H NMR δ 9.1 (s, 1H), 8.1 (s, 1H), 7.6 (t, 1H *J*= 8 Hz), 6.9 (app. dd, 2H, *J*= 8, 3 Hz), 4.1 (m, 4H), 3.4 (s, 3H), 3.2 (d, 1H *J*= 14 Hz), 2.9 (m, 5H), 2.6 (m 4H), 2.35 (d, *J* = 14Hz), 1.6 (bs, 2H), 1.5 (s, 3H), 1.4 (s, 3H), 1.33 (s, 3H), 1.31 (s, 3H), 1.2 (s, 3H), 1.1 (s, 3H). ^{13}C NMR δ 173.5, 172.9, 162.9, 158.4, 137.2, 119.1, 118.8, 82.67, 79.65, 74.49, 72.78, 69.17, 67.32, 65.71, 64.74, 55.93, (54.87), 51.93, 50.28, 26.31, 25.67, 23.67, 23.54, 19.25. IR (neat) ν 1660

(C=O) (cm^{-1}). FAB mass spectrum *m/e* 476.2 (m+1). The structure of **5a** was determined by X-ray analysis, and the results of the study are presented in the supplementary material.



Pyridine Capped *centro* (Methyl) (Benzyloxy) Dioxocyclam 6b. In a 100 mL three neck flask equipped with a condenser 150 mg (0.29 mmol) of centrosymmetric (methyl) (benzyloxy) dioxocyclam **(4b)** was dissolved in 60mL of CH_3CN. To this solution 121 mg (1.14 mmol, 4.0 eq) of Na_2CO_3 was added and the turbid solution was heated to reflux. Then 75 mg (0.29 mmol) of 2,6-bis-(bromomethyl)pyridine in 5 mL of CH_3CN was added over 20 min. via syringe pump. The solution was then allowed to stir at reflux for 4 days after which the reaction mixture was filtered through a pad of Celite and the solvent was removed *in vacuuo*. The resulting yellow oil was purified by radial chromatography on a 1 mm silica gel plate ($CHCl_3$ to 1:9 MeOH/$CHCl_3$) and then crystallized from CH_2Cl_2/Hexanes to yield 111 mg (0.176 mmol, 61%) of a colorless crystalline solid. m.p. >250 °C ^1H NMR δ 9.15 (s, 1H), 8.85 (s, 1H), 7.4 (m, 3H), 7.2-7.35 (m, 3H), 7.1 (m, 1H), 7.0 (t, 2H, *J*= 7 Hz), 6.9 (d, 1H, *J*= 7 Hz), 6.7 (d, 3H, *J*= 7 Hz), 4.8 (d, 1H, *J*= 12 Hz), 4.7 (d, 1H, *J*= 12 Hz), 4.5 (d, 1H, *J*= 17 Hz), 4.25 (d, 1H, *J*= 11 Hz), 4.05 (s, 2H), 3.95-3.85 (m, 2H), 3.4 (d 1H, *J*= 14 Hz), 3.15-2.8 (m, 5H), 2.4 (dd, 2H, *J*= 6, 14 Hz), 1.6 (s, 3H), 1.5 (s, 3H), 1.34 (s, 3H), 1.33 (s, 3H), 1.27 (s, 3H), 1.2 (s, 3H). ^{13}C NMR δ 173.72, 173.33, 160.66, 158.35, 140.51, 138.63, 137.44, 128.38, 128.09, 127.59, 127.31, 127.15, 119.37, 118.53, 83.26, 80.77, 73.38, 66.65, 66.38, 66.13, 65.41, 65.36, 55.52, 26.26, 25.82, 25.24, 23.74, 23.66, 20.21. IR

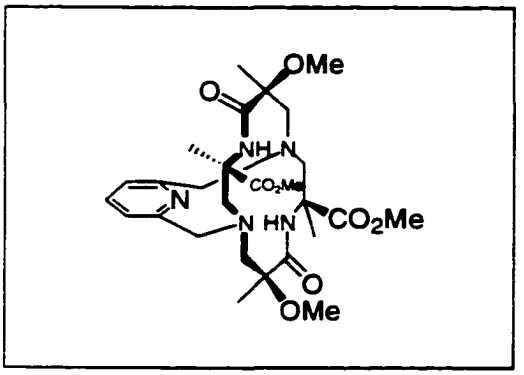
(neat) ν 1659 (C=O) (cm^{-1}). Anal. Calcd. for $C_{37}H_{49}N_5O_4$: C, 70.79, H, 7.87, N, 11.15, Found: C, 70.66, H, 8.00, N, 10.95.



Pyridine Capped *d,l* (Methyl) (Methoxy) Dioxocyclam. In a 100 ml round bottom flask equipped with a condenser 125 mg (0.34 mmol) of C_2 (methyl) (methoxy) dioxocyclam **(4a')** was dissolved in 60 mL of CH_3CN. To this solution 284 mg (2.68 mmol, 8.0 eq) of Na_2CO_3 was added. The turbid mixture was then allowed to reflux for an hour, followed by the addition of and 88 mg (0.34 mmol) of 2,6-bis-(bromomethyl)pyridine. After 6 days at reflux the reaction mixture was filtered through a pad of Celite and the solvent was removed *in vaccuo*. The resulting yellow oil was purified by column chromatography (1:99, Et_3N/CH_2Cl_2 to 1:1:98 $Et_3N/MeOH/CH_2Cl_2$) to yield, after a sat. Na_2CO_3 wash to remove the Et_3N, 90 mg (189 mmol 56%) of the major isomer **8** as a clear wax and a mixture of the minor isomer **7** and the starting C_2 dioxocyclam **4a'**. A second column (2:98, $MeOH/CH_2Cl_2$) yielded 40 mg (84 mmol, 25%) of the minor isomer **7** as a clear wax.

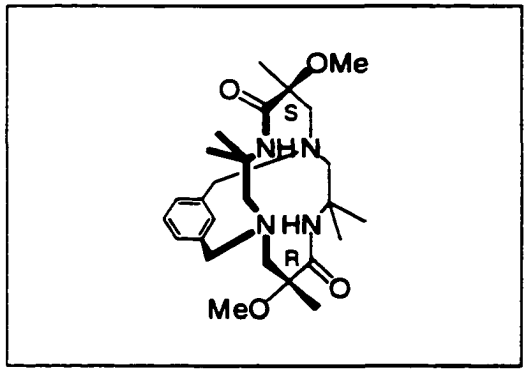
Major isomer **8** ^1H NMR δ 8.82 (bs, 2H), 7.49 (t, 1H *J* = 7.7 Hz), 6.85 (d, 2H *J* = 7.7 Hz), 3.94. (dd, 4H *J* = 16.8, 10.3 Hz), 3.35 (s, 6H) 3.20 (d, 2H *J* = 14.6 Hz), 2.86 (d, 2H *J* = 14.3 Hz), 2.84 (d, 1H *J* = 13.6 Hz), 2.57 (d, 2H *J* =13.6 Hz), 1.47 (m, 2H), 1.34 (s, 6H), 1.20 (s, 6H), 1.17 (s, 6H). ^{13}C NMR δ 172.96, 159.16, 136.45, 118.95, 81.76, 71.44, 66.55, 66.05, 54.37, 51.58, 27.07, 25.36, 21.60. IR (neat) ν 1658 (C=O) (cm^{-1}) Anal. Calcd. for $C_{25}H_{42}N_5O_4$: C, 63.13, H, 8.69, N, 14.72, Found: C, 62.95 H, 8.50, N, 14.68.

Minor isomer 7 ^{1}H NMR δ 8.98 (bs, 2H), 7.55 (t, 1H *J* = 7.7 Hz), 6.85 (d, 2H *J* = 7.7 Hz), 4.36 (d, 2H *J* = 16.5 Hz), 3.83 (d, 2H *J* = 16.5 Hz), 2.98 (dd, 4H *J* = 14.1, 10.6 Hz), 2.88 (d, 1H *J* = 14.3 Hz), 2.75 (s, 6H), 2.45 (d, 2H *J* = 14.3 Hz), 1.61 (bs, 2H), 1.45 (s, 6H), 1.25 (s, 6H), 1.20 (s, 6H). ^{13}C NMR δ 173.31, 161.20, 136.71, 118.24, 83.05, 73.41, 67.72, 66.26, 55.44, 50.64, 25.71, 23.72, 19.58. IR (neat) ν 1652 (C=O) (cm^{-1}) MS (HR FAB) MW calculated for $C_{25}H_{42}N_5O_4$: 476.323 680, found 476.3222 (Δ = 3.1 ppm) (m + 1)

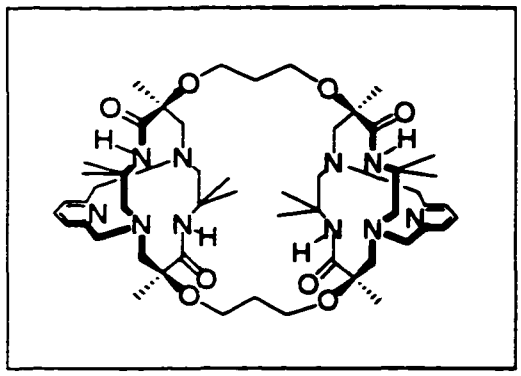


Pyridine Capped (S)-(Methyl) (Methoxy)Dioxocyclam +10. In a 100 ml round bottom flask equipped with a condenser 120 mg (0.26 mmol) of (S,+)-(methyl) (methoxy) dioxocyclam **+9** was dissolved in 50 mL of CH_3CN. To this solution 220 mg (2.08 mmol 8 eq.) of Na_2CO_3 was added and the turbid mixture was then heated at reflux for 1 hr. Next 70 mg (0.26 mmol) of solid 2,6-bisbromomethyl pyridine was added. After 6 days at reflux the reaction mixture was filtered through a pad of Celite and the solvent was removed *in vaccuo*. The resulting yellow oil was purified by flash column chromatography first by eluding (5:95 $MeOH/CH_2Cl_2$) to remove the dioxocyclam (**8**) then with (5:95 Et_3N/CH_2Cl_2) to yield, after a sat. Na_2CO_3 wash to remove the Et_3N, 65mg (0.12 mmol, 45%) of the capped dioxocyclam **+10** as a clear wax. X-ray quality crystals of **+10** were generated by slow diffusion of water into methanol. m.p. 187° C ($MeOH/H_2O$), $[\alpha]^{21}_D$ +57° (c = 1.03, $CHCl_3$), ^{1}H NMR δ 8.56 (bs, 2H), 7.56 (t, 1H *J*= 7.7 Hz), 6.86 (d, 2H *J*= 7.7 Hz), 3.72 (dd, 4H *J*= 14.4, *J*= 10.9 Hz), 3.71 (s, 6H), 3.27 (s 6H), 3.14 (dd, 4H *J*= 11.0 *J*= 4.0 Hz) 3.16 (d, 2H *J*= 15.0 Hz), 3.12 (d, 2H *J*= 12.8 Hz), 2.91(d, 2H *J*= 13.1 Hz), 2.78 (d, 2H *J*= 15.0 Hz), 1.54 (s 6H), 1.12 (s 6H).

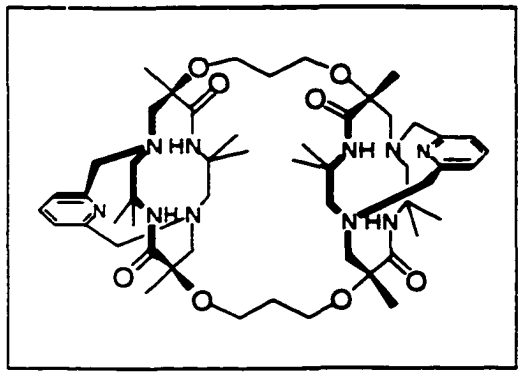
^{13}C NMR δ 175.10, 172.03, 158.55, 136.054, 119.51, 82.42, 65.89, 62.72, 61.86, 61.39, 52.12, 50.06, 21.61, 19.32. IR (neat) ν 1738, 1648 (C=O) (cm^{-1}). MS (HR FAB) MW calculated for $C_{27}H_{42}N_5O_8$: 564.303 339, found 564.3030 (Δ = 0.8 ppm) (m + 1). The structure of **5a** was determined by X-ray analysis, and the results of the study are presented in the supplementary material.



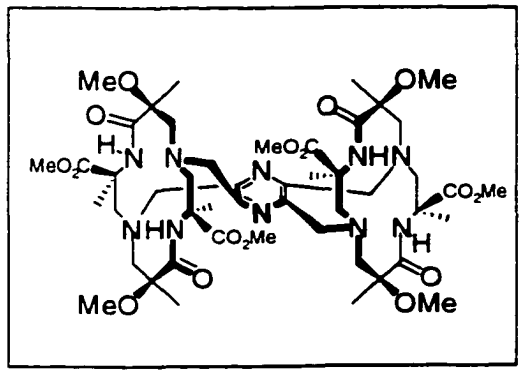
***m*-Xylene Capped *centro* (Methyl) (Methoxy) Dioxocyclam 12.** In a 100 mL round bottom flask equipped with a condenser 100 mg (0.26 mmol) of *centro* (methyl) (methoxy) dioxocyclam **(4a)** was dissolved in 45 mL of CH_3CN along with 100 mg (1.04 mmol, 4.0 eq.) of Na_2CO_3. This turbid solution was heated to reflux followed by the addition of 68 mg (0.26 mmol, 1 eq.) of α,α′-dibromo-*m*-xylene **11**. The solution was allowed to stir at reflux for 4 days after which the reaction mixture was filtered through a pad of Celite and the solvent was removed *in vaccuo*. The resulting yellow oil was purified by radial chromatography ($CHCl_3$ to 5% MeOH/$CHCl_3$) and then crystallized from toluene to yield 37 mg (0.078 mmol 30%) of a white powder. ^1H NMR δ 9.21 (bs, 1H), 7.45 (bs, 1H), 7.08 (t, 1H *J*= 7 Hz), 6.8 (m, 2H), 5.9 (bs, 1H), 4.0 (d, 1H *J*= 13.8 Hz), 3.78 (dd, 2H *J*= 20.9, 17.2 Hz), 3.78 (d, 2H *J*= 7.7 Hz), 3.11 (m, 3H), 3.06 (s, 3H), 2.90 (s, 2H), 2.84 (d, 1H *J*= 14.6 Hz), 2.34 (d, *J* = 12.7 Hz), 1.70 (m, 1H), 1.35 (s, 6H), 1.34 (s, 3H), 1.27 (s, 3H), 1.21 (s, 3H), 1.08 (s, 3H). ^{13}C NMR δ 173.65, 172.88, 142.18, 140.25, 131,81, 127.07, 122.54, 122.47, 83.01, 82.91, 72.49, 69.14, 67.86, 63.13, 62.74, 62.53, 55.12, 53.31, 51.53, 49.81, 30.42, 28.11, 27.64, 24.63, 20.62, 20.28. MS (HR FAB) MW calculated for $C_{26}H_{43}N_4O_4$: 475.328 431, found 475.3278 (Δ = 1.2 ppm) (m + 1)



Bis-capped *meso* (C3) Bis-dioxocyclam 14. In a 50 mL round bottom flask equipped with a condenser 70 mg (0.09 mmol) of *meso*-C3 bis-dioxocyclam **13** was dissolved in 20 mL of CH_3CN. To this solution 75 mg (.72 mmol, 8.0 eq.) of Na_2CO_3 was added and this turbid solution was heated to reflux. Then 47 mg (0.18 mmol, 2 eq.) of 2,6-bis-(bromomethyl) pyridine was added. The solution was allowed to stir at reflux for 5 days after which the reaction mixture was filtered through a pad of Celite and the solvent was removed *in vaccuo*. The resulting yellow oil was dissolved in 20 mL of CH_2Cl_2 and washed 3 times with 10 mL of water. The CH_2Cl_2 was dried with Na_2SO_4 and the solvent was removed *in vacuuo*. The resulting clear wax was crystallized by slow diffusion of Et_2O into CH_2Cl_2 to yield 50 mg (0.051 mmol, 58%) of **14** as white powder. m.p. >250 °C, ^1H NMR δ 7.81 (bs, 4H), 7.38 (t, 2H *J* = 7.3 Hz), 6.75 (d, 4H *J* = 7.3), 3.74 (s, 8H), 3.54 (dt, 4H *J* = 5.9, 10.3 Hz), 3.36 (dt, 4H *J*=5.1, 10.3 Hz), 3.10 (d, 4H *J*= 15.0 Hz), 2.77 (d, 4H *J* = 15.0), 2.70 (dd, 8H *J* = 13.3, 7.7 Hz), 1.97 (m, 2H), 1.83 (m 2H), 1.30 (s, 12H), 1.19 (s, 12H), 1.17 (s, 12H). ^{13}C NMR δ 172.64, 158.70, 135.87, 118.84, 84.14, 68.47, 66.64, 66.29, 60.92, 54.05, 33.28, 28.59, 25.34, 21.14. IR (neat) ν 1651 (C=O) (cm^{-1}). Anal. Calcd for $C_{52}H_{82}N_{10}O_8$: C, 64.04, H, 8.47, N, 14.36. Found: C, 64.37, H, 8.35, N, 14.39.

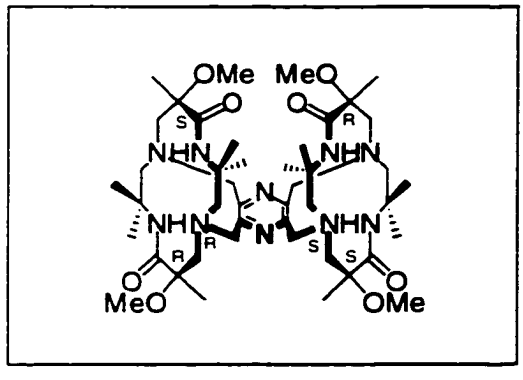


Bis-capped D_2 (C3) Bis-dioxocyclam 16 In a 50 mL round bottom flask equipped with a condenser 83 mg (0.11 mmol) of D_2 (C3) bis-dioxocyclam **15** was dissolved in 20 mL of CH_3CN. To this solution 75 mg (0.42 mmol, 4.0 eq.) of Na_2CO_3 was added and this turbid solution was heated to reflux. Then 56 mg (0.21 mmol, 2 eq.) of 2,6-bis-(bromomethyl) pyridine was added. After the 6 days at reflux the cooled reaction mixture was filtered through a pad of Celite and the solvent was removed *in vacuuo*. The resulting yellow oil was crystallized from $CHCl_3$ to yield 25 mg (0.026 mmol, 24%) of **16** as white powder. ^1H NMR (CD_3OD) δ 8.47 (t, 2H *J* = 8.1 Hz), 7.80 (d, 4H *J* = 7.7), 7.31 (s, 4H), 4.28 (dd, 8H *J* = 7.3, 18.3 Hz), 3.81 (m, 8H), 3.45 (d, 4H *J*= 15.7 Hz), 3.00 (d, 4H *J* = 13.2), 2.98 (d, 4H *J* = 15.4 Hz), 2.82 (d, 4H *J* = 13.5 Hz) 2. 29 (m, 4H), 1.46 (s, 12H), 1.38 (s, 12H), 1.30 (s, 12H). ^{13}C NMR δ 175.74, 154.65, 148.29, 125.21, 85.77, 68.01, 65.63, 63.24, 62.33, 55.91, 34.51, 29.67, 26.05, 21.36. IR (neat) ν 1664 (C=O) (cm^{-1}). MS (HR FAB) MW calculated for $C_{52}H_{83}N_{10}O_8$: 975.639 536, found 975.6379 (Δ = 1.7 ppm) (m + 1)



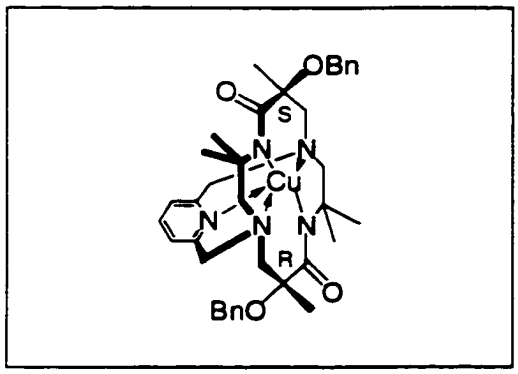
Pyrazine bridged S- (Methyl) (Methoxy) Bis-dioxocyclam +18 In a 100 mL round bottom flask equipped with a condenser 259 mg (0.56 mmol) of (S,+)-(methyl) (methoxy) dioxocyclam **8** was dissolved in 50 mL of CH_3CN. To this solution 238 mg (2.25 mmol, 8.0 eq.) of Na_2CO_3 was added and this turbid solution was heated to reflux. Then 56 mg (0.21 mmol, 2 eq.) of tetrakis-bromomethyl pyrazine **17** was

added. The solution was allowed to stir at reflux for 6 days after which the reaction mixture was filtered through a pad of Celite and the solvent was removed *in vaccuo*. The resulting yellow oil was purified by flash column chromatography first by eluding (5:95 $MeOH/CH_2Cl_2$) to remove the dioxocyclam (**8**) then with (5:95 Et_3N, CH_2Cl_2) to yield, after a sat. Na_2CO_3 wash to remove the Et_3N, 59 mg (0.17 mmol, **10%**) of the bridged bis-dioxocyclam **+18** as a clear wax. X-ray quality crystals of **+18** were generated by slow diffusion of water into methanol. m.p 160 (dec.) $[\alpha]^{21}_D$ +20.4° ^1H NMR ($CDCl_3$, -10° C) δ 9.34 (s, 2H), 7.49 (s, 2H), 4.30 (d, 2H, *J* = 12.1 Hz), 4.03 (d, 2H, *J* = 10.5 Hz), 3.83 (d, 2H, *J* = 10.5 Hz), 3.75 (s, 6H), 3.70 (s, 6H), 3.47 (m, 4H), 3.28 (s, 6H), 3.25 (m, 8H), 3.09 (d, 2H, *J* = 15.4 Hz), 3.00 (m, 4H), 2.86 (d, 2H, *J* = 12.5 Hz), 2.77 (d, 2H, *J* = 15.3 Hz), 2.46 (d, 2H, *J* = 14.3 Hz), 2.00 (s, 6H), 1.29 (s, 6H), 1.13 (s, 6H), 1.05 (s, 6H). ^{13}C NMR δ 174.61, 174.50, 173.53, 172.41, 150.32, 150.04, 81.89, 79.04, 77.42, 68.62, 66.12, 62.23, 61.51, 59.66, 57.26, 56.88, 56.12, 52.77, 52.46, 51.23, 25.67, 23.66, 18.59, 17.51. IR (neat) ν 1741, 1667 (C=O) (cm^{-1}) The structure of **14** was determined by X-ray analysis, and the results of the study are presented in the supplementary material.



Pyrazine bridged *centro*- (Methyl) (Methoxy) Bis-dioxocyclam (20,22). In a 100 mL three neck flask equipped with a condenser 247 mg (0.66 mmol 2.0 eq.) of *centro* (methyl) (methoxy) dioxocyclam **4a** was dissolved in 50 mL of CH_3CN. To this solution 280 mg (2.64 mmol, 8.0 eq) of Na_2CO_3 was added and this turbid solution was heated to reflux. Then 50 mg (0.33 mmol) of tetrakis-bromomethyl pyrazine **17** was added. The solution was allowed to stir at reflux for 6 days after

which the reaction mixture was filtered through a pad of Celite and the solvent was removed *in vaccuo*. The resulting yellow oil was recrystallized from MeOH/H_2O. The first crop of crystals yielded 30 mg of capped monomer. The mother liquor was allowed to evaporate and a second crop of crystals was collected 177 mg (0,20 mmol, 61%) as a 3:4 mixture of diastereomers of **20** and **22**. ^1H NMR 400 MHz ($CDCl_3$, -30° C) δ 9.91 (s, 2H), 9.77 (s, 2H), 8.53 (s, 2H), 8.37 (s, 2H), 5.24 (d, 2H, *J* = 12.5 Hz), 5.20 (d, 2H, *J* = 12.8 Hz), 4.25 (d, 2H, *J* = 11.7 Hz), 4.14 (d, 2H, *J* = 11.7 Hz), 3.63 (d, 2H, *J* = 11.7 Hz), 3.46 (d, 2H, *J* = 11.7 Hz), 3.37 (m, 8H), 3.16 (d, 2H, *J* = 13.6 Hz), 3.00 (m, 8H), 2.84 (d, 2H, *J* = 14.4 Hz), 2.82 (d, 2H, *J* = 13.6 Hz), 2.62 (m, 8H), 2.15 (d, 2H, *J* = 14.0 Hz), 2.03 (d, 2H, *J* = 14.0 Hz), 1.52 (s, 12H), 1.49 (s, 12H), 1.28 (s, 6H), 1.27 (s, 6H), 1.24 (s, 12H), 1.18 (s, 6H), 1.14 (s, 6H), 1.02 (s, 6H), 1.01 (s, 6H). ^{13}C NMR δ 171.34, 171.21, 170.13, 169.51, 151.52, 150.72, 150.52, 149.27, 80.95, 80.81, 80.32, 79.84, 70.17, 66.55, 66.01, 63.94, 63.42, 63.08, 62.61, 58.58, 53.36, 53.25, 53.14, 51.10, 51.04, 50.79, 28.63, 28.30, 27.56, 27.18, 25.67, 24.92, 19.70, 19.26, 18.93, 18.85. IR (neat) ν 1671 (C=O) (cm^{-1}).



Cu(II) complex of *centro*- (Methyl) (Benzyloxy) capped Dioxocyclam 23. To 5 mL of CH_2Cl_2 in a pressure tube 70 mg (0.11 mmol) of **6b** was added along with 187 mg (0.55 mmol, 5.0 eq.) of $Cu(BF_4)_2 \bullet 6H_2O$ and 76 mg (0.55 mmol, 5.0 eq.) of K_2CO_3. The pressure tube was capped and the reaction was heated to 65 °C for 2 d. The green reaction mixture was then filtered through a pad of Celite and the solvent was removed *in vaccuo*. The resulting green tar was dissolved in CH_2Cl_2, and the organic layer was extracted with water. During the extraction the aqueous layer turned blue. The blue aqueous layers were combined and the

water was removed *in vaccuo*. The resulting blue tar was recrystallized from CH_2Cl_2/Hexanes to give 57 mg (0.082 mmol, 75%) of separate green and blue crystals. m.p. (green) 126° C, m.p. (blue) 93° C. UV/VIS (MeOH, blue solution) λ 339 nm, 658 nm. (CH_2Cl_2, green solution) λ 368 nm, 659 nm. FAB mass spectrum *m/e* 689.2 (m+1) IR (neat) ν 1573 (C=O) (cm^{-1}). The structure of **23a** and **23b** were determined by X-ray analysis, and the results of the studies are presented in the supplementary material.

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CHAPTER FOUR

SYNTHESIS AND APPLICATION OF BIS-DIOXOCYCLAMS

4.A. INTRODUCTION AND BACKGROUND

4.A.1. Phosphate Diester Hydrolysis

The half-life of a typical phosphate diester bond in DNA in neutral water at 25° C has been estimated to be on the order of tens to hundreds of *billions* of years.[1] In comparison, the age of the earth is estimated to be only 4 billion years. This remarkable stability is reasoned to be why nature chose phosphate diesters in the storage mechanism for genetic information.[2] This stability to hydrolysis, while important for storing the genetic information, is detrimental to the encoding and transfer of this genetic information if the rate of hydrolysis cannot be increased so as to insert the information and to correct mistakes. Nature has, however, developed metalloenzymes that can hydrolyze DNA within 1 second. This is one of the most stunning examples of nature's mastery of catalyst design.

There are many different types of enzymes that affect hydrolysis of different bonds and several dinuclear metalloenzymes have been identified that catalyze the hydrolysis of peptides and phosphate esters.[3] In these enzymes, two or more metal centers are found in the active site, but, as yet, the exact the role of these metal centers is not well understood. Their positions in the active

site do give some clues as to their possible role in the hydrolysis, and several possible mechanisms involving the metals have been proposed.[4] Detailed mechanistic studies are often difficult to perform on enzymes due to their large size, so model systems of the active sites of enzymes are synthesized to probe subtle structural effects involved in the catalyzed reactions.

Chin has recently published modification of metal complexes in phosphate diester hydrolysis, to model dinuclear metalloenzymes.[1] In the hydrolysis of phosphate diesters, Chin proposes three direct and three indirect modes of activation by a metal ions. The first direct mode is Lewis acid activation, for which the phosophoryl oxygen(s) coordinate to the metal center (**A**). Second, an incoming nucleophile such as hydroxide can be activated by coordination to the metal center (**B**). Third, the leaving group can be activated by coordination to the metal center (**C**). The three indirect modes of activation are; first, coordination of hydroxides that act as intramolecular general base catalysts (**D**); second, water molecules coordinated to the metal center can act as intramolecular general acid catalysts (**E**) (Figure **4.1**). Finally, electrostatic interaction of the uncoordinated phosphate and the metal center can provide some rate acceleration for hydrolysis and is the third indirect mode.

For dinuclear metal complexes there are three possible direct modes of phosphate diester activation by both metal centers (Figure **4.2**). These three modes are: double Lewis acid activation by the phosphate diester bridging the two metal centers (**F**); one metal can act as a Lewis acid towards the phosphate diester and the other can activate a coordinated hydroxide (**G**); one metal center activates the phosphate while the second metal activates the leaving group (**H**).

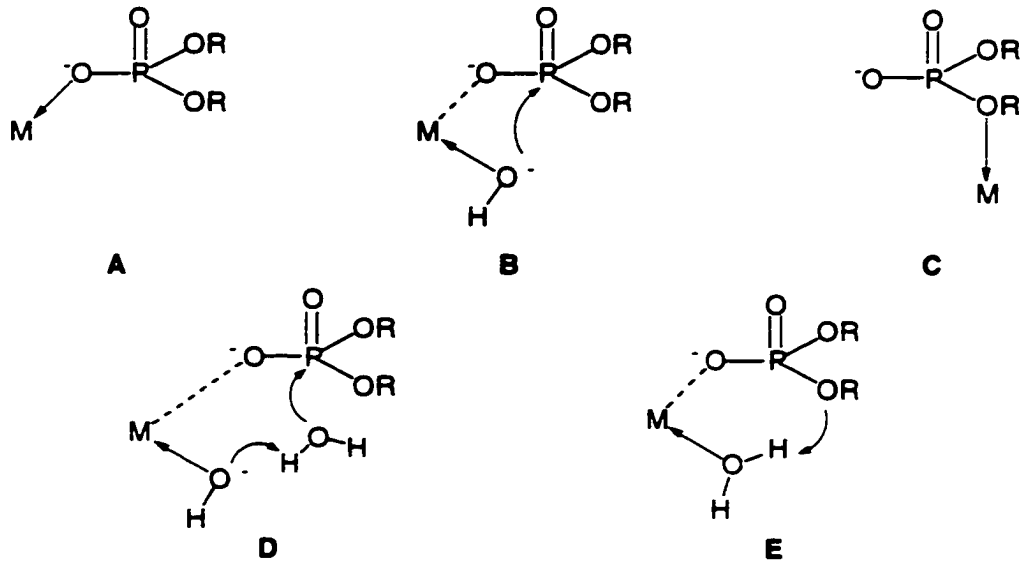


Figure 4.1 Possible modes of activation by metals in phosphate diester hydrolysis.

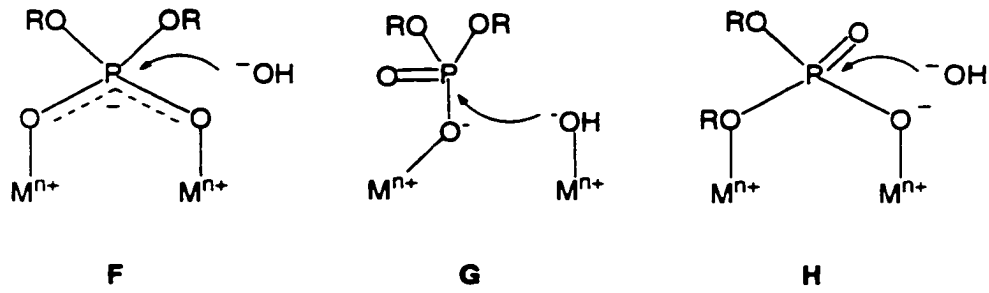


Figure 4.2 Activation modes of bimetallic complexes.

A desirable trait of dinuclear catalysts is a variable but rigid system that places the metal centers at specific distances and specific orientations. For example, some systems hold the two metal centers too far apart for the phosphate to bridge the two centers, so these systems are more useful in the study of metal coordinated hydroxide delivery (**G**, Figure **4.2**). Other systems that hold the metal centers in very rigid ligands are used to study the effects of metal orientation. There have been several hydrolysis systems that address one

or the other of these issues, but designing ligand systems that are both rigid and can vary metal-metal distances has proven difficult.

Chin developed a substitutionally inert bis-cobalt(III) complex with a bridging phosphate diester to study the effects of a rigid bimetallic system and found a 4 x 10^5 rate increase over the hydrolysis of free diester (Figure **4.3**).[5] For this study 2-hydroxypropyl-*p*-nitrophenyl-phosphate was chosen as a model for RNA hydrolysis. The bis-cobalt(III) catalyst was also compared to a mono cobalt (III) catalyst which exhibited a 50-fold rate increase of hydrolysis over free

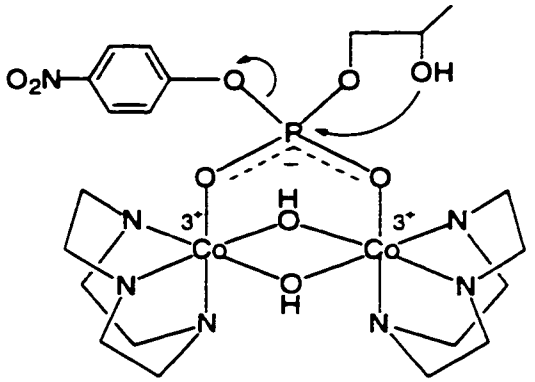


Figure 4.3 Bis-cobalt(III) phosphate diester complex

diester hydrolysis. If the effects of the two cobalt centers were simply additive one would expect the rate increase to be 50^2 (2.5 x 10^3), but for the bis-cobalt complex the rate of hydrolysis showed a 4 x10^5-fold rate increase, which was evidence for considerable cooperativity between the two cobalt centers. Chin also studied the effect of the bridging hydroxides in a similar bis-cobalt system Figure **4.4**). ^{18}O isotope labeling studies showed that the bridging oxide was involved in the hydrolysis of methyl-*p*-nitrophenyl-phosphate.[6] The mode of hydrolysis was expected to be slightly different for this phosphate diester because it lacks the tethered alcohol.

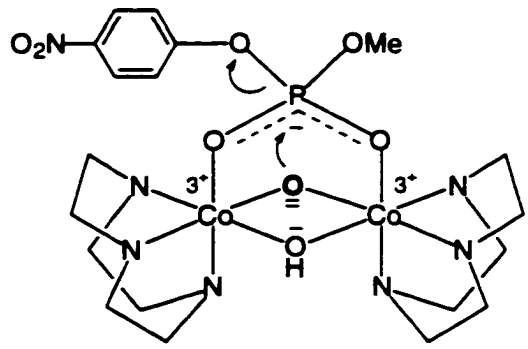


Figure 4.4 Intramolecular oxide attack.

The bridging of the two phosphoryl oxygens of the phosphate diester in the two complexes was confirmed by X-ray crystallographic analysis of a similar complex. This crystallographic data lends credence to the proceeding arguments which were based on a bridging phosphate, but with substitutionally labile complexes, leaving group activation could also be a pathway for the hydrolysis. To date there have been no reports invoking leaving group activation as a mode of phosphate ester hydrolysis.

Several other dinuclear complexes that are more substitutionally labile than the previous bis-cobalt complexes have been developed to study phosphate diester hydrolysis. Chin also developed a bis-copper(II) complex that showed a modest rate increase (5 orders of magnitude over background) in the hydrolysis of adenylyl(3'-5')adenosine (ApA), a much more realistic model for RNA hydrolysis (Figure **4.5**).

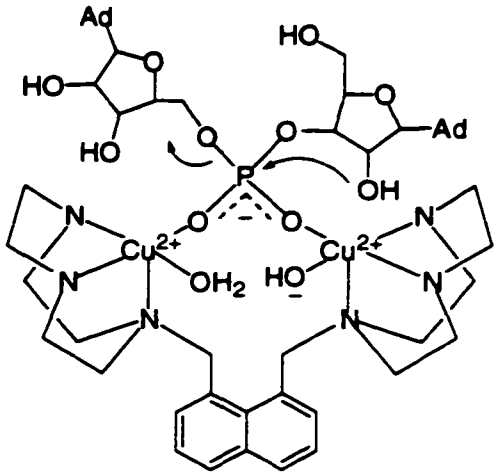


Figure 4.5 Hydrolysis of ApA by a dinuclear copper (II) complex

Breslow synthesized a series of zinc(II) complexes of bis-triazamacrocycles to study the effects of chain lengths of the linker on the rate of hydrolysis.[7] In these systems the two macrocyclic rings were joined by various aromatic and aliphatic linkers of different lengths. A correlation was seen between linker length and rate acceleration, with the biphenyl-linked bis-azamacrocycle showing 2000-fold rate increase (Figure **4.6**), which was far greater than that for the other linkers. Although there was a difference seen due to linker length, the two rings were not locked into a specific orientation and distance because of the

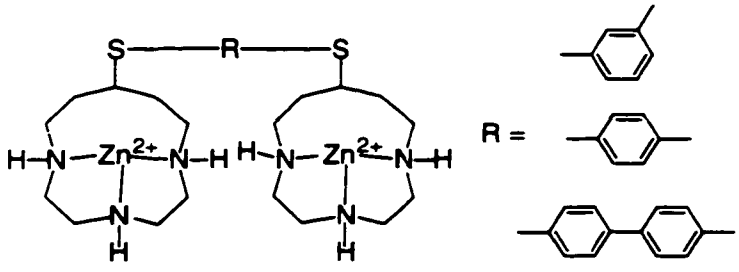


Figure 4.6 Bis-macrocyclic ligands for zinc(II) catalyzed hydrolysis

single point of attachment between them. Other bis-zinc(II) complexes that used calix[4]arenes appended with two 2,6-bis(aminomethyl) pyridine ligands were

developed. These complexes accelerated the rate of hydrolysis by four orders of magnitude.[8] Once again the distance between the two metal centers is not fixed. The calix[4]arene structure is not static and it tends to "breathe." This breathing moves the zinc centers that are attached to the calix[4]arene, varying the distance between the two metals.

An analog of Chin's bis-copper system which replaced the naphthalene linker with an anthracene was developed by Czarnik[9]. Replacing the naphthalene ring increased the distance between the two cobalt (III) ions. The rate of hydrolysis of bis(*p*-nitrophenyl) phosphate, (BPNPP), (an activated phosphate diester often used in hydrolysis studies), was increased by 7 orders of magnitude over uncatalyzed hydrolysis. In this complex, the two cobalt centers were thought to be too far apart to be bridged by the phosphate, so the rate increase was proposed to come from coordination of the phosphate to one cobalt and delivery of a molecule of water from the second cobalt.

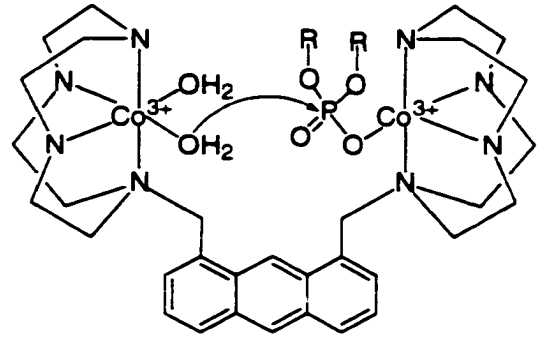
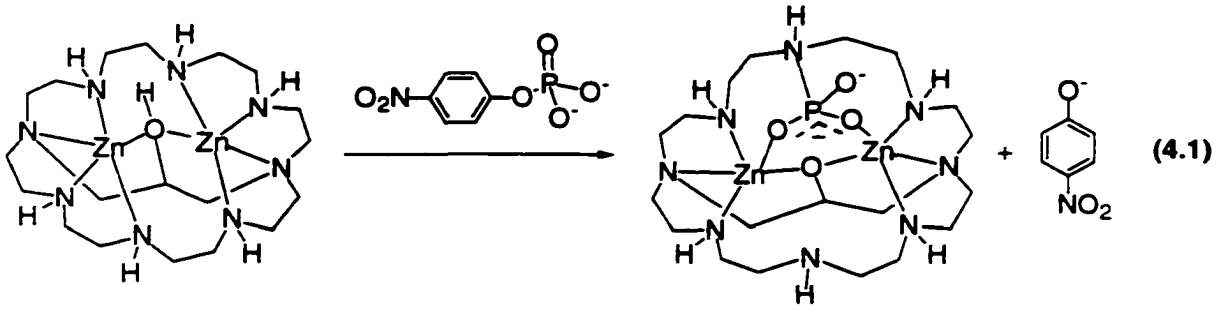


Figure 4.7 Czarnik's anthracene linked bis-cobalt(III) complex

Kimura developed a rigid, bis-zinc macrocyclic complex that selectively de-phosphorylated phosphate *mono*esters (Equation **4.1**).[10] This complex consisted of two zinc(II) ions coordinated by a bicyclic octa-amine to form a very rigid bimetallic complex. This system did not hydrolyze the phosphate

monoester, but transferred the phosphate group to the bis-zinc complex with concomitant release of *p*-nitro phenolate.



(4.1)

A related system for the hydrolysis of phosphate diesters was developed by Krämer.[11] In his system, a monometallic complex with pendant tertiary amines was used instead of a bimetallic complex (Figure 4.8). This monometallic system closely mirrors phosphodiesterases that contain positively charged aminoacid side chains in the active site. The pendant tertiary amines were protonated at the pH that the hydrolysis studies were run. The complex was thought to function by coordination of the phosphate to the copper ion and then the protonated amine acted as an intramolecular general acid catalyst to activate the phosphate. Tertiary amines were used to increase the basicity of the amines and to negate the possibility of phosphoryl transfer to the amine.

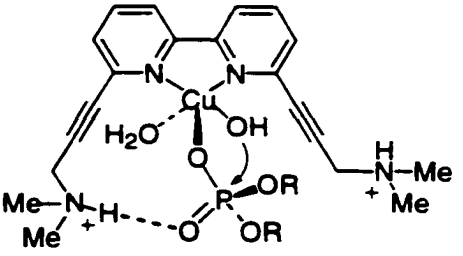


Figure 4.8 Krämer's bis-amino copper complex

Most of the proceeding hydrolysis systems were studied with the complexes in excess to the phosphate diester, and rarely was the *catalytic* activity studied. The need for stoichiometric amounts of the complexes was due to several reasons: First, the reaction rates were very slow under physiological conditions (pH 7, 25° C) even with activated phosphate esters (e.g. BPNPP). Second, as with Kimura's system, catalytic turnover was often blocked by coordination of the hydrolysis product. These are two of the major issues that need to be resolved to generate successful, synthetic phosphate ester hydrolysis catalysts. The development of ligands that can chelate to two metals simultaneously is pursued by many research groups, with the development of a successful hydrolysis agent as the goal.[12]

Hegedus has reported the synthesis of several bis-dioxocyclam nickel(II) complexes derived from dimerization bis-azapenams (Figure **4.9**).[13] Following this synthetic method, two diastereomers of the bis-dioxocyclam were produced. The two bridges between the two dioxocyclam rings produces a much more rigid structure than other systems that only have one linking bridge (e.g. Breslow bis-zinc complexes (Figure **4.6**). Crystal structures of both of the diastereomers of the bis-nickel complex of 1,3-propanediol-linked bis-dioxocyclam were solved. From the crystal structures differences in the cavity between the two metal centers in the two different diastereomers were observed.

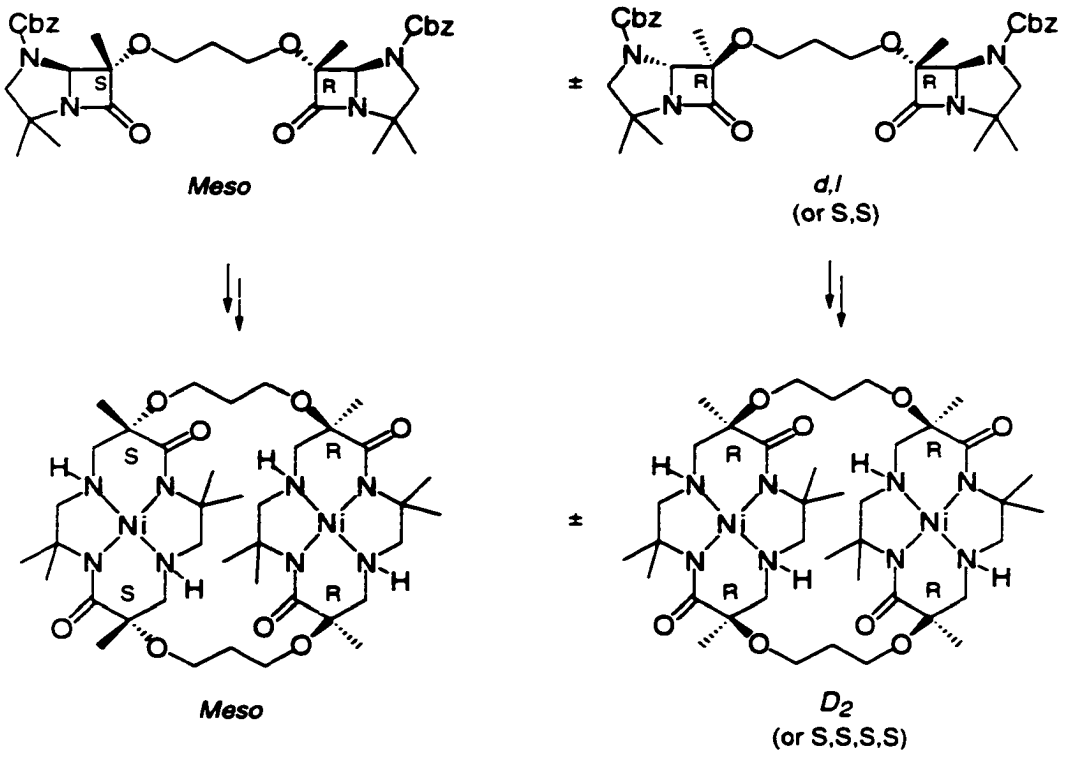


Figure 4.9 Diastereomeric bis-dioxocyclam complexes reported by Hegedus

For the *meso* diastereomer, the planes of the two dioxocyclams are parallel with a mirror plane passing between the two rings. In the D_2 diastereomer the two dioxocyclam rings are at an angle to each other, like an open book, with the vacant coordination sites on each nickel at an acute angle (Figure **4.10**). With both of the (1,3-propanediol)-linked bis-dioxocyclams, the two nickel(II) ions are separated by ~7.5 Å. For the D_2 symmetric diastereomer the cavity between the

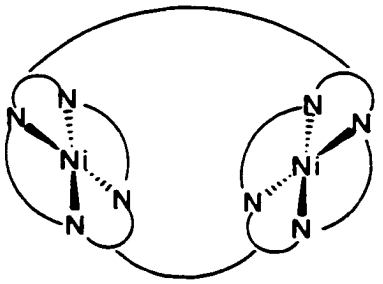


Figure 4.10 Orientation of dioxocyclam rings in the D_2 bis-dioxocyclams

two dioxocyclam rings appears ready to accept a Lewis base (e.g., the phosphate oxygens of a phosphate diester) by coordination to one of the nickel ions. Once within the cavity between the two metal centers the Lewis base could then be activated toward further reactions by the other metal. Because the distance between the two metal centers can be controlled by the choice of chain length of the linker, and the orientation of the two metal centers can be controlled by choice of diastereomer, these bis-dixoxcyclam complexes are attractive for the study phosphate diester hydrolysis. The rigidity of the structure, because of the two bridges between the two rings, could be helpful in quantifying the effects of inter-atomic distance and relative orientation of the metal centers if a successful hydrolysis system is developed. Thus, bis-dioxocyclam metal complexes appear to be promising candidates for tunable, phosphate diester hydrolysis agents.

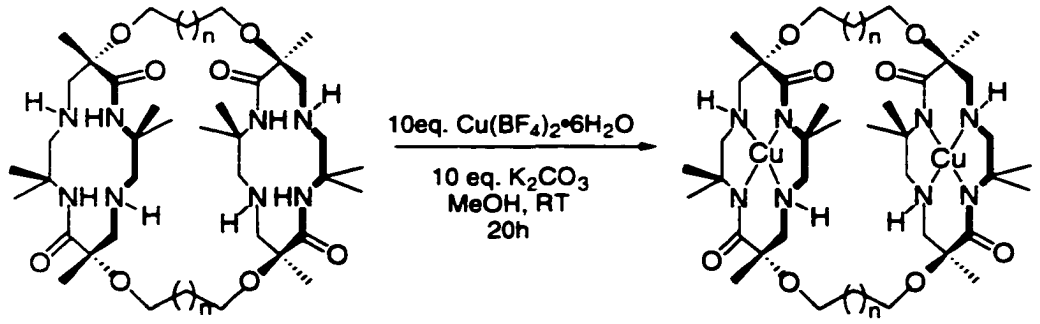
4.B. RATIONALE

The bis-dioxocyclams produced from bis-azapenams have a cavity between two coordinated metal centers, the dimensions of which can be controlled by choice of diastereomer and length of bridging alkyl groups. This control over the dimensions of the cavity can be used in the analysis of the optimal conditions for phosphate diester hydrolysis. The following chapter presents some initial studies on the use of bis-dioxocyclam, bis-copper(II) complexes as phosphate diester hydrolysis agents. Also, the synthesis of several new bis-dioxocyclams, with the goal of producing successful phosphate diester hydrolysis agents, is presented.

4.C. RESULTS AND DISCUSSION

4.C.1. Phosphate Diester Hydrolysis Studies

The bis-nickel complexes of bis-dixoxcyclams proved to be insoluble in water, but the analogous bis-copper(II) complexes were soluble, so the bis-copper complexes were used in the phosphate diester hydrolysis studies. The first two bis-copper complexes that were synthesized were of the ethylene glycol-linked and 1,3-propanediol-linked bis-dioxocyclams. The synthesis of these two bis-dioxocyclam was previously reported,[11] and the D_2 symmetric isomer of the 1,3 propanediol-linked bis-dioxocyclam **24** was isolated following the published procedure. The D_2 symmetric isomer of the ethylene glycol-linked bis-dioxocyclam **23** proved more difficult to isolate, but fractional crystallization of the tetra-imine intermediate (Equation **3.8**) separated the *meso* from the D_2 diastereomer. The bis-copper(II) complexes of the two D_2 isomers **25** and **26** were synthesized with an excess of $Cu(BF_4)_2 \bullet 6\ H_2O$ as the Cu(II) source (Equation **4.2**). With the two complexes prepared, the phosphate diester hydrolysis studies were then undertaken.

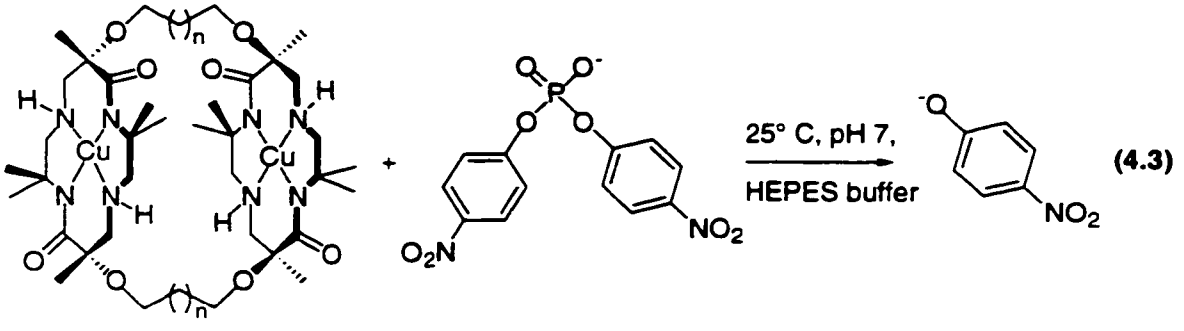


(4.2)

(D_2) **23** n = 0
(D_2) **24** n = 1

(D_2) **25** n = 0, 63%
(D_2) **26** n = 1, 70%

Bis(4-nitrophenyl) phosphate (BNPP) **27** (Equation **4.3**) has been used as a substrate in many hydrolysis studies for several reasons: The *p*-nitrophenyl groups activate the phosphoryl group towards hydrolysis, increasing the hydrolysis rate to levels that are more easily measured. Also, the *p*-nitro phenolate **28** that is produced has a strong absorption at 400 nm over a broad range of temperatures and pH's.[9,14] Therefore, the rate of hydrolysis can be followed by the increase of the absorption at 400 nm caused by the appearance of *p*-nitro phenolate. Fortuitously, the two copper bis-dioxocyclam complexes **25** and **26** show minimal absorption at 400 nm, so there is little contribution from the copper complexes to the absorption at this wavelength.



(D_2) **25** n = 0
(D_2) **26** n = 1

27

28

The rate enhancement for both bis-copper complexes was disappointing. The use of 4-atom bridged **25** resulted in only a five-fold rate increase over the background hydrolysis, and the 5 atom bridged **26** showed only a 10-fold rate enhancement over background hydrolysis. Also, in the hydrolysis experiments the copper complexes were used in 10-fold excess over the BPNPP, so not only was the rate enhancement low, the systems were not catalytic. The very slow rate of hydrolysis precluded testing the complexes under sub-stoichiometric conditions to test for catalytic turnover. The copper complexes also appeared to

decompose slightly over the course of the hydrolysis experiment which could explain the deviation from the least squares line seen in the graph of the data (Figures **4.12, 4.13**).

Although both systems showed very poor rate increases over background hydrolysis, the possible mode of action of the hydrolysis should be put forward to be applied to future, more successful hydrolysis systems. The two nickel centers in the 1,3-propanediol-linked bis-dioxocyclam are too far apart (7.54 Å) to be bridged by the phosphate (typical metal-metal distances for phosphate bridged systems are 3 to 5 Å[1]), but analogous to Czarnik's system, a coordinated water could be delivered by the second metal center to hydrolyze the phosphate diester (Figure **4.11**). The crystal structure of the ethylene glycol-

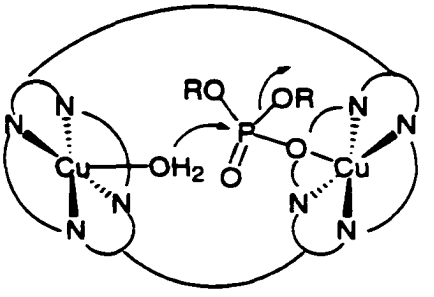


Figure 4.11 Possible mechanism for phosphate diester hydrolysis by **26**

linked bis-dixoxyclam has not been solved, so the distance between the two copper centers is not known. However, the distance is expected to be shorter than the 1,3-propanediol-linked bis-dioxocyclam. The distance between the two metals could be short enough to be bridged by the phosphate group and lead to double Lewis acid activation in the hydrolysis (Figure **4.14**).

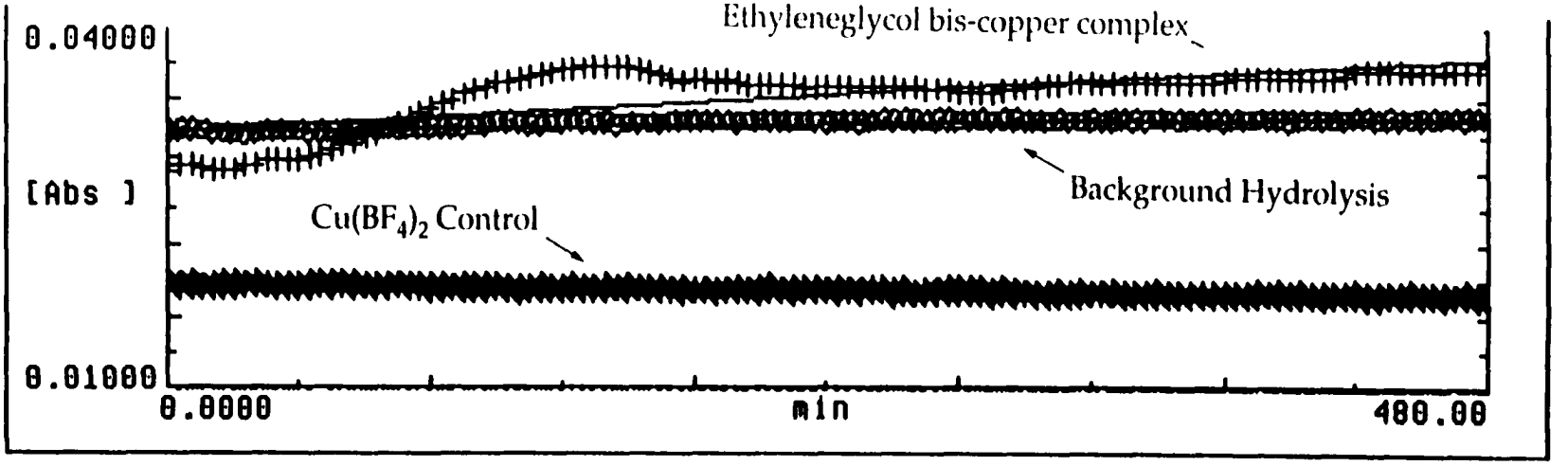


Figure 4.12 Hydrolysis data for ethyleneglycol-linked bis-copper complex

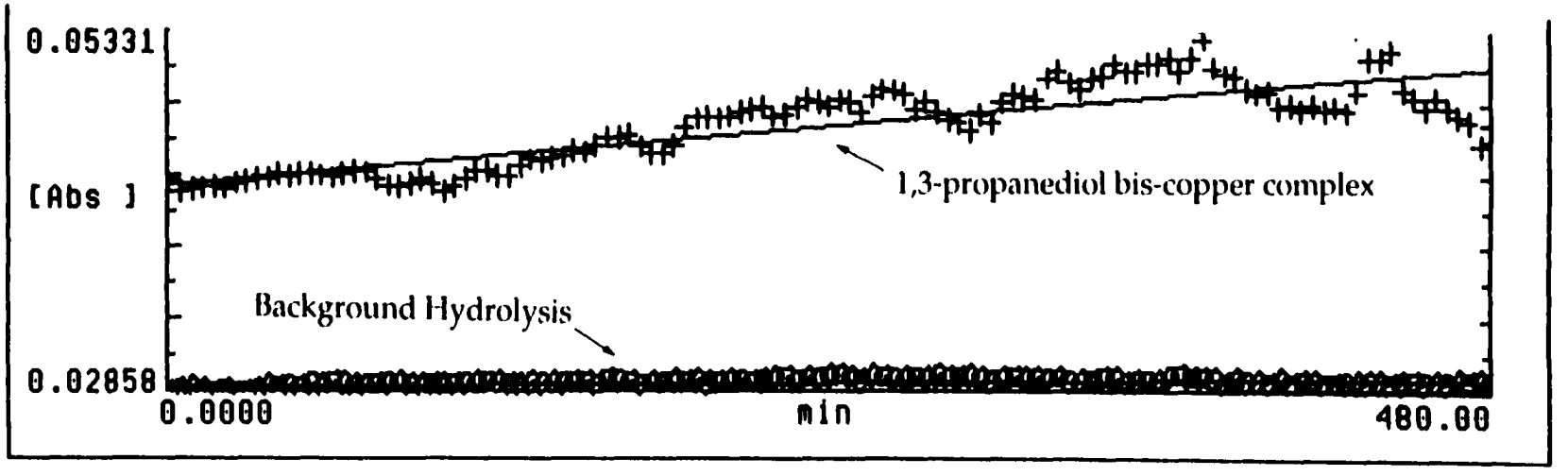


Figure 4.13 Hydrolysis data for 1,3-propanediol-linked bis-copper complex

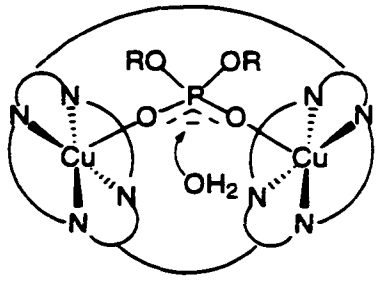


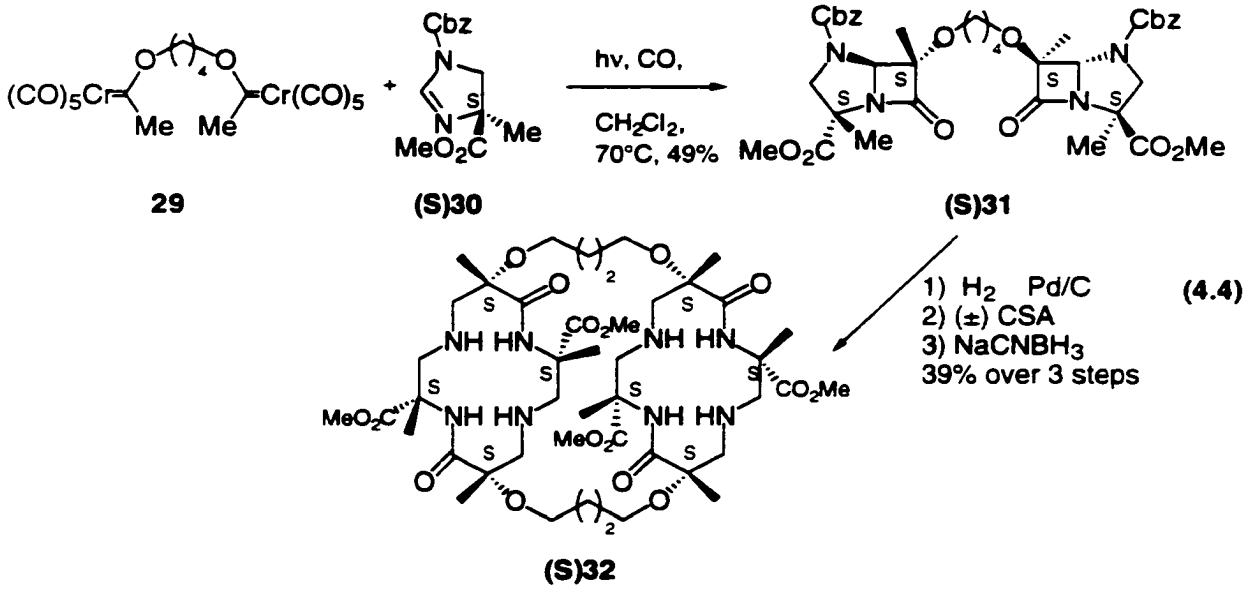
Figure 4.14 Possible mechanism for phosphate diester hydrolysis by **25**

The reason for the poor activity of these two systems could come from several source: The Lewis acidity of the copper centers could be too weak to even coordinate to the phosphate, yet alone activate it towards hydrolysis. Also the geminal dimethyl groups on the dioxocyclam ring and the bridging alkyl groups are in the cavity between the two rings, and this steric bulk could block the approach of the phosphate diester. In any event, the poor results from the initial hydrolysis studies prompted the synthesis of other dioxocyclams in the hope that complexes with better activity could be produced.

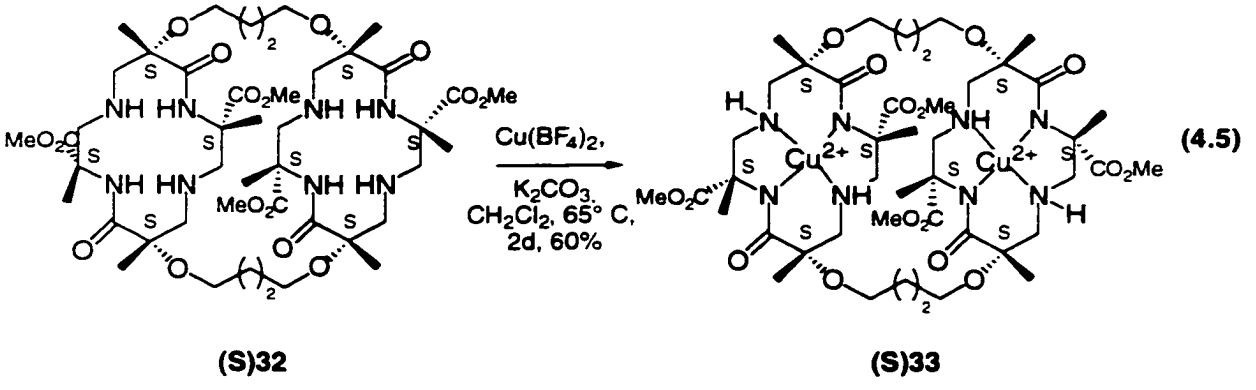
4.C.2. Syntheses of New Bis-dioxocyclams for Hydrolysis Studies

To test whether the two metal centers were too close together the longer 1,4 butanediol linked bis-dioxocyclam was investigated. Following the published procedure,[11] the 1,4 butanediol-linked bis-dioxocyclam was synthesized, but the *meso* and D_2 diastereomers were not separable at any step in the reaction sequence, so a method to synthesize solely the D_2 symmetric isomer of the 1,4-butanediol-linked dioxocyclam was needed. The published synthesis of optically active bis-dioxocyclam[15] produced a single, D_2 symmetric enantiomer of the 1,3-propanediol-linked bis-dioxocyclam (Equation **3.12**). Following the general

procedure published for the synthesis of optically active bis-dioxocyclams the 1,4-butanediol linked bis-dioxocyclam **(S)32** was synthesized (Equation **4.4**).



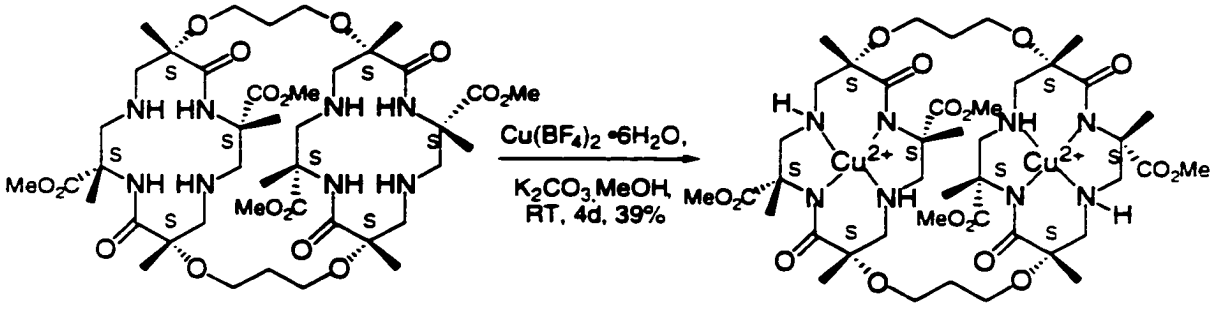
Then bis-dioxocyclam **(S)32** was subjected to the copper complexation conditions to yield the bis copper(II) complex **(S)33** (Equation **4.5**).



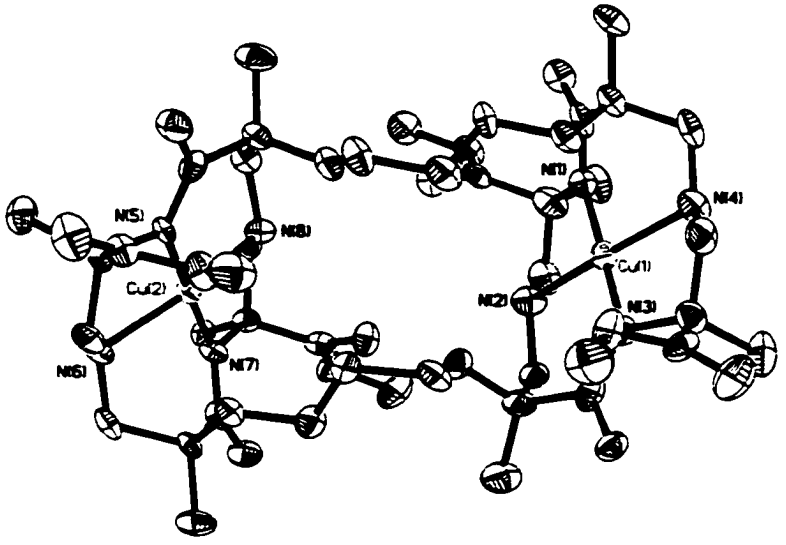
To test whether the optically active bis-copper complexes show a similar conformation to the racemic D_2 bis-nickel complex (Figure **4.9**), the bis-copper complex of optically active 1,3-propanediol-linked bis-dioxocyclam **(S)34** was

synthesized and its X-ray crystal structure solved (Figure **4.15**). The crystal structure demonstrated that the dioxocyclam rings were in similar orientations to the D_2 bis-nickel complex seen previously (Figure **4.16**, **4.17**). The distances between the two metal centers are very similar (Ni-Ni 7.54 Å, and Cu-Cu 7.59 Å) along with the angles between the two rings (Ni-Ni 65°, Cu-Cu 67°). The synthesis of optically active bis-dioxocyclams was then shown to be a viable method to produce the D_2 symmetric isomers of bis-dioxocyclam complexes. This is important because the diastereomers of several bis-dioxocyclams could not be separated in the racemic series.

With similarities of the two D_2 symmetric bis-dioxocyclam established by X-ray crystallography the 1,4- butanediol-linked bis-copper complex was ready to be tested for phosphate diester hydrolysis activity. Unfortunately, this bis-copper complex **(S)33** proved sparingly soluble in water. Thus, this complex could not be tested for phosphate ester hydrolysis activity under physiological conditions worked out in the previous hydrolysis studies. Phosphate diester hydrolysis experiments have been run in mixed solvent systems,[7] and running the hydrolysis studies in a more amenable solvent system is an experiment that should be attempted in the future.



(S)34 **(S)35**



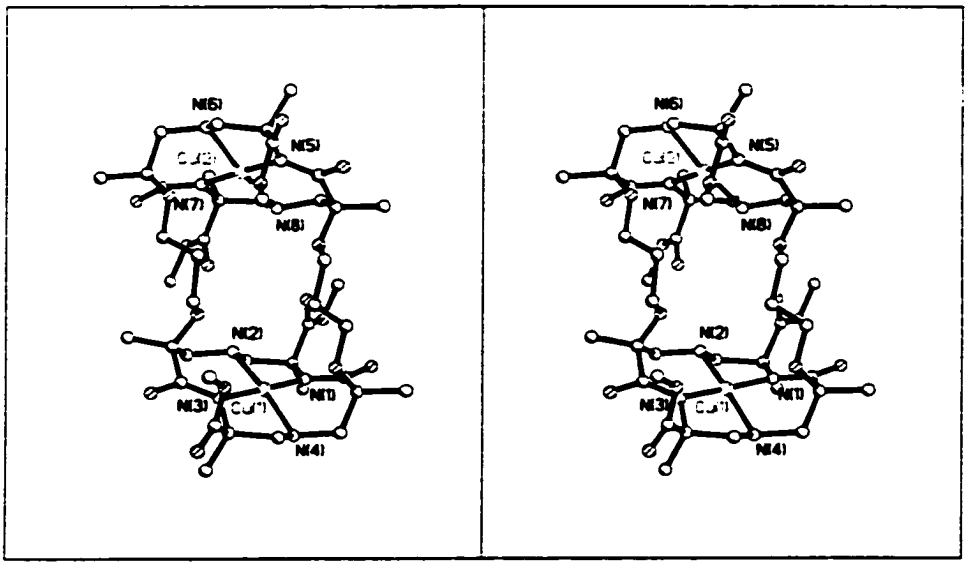


Figure 4.15 Synthesis, X-ray crystal structure and stereo view of **(S)35**

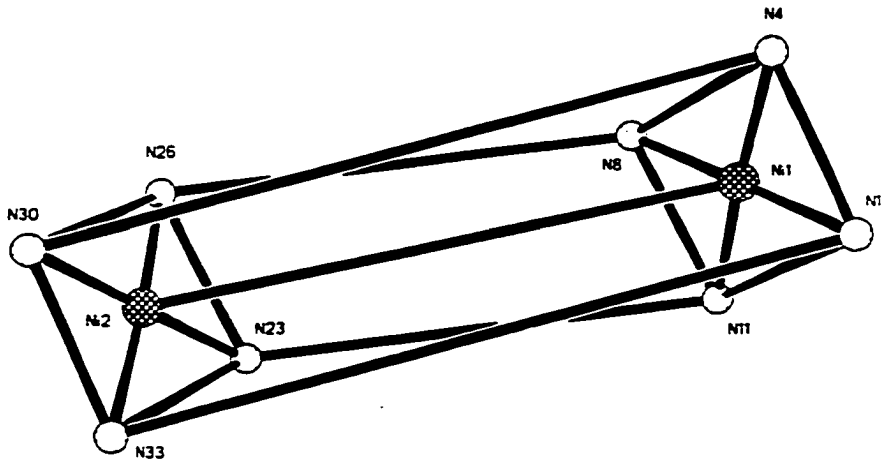


Figure 4.16 Representation of cavity in D_2 1,3 propanediol-linked bis-nickel complex[13]

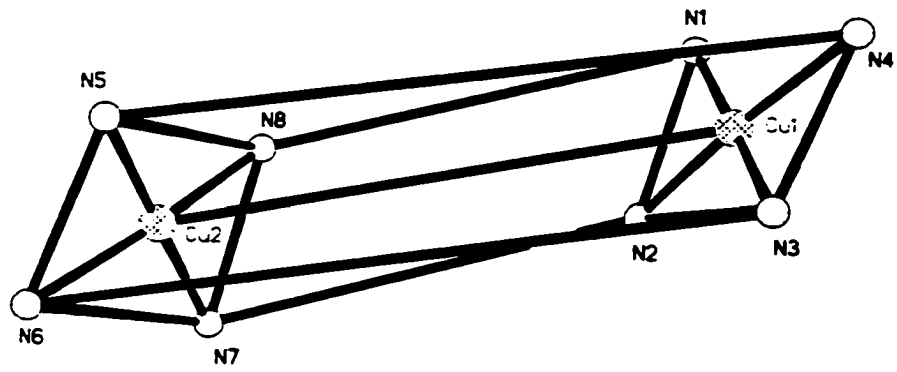
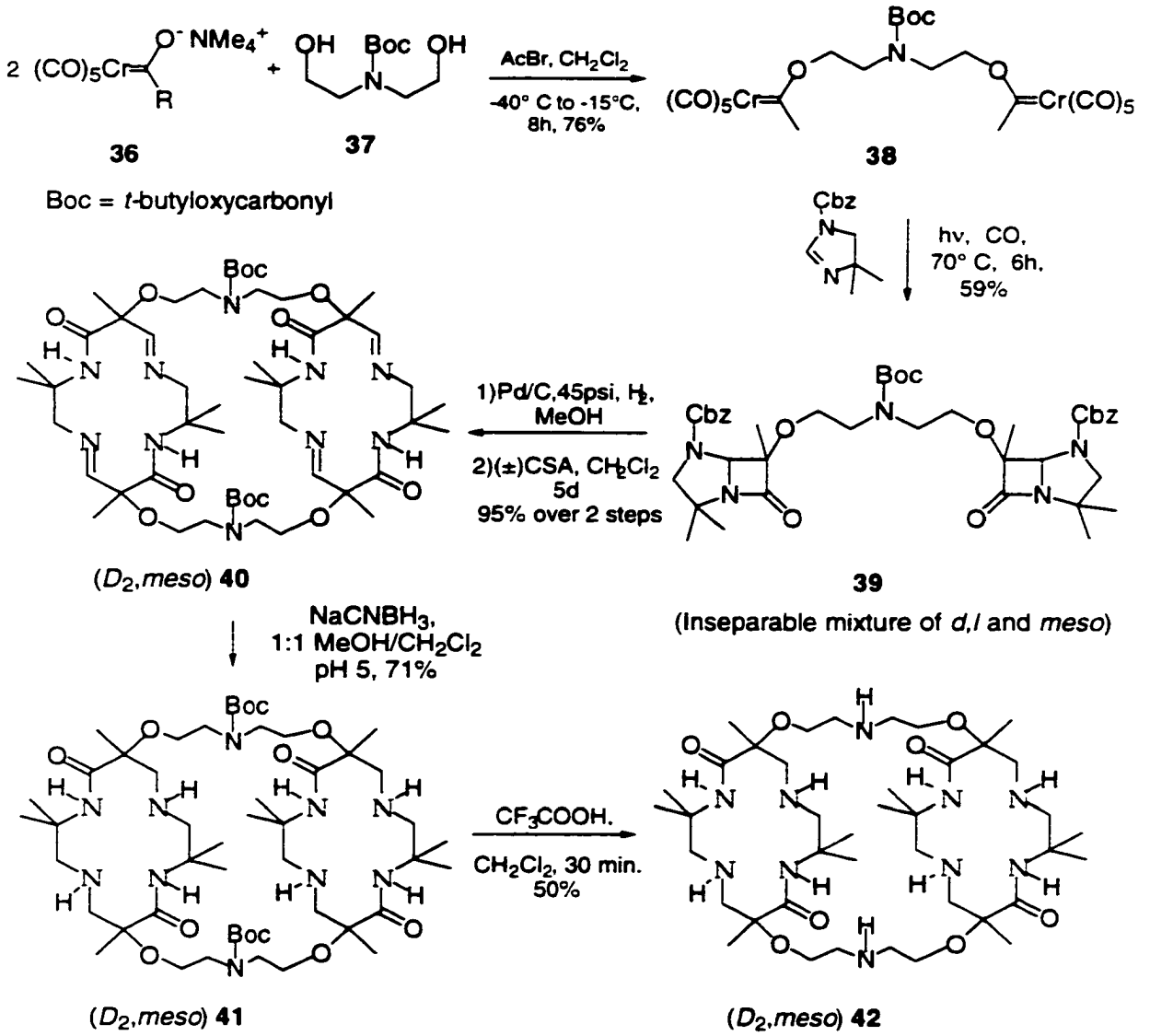


Figure 4.17 Representation of cavity in optically active 1,3 propanediol-linked bis-copper complex **(S)35**

Diethanolamine-linked bis-dioxocyclam **42** (Scheme **4.1**) was also synthesized as a possible phosphate diester hydrolysis agent.



Scheme 4.1 Synthesis of diethanolamine bridged bis-dioxocyclam

The synthesis of bis-dioxocyclam **42** began with the generation of bis-carbene **38** by the exchange reaction with *t*-butyloxycarbonyl (Boc) protected diethanolamine. The Boc protecting group was chosen to deactivate the amine and also because it was stable to the deprotection conditions for the

benzyloxycarbonyl (Cbz) group (Pd/C, H_2). Next, bis-carbene **38** was photolyzed in the presence of an achiral imidazoline, producing bis-azapenam **39** in moderate yield. The *d,l* and *meso* bis-azapenam diastereomers were not separable. After hydrogenolysis to remove the Cbz protecting group and standard dimerization conditions ((±) camphor sulfonic acid (CSA)), the Boc-protected tetraimine bis-dioxocyclam **40** was isolated in low yield as an inseparable mixture of D_2 and *meso* diastereomers. Boc deprotected tetraimine bis-dioxocyclam was also observed after the dimerization reaction which indicated that the (±)CSA was a strong enough acid to remove the Boc group. Reduction of the imines with sodium cyanoborohydride produced Boc bis-dioxocyclam **41** in reasonable yield once again as an inseparable mixture of D_2 and *meso* diastereomers. Finally, deprotection of the Boc group by trifluoroacetic acid produced the free (diethanolamine) bis-dixoxcyclam **42**.

Diethanolamine was chosen as the link between the two dioxocyclam rings for two reasons. First, the two secondary amines should increase the water solubility of the metal complex. Second, under the hydrolysis conditions the protonated amines could activate the phosphate through hydrogen bonding or simply electrostatic activation of the negatively charged phosphate diester.

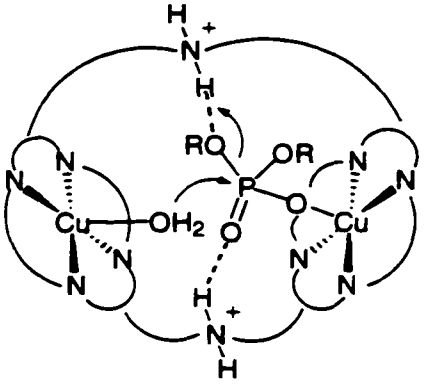


Figure 4.18 Possible hydrolysis mechanism by diethanolamine linked bis-dioxocyclam complexes

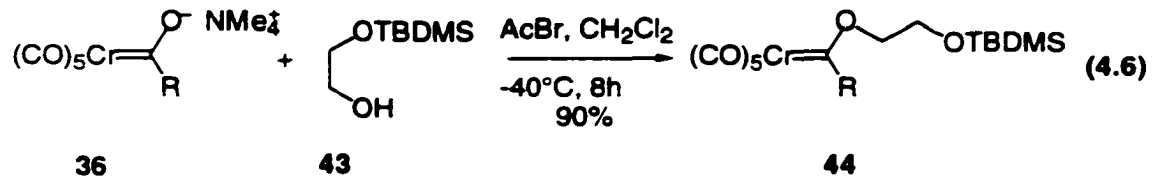
Phosphoryl transfer to the secondary amines in the bridges is a possibility and an analysis of the products of the hydrolysis study will need to be done after any hydrolysis studies.

Unfortunately, the inability to separate the D_2 and *meso* diastereomers at any stage of the reaction sequence rendered this dioxocyclam unusable for phosphate diester hydrolysis studies. In the future, the optically active isomer of diethanolamine linked bis-dioxocyclam could be synthesized to circumvent the separation of diastereomers.

In general, the ground work has been established for the study of phosphate diester hydrolysis by bimetallic complexes of bis-dioxocyclams. Although a useful hydrolysis catalyst was not developed, several new dioxocyclams were synthesized, and if the problems of solubility and diastereomeric mixtures encountered could be solved, these complexes could be used to study phosphate diester hydrolysis. Also, applications other than phosphate diester hydrolysis could be developed for these bimetallic ligands with a tunable cavity between the two metal centers.

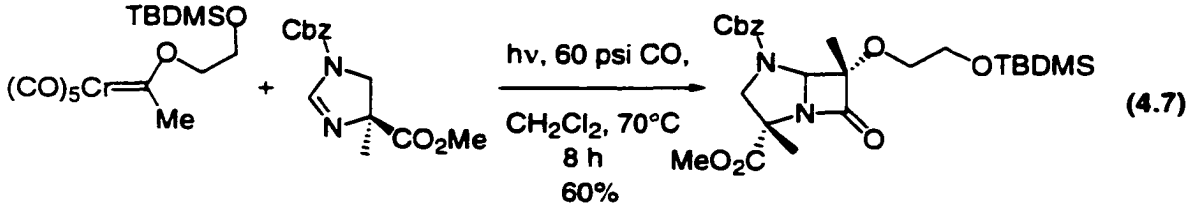
4.C.3. Direct Synthesis of *Meso* Bis-Dioxocyclams

The previously reported synthesis of optically active bis-dioxocyclams produced only the D_2 symmetric isomer. A method for the exclusive synthesis of the *meso* bis-dioxocyclam is also needed in order to study their properties, because of the problems often encountered in separation of the diastereomers. The stepwise synthesis of *meso* bis-dioxocyclams is outlined in the following section. A tert-butyldimethylsilyl (TBDMS) protected carbene complex was synthesized using standard coupling conditions (Equation **4.6**). Carbene complex



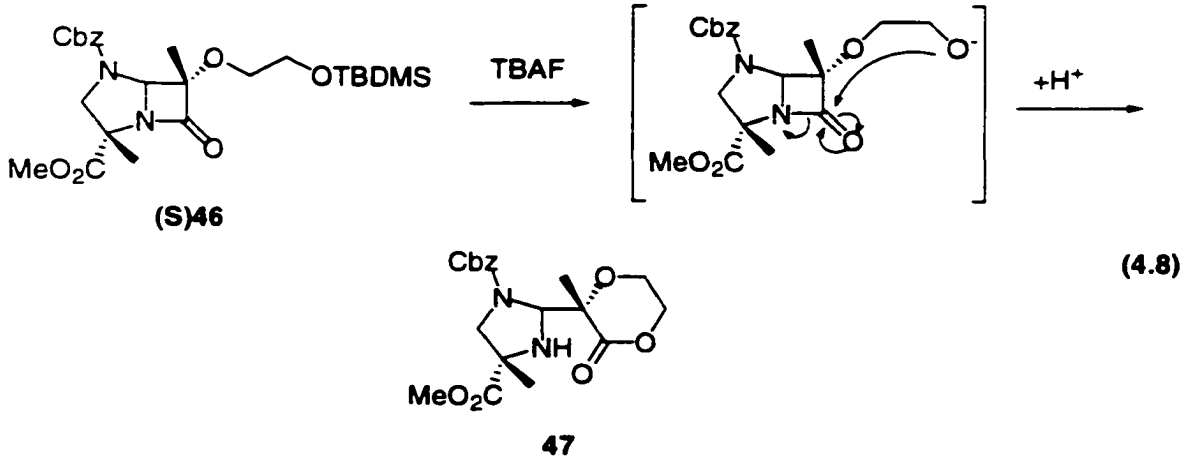
36 43 44 (4.6)

44 was then subjected to the photoreaction conditions in the presence of the optically active (S) imidazoline **(S)30** derived from *l*-alanine and the protected azapenam **(S)46** was then isolated in moderate yield (Equation 4.7).



44 (S)30 (S)46 (4.7)

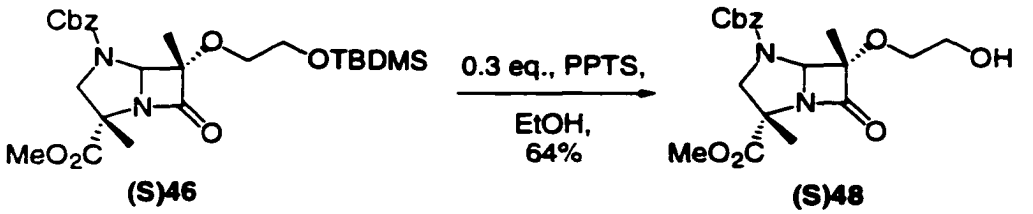
Attempts to remove the TBDMS group with tetrabutylammonium flouride (TBAF) led to ring opening of the β-lactam (Equation 4.8) so an acidic hydrolysis



(S)46 47 (4.8)

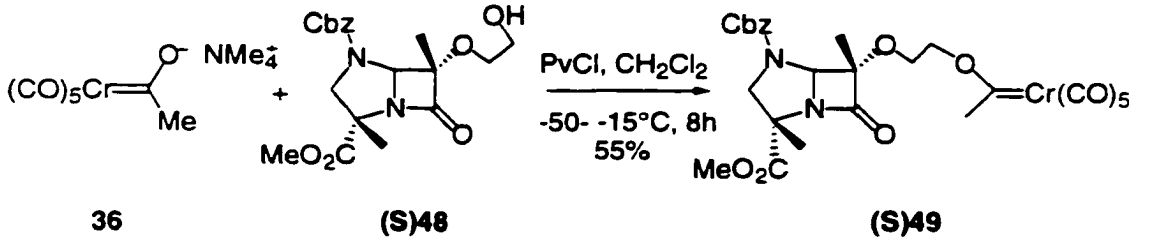
was needed to remove the TBDMS group. Pyridinium *p*-toluenesulfonate (PPTS), a mild acid, was very successful in removing the TBDMS group. The free alcohol **(S)48** was isolated in reasonable yield along with recovery of starting

material, which could be resubmitted to the deprotection conditions (Equation **4.9**).



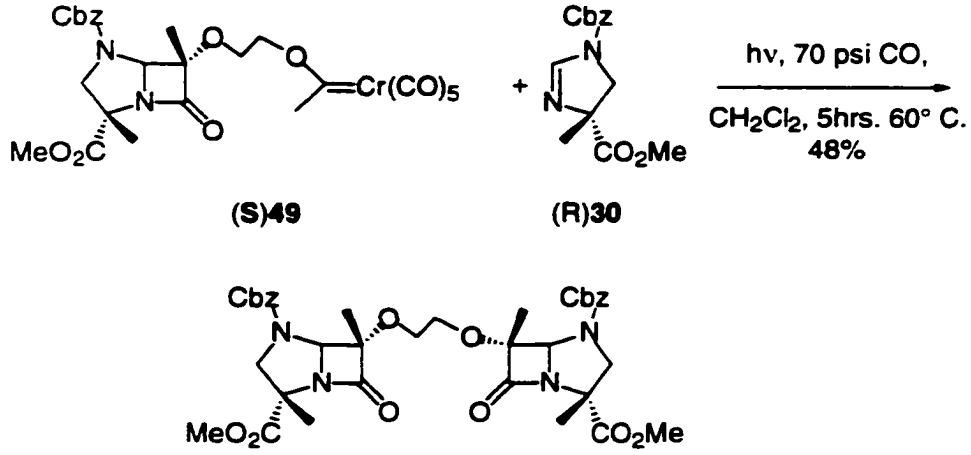
(4.9)

Once the azapenam alcohol **(S)48** was isolated, it was once again subjected to the carbene exchange reaction When acetyl bromide was used as the acylating reagent the yield of the reaction was quite low (10%), but when pivaloyl chloride was used the yields increased (Equation **4.10**). The resulting azapenam- carbene **(S)49** was quite air sensitive and after purification by column



(4.10)

chromatography under an inert atmosphere, the resulting azapenam carbene complex was then immediately used in the next reaction. The photoreaction of the azapenam-carbene complex **(S)49** and the *R*-enantiomer of the optically active imidazoline **(R)30**, (derived from *d*-alanine) was run to produce the *meso* bis-azapenam **50** (Equation **4.11**). Higher temperatures (60°C) were used increase the yield of the bis-azapenam.

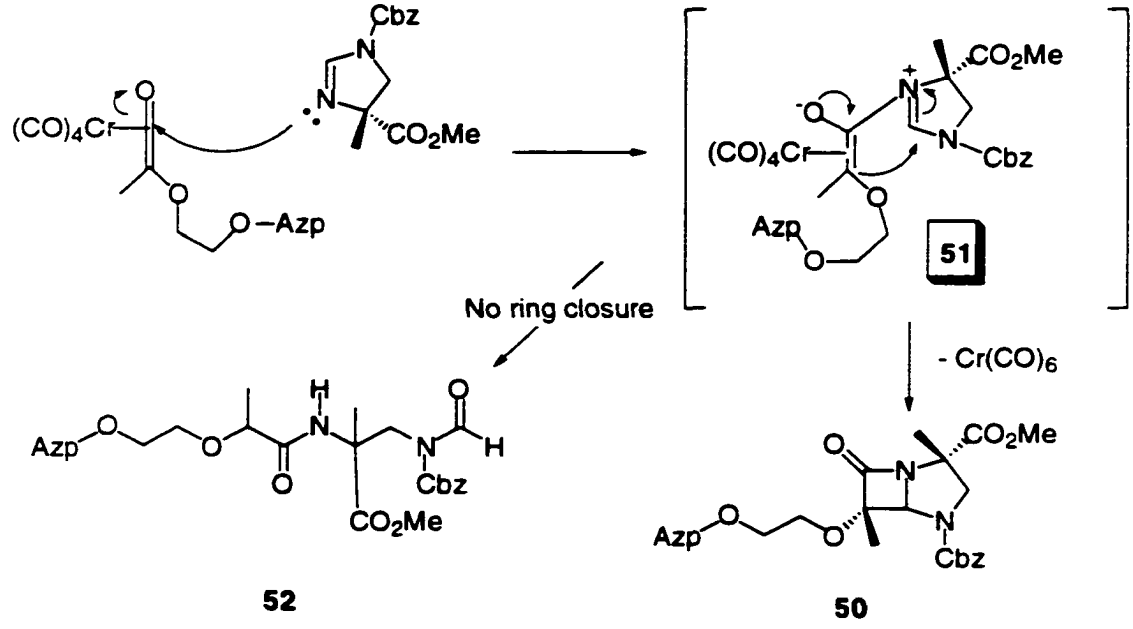


(S)49 (R)30

(4.11)

50

When the photoreaction was run at 50° C a significant amount of a ring-opened side product was observed. The ring-opened product **52** resulted from attack of the imidazoline on the photo-generated ketene (Figure **4.19**), but the resulting zwitter ion **51** did not close to form the β-lactam and the resulting iminium ion

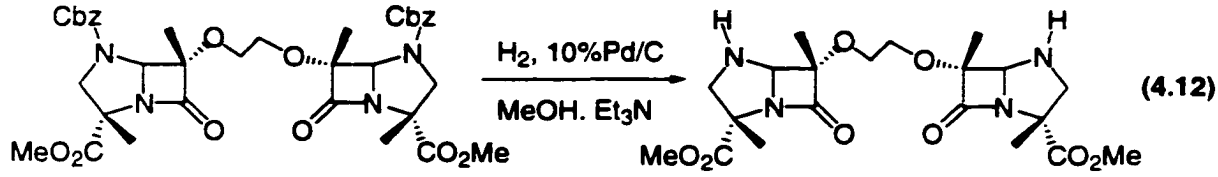


52 50

Figure 4.19 Ring opened product from the photoreaction

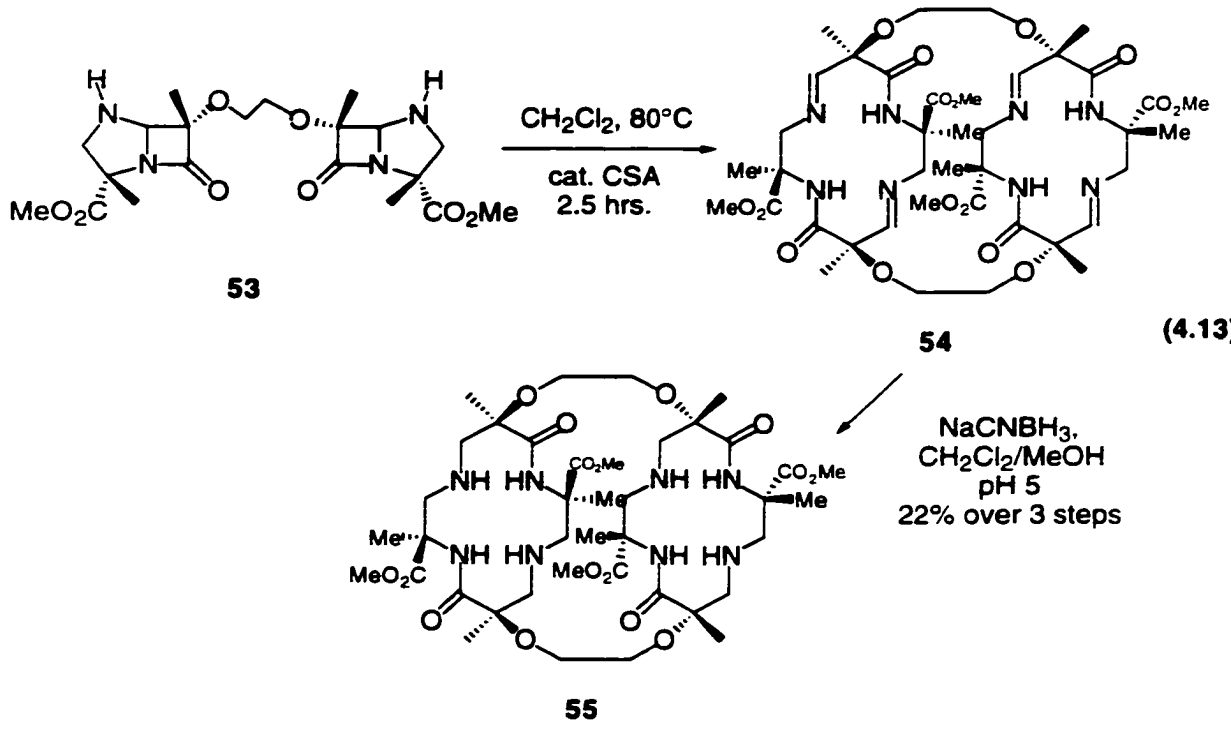
was hydrolyzed upon workup. This hydrolysis opened the imidazoline ring to produce the amide aldehyde **52**. The ring closure to form the β-lactam is a thermal process so higher temperatures were needed to drive the reaction to completion

The Cbz protecting group was removed under standard hydrogenolysis conditions (Equation **4.12**), and the deprotected azapenam **53** was subjected to the acid catalyzed dimerization at high temperature.



50 **53** **(4.12)**

After the dimerization, the imine dioxocyclam **54** was directly taken on to the reduction step without further purification. Thus the *meso*-bis-dioxocyclam **55** was produced in poor combined yield over the last two steps, but the stereoselective synthesis of a two carbon linked *meso*-bisdioxocyclam was accomplished (Equation **4.13**). This synthetic sequence is quite lengthy, but it is the only route available to produce exclusively the *meso* bis-dioxocyclam of certain linker lengths.



The lack of activity of the bis-copper complexes and the limited number of complexes that were studied limit the analysis into the mode of action of the hydrolysis that can be performed. This will change as more complexes are synthesized and tested. Although care must always be taken when relating the conformation of molecules in the solid state and in solution, the possibility of X-ray crystal structures of these often crystalline complexes would also help greatly in the analysis of hydrolysis systems. There are many other systems that can be tested based on these preliminary results, including the use of metals other than copper, even more rigid linkers between the two dioxocyclam rings, and reduction of the amides on the dioxocyclam rings so that charged complexes are formed with metal ions.

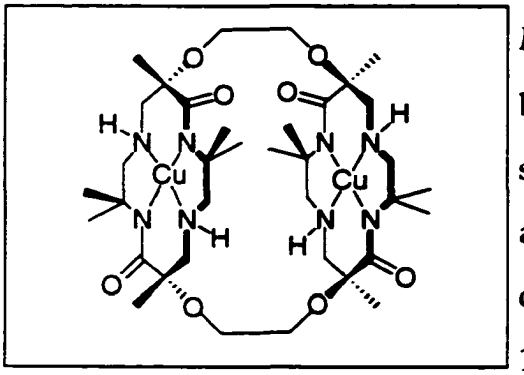
Bis-dioxocyclams represent an interesting new class of ligands capable of coordination to two metal centers. The cavity that is generated between the two rings is quite rigid but the cavity size and shape can be changed by simple

modification in the synthetic sequence. The bis-metal complexes of these ligands show much promise as bis-Lewis acids used in the capture of small molecules. Once a small molecule is positioned between the two metal centers novel chemistry might then be performed, that may normally not be accessible when the small molecule is not held within the controlled environment inside the ligand cavity. By using the different cavity shapes available, subtle differences can be studied as they effect molecules within the cavity. Also the effects of cavity shape and size on the electronic communication between the two coordinated metal centers can be investigated with bis-dioxocyclams.

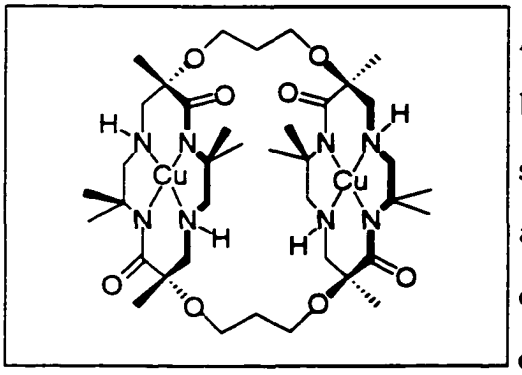
4.D. SUMMARY

The study of phosphate diester hydrolysis by bimetallic coordination complexes helps in understanding how nature achieves such spectacular rate enhancements in the hydrolysis of the phosphate backbone of DNA and RNA. Although the two bis-copper systems that were presented show very poor rate enhancement over background hydrolysis, it was hoped that changes in the bimetallic bis-dioxocyclam systems could be made to produce a system that activate phosphate diesters toward hydrolysis. The two other bis-dioxocyclam systems that were presented were, unfortunately, not suitable for the hydrolysis studies, but they might be used to study the change in reactivity of other small molecules captured inside the well defined cavity between the two dioxocyclam rings. The ground work has now been established and further studies will hopefully develop a successful hydrolysis catalyst that can shed some light on the optimal conditions needed to effect hydrolysis of phosphate diesters.

4.E. EXPERIMENTAL



***D_2* ethylene glycol-linked bis-dioxocyclam bis-copper complex 25** To 10 mL of argon sparged MeOH 74 mg (0.1 mmol) of **23** was added along with 333 mg (1.0 mmol, 10.0 eq.) of $Cu(BF_4)_2 \bullet 6H_2O$ and 138 mg (0.6 mmol, 10.0 eq.) of K_2CO_4. The resulting solution turned violet immediately and was allowed to stir at room temperature for 2 days. The deep blue reaction mixture was then filtered through a pad of Celite and the solvent was removed *in vaccuo*. The resulting blue tar was dissolved in CH_2Cl_2 and extracted with water. The blue water layers were combined and the water was removed *in vaccuo*. The resulting blue tar was then recrystallized from CH_2Cl_2/Hexanes to yield 54 mg (0.063 mmol, 63%) of **25** as deep blue plates. FAB mass spectrum *m/e* 865.2 (m+1) UV/VIS

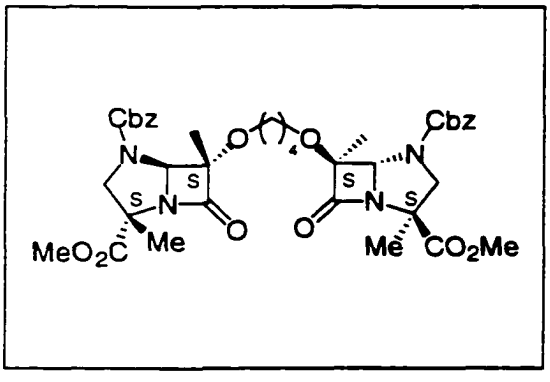


***D_2* 1,3-propanediol-linked bis-dioxocyclam bis-copper complex 25** To 2 mL of argon sparged MeOH 50 mg (0.06 mmol) of **24** was added along with 146 mg (0.6 mmol, 10.0 eq.) of $Cu(BF_4)_2 \bullet 6H_2O$ and 83 mg (0.6 mmol, 10.0 eq.) of K_2CO_4. The resulting solution was allowed to stir at room temperature for 4 days. The deep blue reaction mixture was then filtered through a pad of Celite and the solvent was removed *in vaccuo*. The resulting blue tar was titurated with CH_2Cl_2 and $CHCl_4$. The blue tar was then redissolved in MeOH and recrystallized from 1:1 MeOH, Et_2O to yield 37

mg (0.04 mmol, 70%) of **26** as deep blue plates. FAB mass spectrum *m/e* 828.2 (m+1) UV/VIS (H_2O) λ(max) = 503 nm (ε = 240)

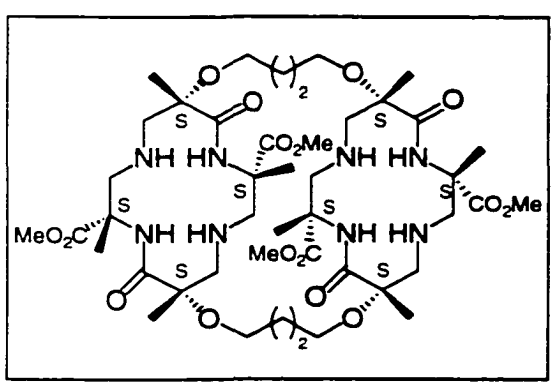
Phosphate Diester Hydrolysis Conditions

General Procedure: The hydrolysis experiment was performed in a 20 mmol HEPES buffer in water at pH of 7.05. For the experiment identical cuvettes were prepared and were analyzed sequentially by the UV/VIS spectrophotometer. The first cuvette contained only the HEPES buffer solution as a blank for the second cuvette. The second cuvette contained a solution of BPNPP, which was a control to measure the background hydrolysis rate. The third cuvette contained a solution of the bis-copper bis-dioxocyclam in HEPES buffer and was the blank for the fourth cuvette which held a solution of BPNPP and the bis-copper catalyst. The fifth cuvette contained a solution of $Cu(BF_4)_2$ and was the blank for the sixth cuvette that contained a solution of BPNPP and $Cu(BF_4)_2$. The absorbence at 400 nm was measured every 4 minutes for 8 hours at a constant temperature of 25° C.



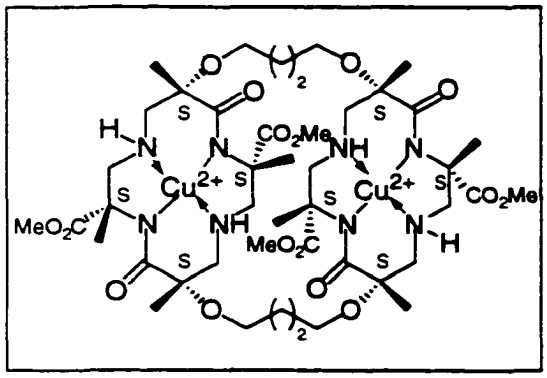
Optically active 1,4-butanediol-linked bis-azapenam (S)31. 1,4-butandiol linked carbene complex **29** (1.0 g, 1.9 mmol) and (S)imidazoline **(S)30** (1.05 g, 3.8 mmol, 2 eq.) were dissolved in 100 mL of dry CH_2Cl_2 under argon in a Pyrex pressure tube. After three freeze-thaw degassing cycles, the resulting yellow solution was irradiated with 4 x 500-W halogen lamps under 70 psi of CO pressure at 70 °C. The progress of the reaction was indicated by the

fading of the yellow color. After 6 hours, the pale yellow reaction mixture was cooled and the pressure released, followed by removal of the solvent *in vaccuo*. The residue was then titurated in MeOH and the resulting solution was cooled to -20 °C over an hour. Removal of the solid chromium hexacarbonyl by filtration followed by removal of the MeOH *in vaccuo* yielded a pale yellow oil which was taken up in 1:1 Hexane/EtOAc and was photoxidized for 1 day. The pale green solution was then filtered through a pad of Celite and the solvent was removed *in vaccuo*. Purification by column chromatography on silica gel (1:1 Hexanes /EtOAc) gave 700 mg (0.93 mmol, 49%) the optically active azapenam **(S)31** as a clear oil. ^{1}H NMR δ 7.35 (bs, 10H), 5.19 (m, 6H), 3.37 (bd, 2H *J* = 11.3 Hz), 3.74 (s, 6H), 3.56 (bs, 2H), 3.43 (bs, 2H), 3.24 (bd, 2H *J* = 11.3 Hz), 1.81 (s, 6H), 1.63 (bs, 2H), 1.54 (bs, 2H), 1.32 (s, 2H), 1.23 (s, 4H). ^{13}C NMR δ 173.3, 171.2, 153.3, 135.7, 128.8, 128.6, 128.2, 90.7, 76.3, 67.9, 66.1, 65.8, 65.5, 58.7, 58.5, 53.3, 26.6, 18.2, 13.5 IR (neat) ν 1780, 1713 (C=O) (cm^{-1}).

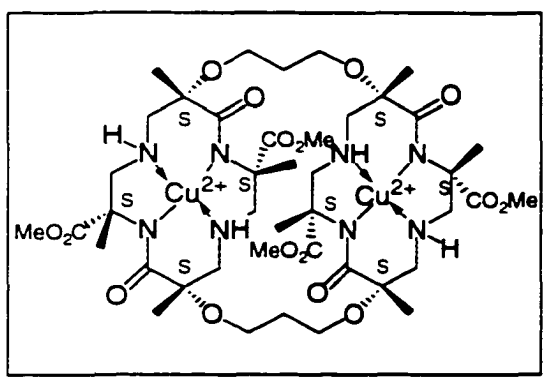


Optically active 1,4-butanediol-linked bis-dioxocyclam (S)32. 360mg (0.48 mmol) of Bis azapenam **(S)31** was dissolved in 10 mL of 1:1 MeOH/CH_2Cl_2 to which 5 drops of triethylamine was added. Then 180 mg of 10% Pd/C was added and the reaction was pressurized with 45 psi of H_2. The resulting slurry was vigorously stirred at room temperature for 2 h. Filtration through a pad of Celite to remove the Pd/C and removal of the solvent *in vaccuo*. yielded a pale yellow wax. The wax was dissolved in CH_2Cl_2 and was washed with a sat. solution of Na_2CO_3 and the combined CH_2Cl_2 layers were dried with Na_2SO_4. The solvent was removed *in vaccuo* and then resulting wax was dried under high

vacuum. The resulting foam was then dissolved in 50 mL of dry CH_2Cl_2 and 15 mg of (±)CSA was added. The solution was allowed to stir at room temperature for 5 days. After 5 days the solution was washed with a sat. solution of Na2CO3 and the combined CH_2Cl_2 layers were dried with Na_2SO_4. The solvent was removed *in vaccuo* to yield a pale yellow powder. The crude tetra-imine dioxocyclam (~190 mg) was dissolved in 10 mL of 1:1 CH_2Cl_2/MeOH and a small amount of bromocreosol green was added to the solution. The solution was then cooled to 0 °C and 103 mg of $NaCNBH_3$ (1.64 mmol, 4.0 eq) was added. Anhydrous 1M HCl in MeOH was slowly added to the solution until a yellow/green color persisted (pH ~5). The resulting yellow/green solution was allowed to warm to room temperature and was stirred overnight. Excess 1.0 M HCl in MeOH was added to the solution until gas was evolved from the solution to quench the $NaCNBH_3$. 20 mL of CH_2Cl_2 was then added and the reaction mixture was then washed with 10% NaOH and dried over Na_2SO_4, followed by removal of the solvent *in vacuuo*. Purification of the resulting white powder by column chromatography on silica gel (97:3, CH_2Cl_2/MeOH) gave 90mg (0.093 mmol, 39% over 3 steps) of the optically active bis-dioxocyclam **(S)32** as white solid. ^1H NMR δ 8.80 (bs, 4H), 3.74 (s, 12H), 3.52 (bm, 4H), 3.43 (bm, 4H), 3.20 (bd, 4H *J*= 8.4 Hz), 2.88 (m, 12H), 1.83 (bs, 4H), 1.70 (bs, 8H) 1.60 (s, 12H), 1.3 (s 12H). ^{13}C NMR δ 174.1, 172.3, 78.7, 63.2, 60.4, 56.6, 54.8, 52.8, 27.4, 21.3, 19.3 IR (neat) ν 1739 1671 (C=O) (cm^{-1}).

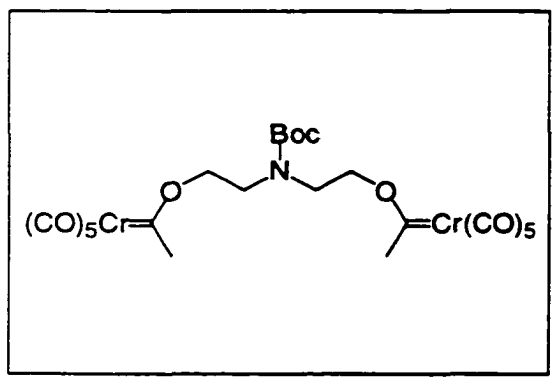


Optically active 1,4-butanediol-linked bis-dioxocyclam bis-copper complex (S)33. To 5 mL of CH_2Cl_2 and 1 ml of MeOH. in a pressure tube 90 mg (0.092 mmol) of **(S)32**, 250 mg (0.74 mmol, 8.0 eq.) of $Cu(BF_4)_2 \bullet 6H_2O$ and 102 mg (0.74 mmol, 8.0 eq.) of K_2CO_3 were added. The pressure tube was capped and the reaction was heated to 65 °C for 2 d followed by stirring at room temperature for 2 days. After four days the green reaction mixture was filtered through a pad of Celite and the solvent was removed *in vaccuo*. The resulting burgundy tar was dissolved in CH_2Cl_2, and the organic layer was washed with water. The burgundy color remained in the CH_2Cl_2 layer, and the organic extract was dried with Na_2CO_3. Crystallization from CH_2Cl_2 /Hexanes yielded 60 mg (0.055 mmol 60 %) of **(S)33** as burgundy plates. FAB MS 1097 (M+1), Anal. Calcd. for $C_{44}H_{72}Cu_2N_8O_{16}$: C, 48.21, H, 6.62, N, 10.22, Found: C, 48.11, H, 6.68, N, 10.18.

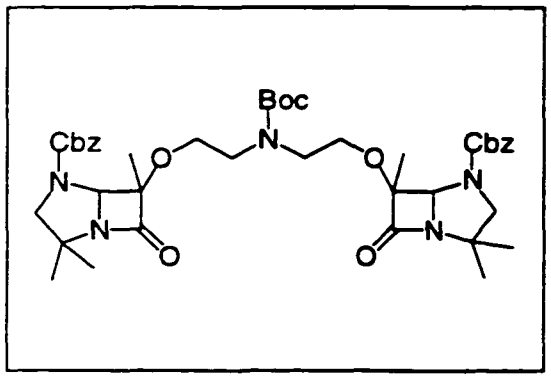


Optically active 1,3-propanediol-linked bis-dioxocyclam bis copper complex (S)35 To 1 ml of MeOH. in a pressure tube 25 mg (0.026 mmol) of **(S)34**, 60 mg (0.26 mmol, 10.0 eq.) of $Cu(BF_4)_2 \bullet 6H_2O$ and 36 mg (0.26 mmol, 10.0 eq.) of K_2CO_3 were added. The pressure tube was capped and the reaction was allowed to stir at room temperature for 4 days. After the four days the green reaction mixture was then filtered through a pad of Celite and the solvent was removed *in vaccuo*. The resulting burgundy tar was dissolved in CH_2Cl_2,

and the organic layer was washed with water. The burgundy color was extracted into the aqueous layer and the water from the combined aqueous layers was removed *in vacuuo*. Recrystallization by slow diffusion of Et_2O into CH_2Cl_2 yielded 9 mg (0.0082 mmol, 31%) of **(S)33**. X-ray quality crystals of **(S)33** were isolated from this solvent system.

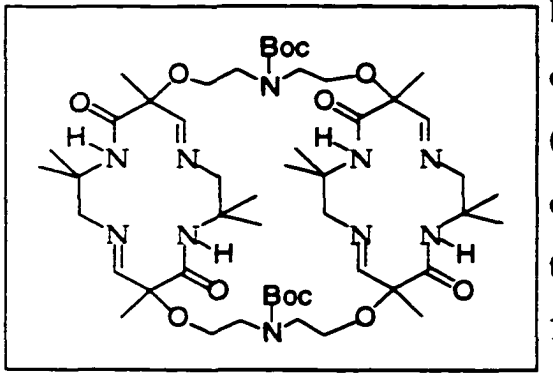


Boc protected, diethanolamine-linked bis-carbene complex (37) 5.13g (16.6 mmol, 2.2 eq.) of methyl tetramethylammonium "ate" complex **36** was dissolved in 100 mL of dry CH_2Cl_2 under an argon atmosphere, and the solution was cooled to -60°C. Acetyl Bromide (0.63 mL, 8.5 mmol) was added dropwise, and the resulting solution was allowed to stir at -60°C for 30 min. Then 1.55g (7.55 mmol) of Boc protected diethanolamine **37** was added. The resulting solution slowly warmed to -20°C over 2 h. The reaction mixture was then held at -20° C for a further 5 hours under argon, after which the mixture was filtered through a pad of silica gel and the solvent was removed *in vacuuo*. The resulting orange simi-solid was adsorbed onto silica gel and was purified by column chromatography (1:1 Hexanes/EtOAc) to yield 3.7g (5.7 mmol 76%) of a bright yellow oil which solidified when stored at -15° C. ^1H NMR δ 5.01 (bs, 4H), 3.94 (bs, 4H), 2.99 (bs, 6H), 1.50 (bs, 9H). ^{13}C NMR δ 360.4, 360.0, 223.4, 223.2, 216.4, 155.1, 81.6, 48.4, 48.1 28.4.

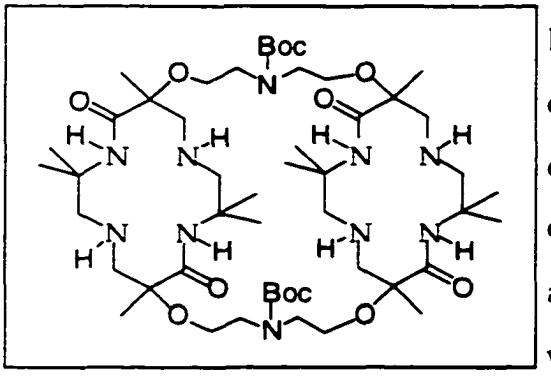


Boc protected, diethanolamine-linked bis-azapenam 39

860 mg (1.34 mmol) of diethanolamine linked carbene complex **38** and 622 mg (2.68 mmol, 2 eq.) of imidazoline **2** were dissolved in 50 mL of dry CH_2Cl_2 under argon in a Pyrex pressure tube. After three freeze-thaw degassing cycles, the resulting yellow solution was irradiated with 4 x 500-W halogen lamps under 70 psi of CO at 70 °C. The progress of the reaction was indicated by the fading of the yellow color. After 6 hours the pale yellow reaction mixture was cooled and the pressure released, followed by removal of the solvent *in vaccuo*. The residue was then titurated in MeOH and the resulting solution was cooled to -20 °C over an hour. Removal of the solid chromium hexacarbonyl by filtration followed by removal of the MeOH *in vaccuo* yielded a pale yellow oil which was taken up in 1:1 Hexanes/EtOAc and was photoxidized for 1 day. The solution was then filtered through a pad of Celite and the solvent was removed *in vaccuo*. Purification by column chromatography on silica gel (1:1 Hexanes/EtOAc) gave 610 mg (0.78 mmol 59%) of **39**. as an inseparable 1:1 mixture of *d,l* and *meso* diastereomers. ^{1}H NMR δ 7.36 (bs, 10H), 5.28 (bd, 2H J = 12.1), 5.15 (bd, 2H J = 13.6 Hz), 5.07 (m, 2H), 3.80-3.35 (m, 12H), 3.16 (bd, 2H J = 10.3 Hz), 1.61 (bs, 6H), 1.45 (bs, 9H), 1.40 (bs, 2H), 1.18 (bs, 12H). ^{13}C NMR δ 173.3, 171.2, 153.3, 135.7, 128.8, 128.6, 128.2, 90.7, 76.3, 67.9, 66.1, 65.8, 65.5, 58.7, 58.5, 53.3, 26.6, 18.2, 14.5 IR (neat) ν 1780, 1713 (C=O) (cm^{-1}).

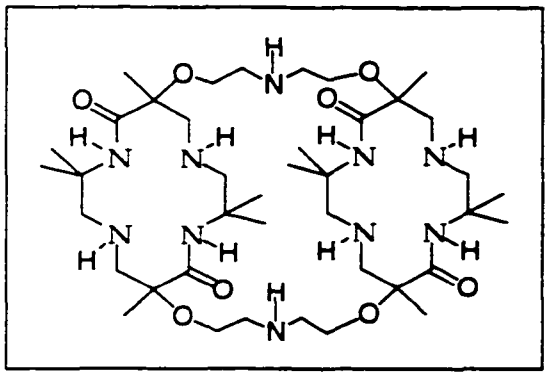


Boc protected, diethanolamine-linked bis-dioxocyclam tetra imine 40. 610 mg (0.78mmol) of bis-azapenam **39** was dissolved in methanol (5 mL) and 4 drops of triethylamine was added. Then 300 mg of 10% Pd/C was added and the reaction was pressurized to 45 psi with H_2 and was stirred vigorously for 2 h. Filtration through a pad of Celite and evaporation of the solvent produced a clear wax which was dissolved in CH_2Cl_2 which was then washed with a sat. solution of Na2CO3 and the combined CH_2Cl_2 layers were dried with Na_2SO_4. Removal of the solvent *in vacuuo* and drying of the resulting clear wax under high vacuum resulted in 390 mg of an off-white foam. This foam was then taken up in 50 mL of dry CH_2Cl_2 and 15 mg of (±) CSA was added the solution. After 5 days at room temperature the reaction was washed with a sat. solution of Na2CO3 and the combined CH_2Cl_2 layers were dried with Na_2SO_4. The solvent was removed *in vacuuo* to yield 375 mg (0.73 mmol, 95%) of **40** as an inseparable 1:1 mixture of D_2 and *meso* diastereomers which was carried on without further purification.



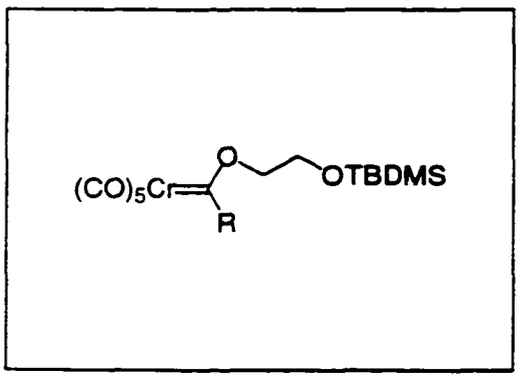
Boc protected, diethanolamine-linked bis-dioxocyclam 41 375 mg (0.36 mmol) of the crude tetra-imine dioxocyclam **40** was dissolved in 10 mL of 1:1 CH_2Cl_2/MeOH and a small amount of bromocreosol green was added to the solution. The solution was then cooled to 0 °C and 92 mg of $NaCNBH_3$ (1.47 mmol, 4.0 eq) was added. Anhydrous 1M HCl in MeOH was slowly added

to the solution until a yellow/green color persisted (pH ~5). The resulting yellow/ green solution was allowed to warm to room temperature and was stirred overnight. Excess 1.0 M HCl in MeOH was added to the solution until gas was evolved from the solution to quench the $NaCNBH_3$. 20 mL of CH_2Cl_2 was added and the reaction mixture was then washed with 10% NaOH and dried over Na_2SO_4, followed by removal of the solvent *in vacuuo*. The resulting crude mixture was recrystallized from CH_2Cl_2/Hexanes to yield 262 mg (0.25 mmol 71%) of **41** as white solid. **41** crystallized as a 1:1 mixture of D_2 and *meso* diastereomers. ^1H NMR δ 7.24 (s, 2H), 6.88 (s, 2H), 4.37 (m, 2H), 3.72-3.59 (m, 12H), 3.48 (m, 4H), 3.10-3.00 (m, 4H), 2.90 (bd, 1H J = 4.0 Hz), 2.86 (bd, 1H J = 4.8 Hz), 2.82 (bd, 1H J = 5.9 Hz), 2.78 (bd, 1H J = 5.1 Hz), 2.64 (m 4H), 2.32 (dd, 2H J = 13.9, 2.9 Hz), 2.0 (m, 2H), 1.84-1.72 (m, 4H), 1.46 (bs, 18H), 1.35 (s, 6H), 1.32 (s, 6H), 1.30 (s, 6H), 1.25 (s, 6H), 1.24 (s, 6H), 1.17 (s, 6H). ^{13}C NMR δ 173.0, 172.5, 156.4, 80.8, 80.2, 79.8, 79.8, 63.1, 59.2, 58.3, 58.0, 56.2, 54.4, 54.0, 49.7, 49.4, 49.1, 47.9, 46.4, 28.9, 28.6, 27.2, 25.6, 24.6, 23.1, 19.5, 19.1.

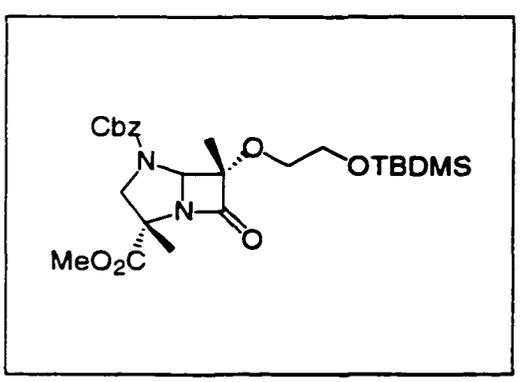


Diethanolamine-linked bis-dioxocyclam 42. 50 mg (0.048 mmol) of Boc protected bis-dioxocyclam **41** was dissolved in 1 mL of CH_2Cl_2 to which 0.5 mL of trifluoroacetic acid was added. The reaction mixture was then allowed to stir at room temperature for 30 minutes. 5 mL of CH_2Cl_2 was added to the reaction mixture which was then washed with 10% NaOH and dried over Na_2SO_4, followed by removal of the solvent *in vacuuo*. 20 mg (0.024 mmol 50%) of **41** was isolated was a white powder. ^1H NMR (CD_3OD, 50° C) δ 8.08 (s, 4H), 4.08 (m, 8H), 3.60 (d, 4H J = 11.7), 3.39 (bs, 8H), 3.24 (d, 4H J = 12.4 Hz), 3.16 (d,

4H J = 12.5 Hz), 2.81 (bd, 4H J = 11.0 Hz), 1.76 (s, 12H), 1.73 (s, 12H), 1.70 (s, 12H). ^{13}C NMR δ 173.5, 81.0, 81.0, 78.7, 78.7, 78.3, 78.3, 77.8, 77.8, 61.5, 58.1, 58.1, 57.3, 57.3, 26.5, 25.7, 20.0. IR (neat) ν 1673 (C=O) (cm^{-1}).

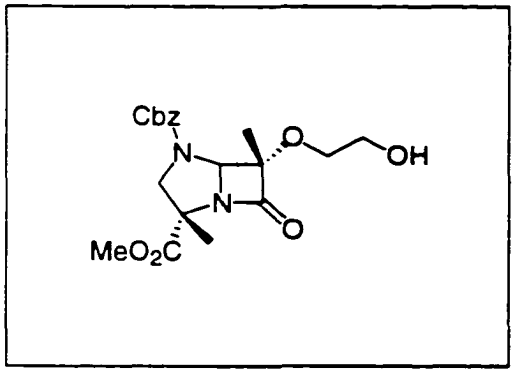


TBDMS protected Chromium Alkoxycarbene Complex 43 Methyl tetramethylammonium "ate" complex **36** (2.63 g, 8.5 mmol) was dissolved in 60 mL of dry CH_2Cl_2 under an argon atmosphere, and the solution was cooled to -60°C. Acetyl Bromide (0.63 mL, 8.5 mmol) was added dropwise, and the resulting solution was allowed to stir at -60°C for 30 min. Then TBDMS protected ethylene glycol **43** was added to the solution in 5 mL of dry CH_2Cl_2. The resulting solution was slowly warmed to -10°C over 4.5 h. Reaction mixture was filtered through a pad of silica gel and the solvent was removed *in vacuuo*. The resulting dark orange oil was then adsorbed onto silica gel purified by column chromatography on silica gel (Hexane/EtOAc 9:1) to give 1.78g (90%) of complex **43** as a yellow-orange oil. ^1H NMR δ 5.0 (bs, 2H), 4.15 (t, J= 4 Hz, 2H), 2.98 (s, 3H), 0.91 (s, 9H), 0.11 (s, 6H).

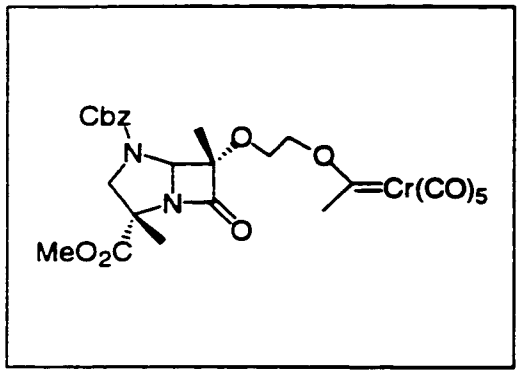


TBDMS protected optically active azapenam (S)46. TBDMS protected carbene complex **43** (1.0 g, 2.8 mmol) and (S) imidazoline **(S)30** (0.75 g, 2.8 mmol) were dissolved in 50 mL of dry CH_2Cl_2 under argon in a Pyrex pressure tube. After three freeze-thaw degassing cycles, the yellow solution was irradiated with 4 x 500-W halogen lamps under 70 psi of CO at 60 °C. The progress of the reaction was indicated by the fading of

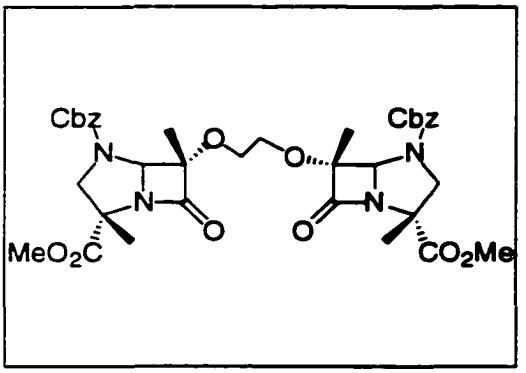
the yellow color. After 4 hours the reaction was cooled to room temperature and the pressure released the solvent followed by removal of the solvent *in vaccuo*. The residue was titurated in MeOH and cooled to -20 °C for 1 hour. Removal of the solid chromium hexacarbonyl by filtration followed by removal of the MeOH *in vaccuo* yielded a pale yellow oil which was taken up in 1:1 Hexane/EtOAc and was photo-oxidized for 1 day. The solution was then filtered through a pad of Celite and the solvent was removed *in vaccuo*. Purification by radial chromatography on silica gel (1:1, Hexane/EtOAc) gave a single diastereomer of the TBDMS protected azapenam **(S)46** as a clear oil (875 mg 63%). ^{1}H NMR δ 7.36 (bs, 5H), 5.2-5.1 (m, 3H), 4.37 (d, *J*= 11 Hz, 1H), 3.85-3.5 (m, 8H), 1.80 (s, 3H), 1.21 (s, 3H) 0.90 (s, 9H), 0.07 (bs, 6H).



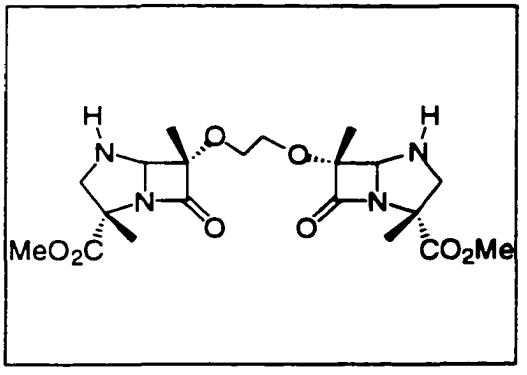
Optically active azapenam alcohol (S)48. Optically active azapenam **(S)46** (875 mg, 1.77 mmol) and pyridinium *p*-toluenesulfonate (134 mg, 0.532 mmol, 0.3 eq.) were dissolved in 20 mL of EtOH. The resulting solution was allowed to stir at RT for 16 h. After the 16 h the EtOH was removed *in vaccuo*, and the resulting oil was redissolved in CH_2Cl_2. The solution was then washed with brine and dried over Na_2SO_4. followed by removal of the solvent *in vacuuo*. The resulting oil was then purified by radial layer chromatography on silica gel (1:1 Hexane/EtOAc) to yield 435 mg (65%) of **(S)48** as a colorless oil. ^{1}H NMR δ 7.37 (s, 5H), 5.30-5.00 (m, 3H), 4.40-4.30 (m, 1H), 3.85-3.45 (m, 8H), 3.25 (m, 1H), 2.25 (bs, 1H), 1.8 (s, 3H), 1.50-1.20 (m, 5H).



Optically active azapenam carbene complex (S)49.. Methyl tetramethyl-ammonium "ate" complex **36** (391 mg, 1.26 mmol) was dissolved in 30 mL of dry CH_2Cl_2 in an airless flask under an atmosphere of Ar and cooled to -40 °C. To the cooled solution pivoyl chloride (0.14 mL 1.26 mmol) was slowly added. The solution was allowed to slowly warm to -20°C over 2 h during which the yellow solution turned brown, after which the azapenam alcohol **(S)48** (435 mg, 1.14 mmol) was added and the solution was stirred at -10°C for 6 h after which the solution was a yellow color. The reaction mixture was then filtered through a pad of silica gel and then the solvent was removed *in vacuuo*. The resulting dark orange oil was then adsorbed onto silica gel was purified by column chromatography under argon on silica gel with 1:1 hexane/EtOAc yielded 330 mg (48%) of the azapenam carbene **(S)49**. Care must be taken with the carbene because of instability to air. Running the column chromatography under argon is recommended along with keeping the carbene under an argon atmosphere at all times. ^{1}H NMR δ 7.35 (s, 5H), 5.3-4.8 (m, 5H), 4.45-3.70 (m, 7H), 3.27 (d, *J*= 11 Hz), 3.0- 2.9 (m, 3H), 1.8 (bs, 3H), 1.45-1.20 (m, 6H).^{13}C NMR δ 360.0, 223.4, 216.4, 172.3, 172.0, 171.0, 153.0, 135.7, 128.8, 128.5, 128.1, 90.8, 68.1, 65.7, 64.2, 58.8, 58.5, 53.3, 27.2, 18.1, 13.9

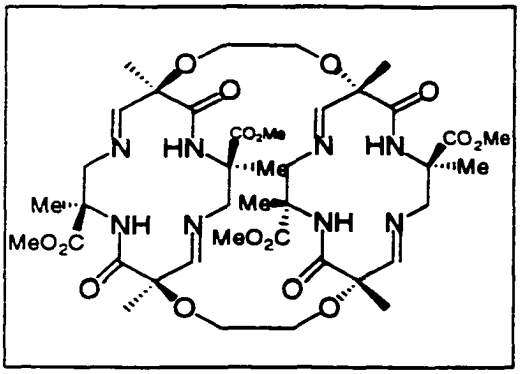


Cbz protected *meso*-bis azapenam 50. Azapenam carbene complex **(S)49** (330 mg, 0.55 mmol) and (R)-imidazoline **(R)30** (0.145 g, 0.55 mmol) were dissolved in 15 mL of dry CH_2Cl_2 under argon in a Pyrex pressure tube. After three freeze- thaw degassing cycles, the resulting yellow solution was irradiated with 4 x 500-W halogen lamps under 60 psi of CO pressure at 60 °C. The progress of the reaction was indicated by the fading of the yellow color. After 4 hours the reaction was cooled to room temperature and the pressure released followed by removal of the solvent *in vaccuo*. The residue was titurated in MeOH and cooled to -20 °C for 1 hour. Removal of the solid chromium hexacarbonyl by filtration followed by removal of the MeOH *in vaccuo* yielded a pale yellow oil which was taken up in 1:1 Hexane/EtOAc and was photo-oxidized for 1 day. The solution was filtered through a pad of Celite and the solvent was removed *in vaccuo*. Purification by radial chromatography on silica gel (1:1, Hexane /EtOAc) gave a single diastereomer of the bis-azapenam **50** as a clear oil (185 mg 48%). ^{1}H NMR δ 7.35 (bs, 10H), 5.3-4.8 (m, 6H), 4.35 (d,*J*= 11 Hz, 2H), 4.00-3.45 (m, 11H), 3.24 (d *J*= 11, 1H), 1.8 (s, 6H), 1.45-1.20 (m, 8H).

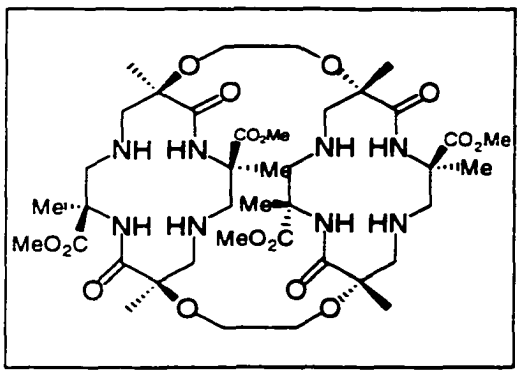


***Meso*-bis-azapenam 53.** Bis-azapenam **50** (181 mg, 0.26 mmol) was dissolved in methanol (5 mL) and 4 drops of triethylamine were added. Then 90 mg of 10% Pd/C was added and the reaction was pressurized to 45 psi with H_2 and was vigorously stirred for 2 h. Filtration through a pad of Celite was followed by removal of the solvent *in vacuuo*. The

resulting clear oil was dissolved in CH_2Cl_2 and the solution was rinsed with a solution of 5% $NaHCO_3$, and dried over Na_2SO_4. Removal of the solvent *in vacuuo* yielded 92 mg of **53** as a white foam. This foam was taken on without further purification. ^{13}C NMR δ 175.2, 173.2, 90.2, 80.4, 66.4, 65.4, 60.8, 52.8, 17.4, 14.6



***Meso*-tetra-imine bis-dioxocyclam 54.** Deprotected bisazapenam **53** (92 mg 0.20 mmol) and (±) CSA (10 mg) were dissolved in 10 mL of dry CH_2Cl_2 in a sealed Pyrex pressure tube. The resulting solution was heated to 80 °C and allowed to stir for 2.5 h at 80 °C, after which the reaction mixture was washed with 5% $NaHCO_3$ and dried over Na_2SO_4. The solvent from the resulting yellow solution was evaporated and the yellow solid that resulted was taken on without purification.



***Meso* bis-dioxocyclam 55.**. The crude tetra-imine bis-dioxocyclam **54** (~ 92 mg) was dissolved in 10 mL of 1:1 CH_2Cl_2/MeOH and a small amount of bromocreosol green was added to the solution. The solution was then cooled to 0 °C and $NaCNBH_3$ (12.5 mg, 0.20 mmol, 2.0 eq) was added. Anhydrous 1M HCl in MeOH was slowly added to the solution to until a yellow/green color persisted (pH ~5). The resulting yellow/green solution was allowed to warm to room temperature and was stirred overnight. Excess 1.0 M HCl in MeOH was added to the solution until gas was evolved from the solution to quench the $NaCNBH_3$. 20 mL of CH_2Cl_2 was

added and the reaction mixture was then washed with 10% NaOH and dried over Na_2SO_4, followed by removal of the solvent *in vacuuo*. Purification by radial layer chromatography (Si gel, 95:5 CH_2Cl_2/MeOH) yielded *meso* bis-dioxocyclam (**16**) (20 mg 21% over 3 steps). ^1H NMR δ 8.95 (s, 4H), 3.70 (s, 12H), 3.61 (s, 8H), 3.11 (d *J*= 11.6 Hz, 4H), 2.87 (d *J*= 11.7 Hz, 4H), 2.75-2.71 (m, 8H), 2.4 (bs, 4H), 1.58 (s, 12H), 1.27 (s, 12H).

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CHAPTER FIVE

CONCLUSIONS

Cyclams and dioxocyclams, both as free ligands and as transition metal complexes, have been extensively studied over the last 35 years. Many modifications can be made to these macrocyclic rings, and these modifications can change the properties of the ligand which can, in turn, change the properties of complexed metals. Applications of these ligands that take advantage of the special properties of different cyclams have been developed. These application range from delivery of a transition metals into humans to catalytic oxidation systems to free cyclams as pharmaceuticals.

The preceding dissertation outlined the development of two new classes of dioxocyclams, capped and bridged, as the first major project. The capped dioxocyclams have markedly different properties from dioxocyclams. First, the capping pyridine group added a fifth donor atom to the ligand. This fifth donor atom changed the coordination geometry that could be presented to a metal from square planar (which was seen with the dioxocyclams) to square pyramidal or trigional bipyramidal. The capping group also blocked one side of the dioxocyclam ring limiting the accessible coordination sites of a complexed metal. Finally, the capping pyridine made the dioxocyclam ring more rigid.

The stereochemcial aspects of the capped dioxocyclam rings also proved very interesting. That the centrosymmetric isomer of the dioxocyclams has two enantiotopic faces became apparent and important in the course of analysis of

the capping reactions. These dioxocyclam contain two quaternary stereocenters on the rings which add to the stereochemical complexity of these rings. When different diastereomers of dioxocyclams were capped, further mixtures of capped stereoisomers were produced and these capped stereoisomers often had different physical properties. Also, an optically active isomer of the dioxocyclam was capped producing a ligand system that possessed a very deep chiral pocket. These capped chiral dioxocyclam ligands are of interest because a transition metal could be coordinated in this deep chiral pocket to produce a complex that might be capable of asymmetric transformations.

An extension of these capping studies produced a bis-dioxocyclam in which two dioxocyclam rings were bridged by a pyrazine group. This produced a ligand system that placed the dioxocyclam rings very close to one another with an aromatic group between them. This bis-ligand showed promise for the coordination of two metal centers. Once coordinated by the bridged dioxocyclam the two metals might communicate with each other either through space or through the aromatic bridge. This communication could change the physical properties of the two metal centers.

An optically active bridged bis-dioxocyclam was synthesized and an X-ray crystal structure of this compound was solved. This crystal structure revealed several interesting aspects of the shape of the molecule. The two dioxocyclam rings were twisted with respect to each other, and the bridging pyrazine group linked the two amines on a dioxocyclam ring differently than the capping studies. This difference in alkylation brought the two bridge-head amines closer together and changed the orientation of the amine nitrogens in the dioxocyclam rings.

When a centrosymmetric dioxocyclam was subjected to the bridging conditions the stereochemical outcome was very complex. From achiral starting

materials six stereoisomers, two racemic pairs and two achiral isomers, could have been produced. These stereoisomers differed by how the two dioxocyclam rings approached each other in the bridging reaction. The two enantiofaces can come together in two different ways and the two quaternary stereocenters can also come together in two different ways. Two X-ray crystal structures of poor quality of the two achiral isomers which demonstrated the connectivity and confirmed the stereochemical assignments were solved. These structures also demonstrated that the two dioxocyclam rings were parallel to each other not twisted as was seen in the optically active bridged isomer. Interestingly, the two racemic pairs were not observed in the reaction, and it was thought that approach of the two dioxocyclam rings that would give the racemic isomers was blocked by groups on the rings. The bridging studies demonstrated that choice of stereoisomer could affect the shape of the molecule that was produced.

Since these dioxocyclams were considered as ligands for transition metals complexes of these new classes needed to the synthesized and studied. A copper(II) complex of one capped, centrosymmetric dioxocyclam was synthesized and it was found that the electronic properties of the copper center were variable. This was demonstrated by a solvent color change of the complex. When the copper complex was dissolved in methanol or water the solution was blue, and when dissolved in dichloromethane the solution was green. X-ray crystal structures of a blue crystal and a green crystal of this complex demonstrated that the color change of the complex , in the solid state, arose from a conformation change in the ligand. This conformation change shifted the coordination geometry about the copper center from a distorted square pyramid to a distorted trigional bipyramid, which was rationalized to be the cause of the difference in the color of the complex.

The second major project of this research was the attempt to develop a metal complex a bis-dixoxcyclam that could increase the rate of hydrolysis of a phosphate diester. Studying how phosphate diesters are hydrolyzed is of interest because it can be used in understanding how nature accomplishes an amazing 17 order of magnitude rate increase in the hydrolysis of DNA. Many bimetallic coordination complexes have been studied as phosphate diester hydrolysis agents. Through chemistry developed in the Hegedus group, bimetallic complexes with a well defined cavities between the two metal centers can be produced.

The bimetallic complexes that were studied were bis-copper complexes of alkoxy-linked bis-dioxocyclams. Two different bis-copper complexes with different linker lengths were synthesized and used in hydrolysis studies with an activated phosphate diester. Unfortunately, neither of the two complexes demonstrated significant rate enhancement of hydrolysis. The lack of activity of these two complexes prompted the synthesis of other new bis-dioxocyclams. Even though these new bis-dioxocyclams had interesting properties, they were not used in the hydrolysis studies because of solubility problems, and problems in the separation of diastereomers. On the whole the phosphate diester hydrolysis study was unsuccessful in developing a hydrolysis agent, but the ground work was developed for testing new bis-dioxocyclam for hydrolysis properties.

The new classes of dioxocyclams that were developed in the course of this research show much promise in the study of transition metal complexes. Ultimately, a useful application of these complexes is desirable. Even though the preliminary studies of an application of similar ligand systems were not very successful, there are many other problems that can be studied using these interesting ligand systems. There are many directions in which future research

using these complexes can proceed, and work on these ligand systems will be the subject of future investigations.

APPENDIX A: TABLES OF X-RAY CRYSTAL STRUCTURE DATA

Table A.1. Crystal data and structure refinement for 6a.

Identification code	lsh8
Empirical formula	$C_{25}H_{41}N_5O_4$
Formula weight	475.63
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	Cc
Unit cell dimensions	a = 17.5675(7) Å alpha = 90° b = 14.4967(5) Å beta = 102.1170(10)° c = 10.2831(4) Å gamma = 90°
Volume, Z	2560.5(2) $Å^3$, 4
Density (calculated)	1.234 Mg/m^3
Absorption coefficient	0.085 mm^{-1}
F(000)	1032
Crystal size	0.18 x 0.20 x 0.40 mm
θ range for data collection	1.84 to 28.27°
Limiting indices	$-22 \le h \le 22$, $-18 \le k \le 8$, $-13 \le l \le 13$
Reflections collected	8292
Independent reflections	5523 (R_{int} = 0.0313)
Absorption correction	SADABS
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5523 / 2 / 307
Goodness-of-fit on F^2	0.984
Final R indices [I>2σ(I)]	R1 = 0.0546, wR2 = 0.1105
R indices (all data)	R1 = 0.1013, wR2 = 0.1396
Absolute structure parameter	1.5(14)
Largest diff. peak and hole	0.180 and -0.179 $eÅ^{-3}$

Table A.2. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 6a. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	2459(1)	1849(2)	8061(2)	53(1)
O(2)	5267(2)	977(2)	5789(2)	59(1)
O(3)	1931(1)	3570(2)	7604(2)	42(1)
O(4)	6390(1)	2570(2)	7995(2)	49(1)
N(1)	3715(1)	2267(2)	8910(2)	37(1)
N(2)	3822(1)	3852(2)	6699(2)	35(1)
N(3)	4902(1)	2379(2)	6439(2)	38(1)
N(4)	5374(1)	2000(2)	9615(2)	38(1)
N(5)	5063(1)	3833(2)	8861(2)	37(1)
C(1)	2971(2)	2445(2)	8311(3)	37(1)
C(2)	2758(2)	3474(2)	7988(3)	35(1)
C(3)	2992(2)	3802(2)	6688(3)	36(1)
C(4)	4029(2)	3591(2)	5434(3)	40(1)
C(5)	4250(2)	2566(2)	5308(3)	38(1)
C(6)	5372(2)	1633(2)	6561(3)	40(1)
C(7)	6082(2)	1652(2)	7750(3)	42(1)
C(8)	5870(2)	1356(2)	9058(3)	44(1)
C(9)	4830(2)	1536(2)	10311(3)	43(1)
C(10)	4007(2)	1366(2)	9485(3)	40(1)
C(11)	3098(2)	4069(2)	9210(3)	44(1)
C(12)	3568(2)	1913(2)	5269(3)	45(1)
C(13)	4529(2)	2496(3)	3990(3)	52(1)
C(14)	6706(2)	990(3)	7462(4)	61(1)
C(15)	3990(2)	638(2)	8405(3)	50(1)
C(16)	3518(2)	1027(3)	10475(4)	57(1)
C(17)	1483(2)	3441(3)	8591(4)	61(1)
C(18)	6695(2)	2992(3)	6956(4)	65(1)
C(19)	5827(2)	2755(2)	10398(3)	45(1)
C(20)	4185(2)	4734(2)	7213(3)	43(1)
C(21)	4973(2)	4607(2)	8123(3)	38(1)
C(22)	5565(2)	5248(2)	8202(4)	49(1)
C(23)	6258(2)	5101(3)	9106(4)	61(1)
C(24)	6350(2)	4310(2)	9849(4)	56(1)
C(25)	5750(2)	3672(2)	9673(3)	39(1)

Table A.3. Bond lengths [Å] and angles [°] for 6a.

O(1)-C(1)	1.234(4)	O(2)-C(6)	1.228(4)
O(3)-C(17)	1.422(4)	O(3)-C(2)	1.430(3)
O(4)-C(18)	1.430(4)	O(4)-C(7)	1.438(4)
N(1)-C(1)	1.348(4)	N(1)-C(10)	1.480(4)
N(2)-C(3)	1.458(4)	N(2)-C(4)	1.471(4)
N(2)-C(20)	1.477(4)	N(3)-C(6)	1.350(4)
N(3)-C(5)	1.476(4)	N(4)-C(9)	1.472(4)
N(4)-C(8)	1.472(4)	N(4)-C(19)	1.487(4)
N(5)-C(25)	1.336(4)	N(5)-C(21)	1.345(4)
C(1)-C(2)	1.557(4)	C(2)-C(11)	1.538(4)
C(2)-C(3)	1.553(4)	C(4)-C(5)	1.548(4)
C(5)-C(12)	1.521(5)	C(5)-C(13)	1.538(4)
C(6)-C(7)	1.554(4)	C(7)-C(8)	1.531(5)
C(7)-C(14)	1.531(4)	C(9)-C(10)	1.535(4)
C(10)-C(15)	1.528(5)	C(10)-C(16)	1.543(5)
C(19)-C(25)	1.517(4)	C(20)-C(21)	1.510(4)
C(21)-C(22)	1.384(4)	C(22)-C(23)	1.385(5)
C(23)-C(24)	1.369(5)	C(24)-C(25)	1.385(5)

C(17)-O(3)-C(2)	118.2(2)	C(18)-O(4)-C(7)	116.8(3)
C(1)-N(1)-C(10)	124.9(2)	C(3)-N(2)-C(4)	114.4(2)
C(3)-N(2)-C(20)	113.7(2)	C(4)-N(2)-C(20)	111.7(2)
C(6)-N(3)-C(5)	125.3(2)	C(9)-N(4)-C(8)	113.4(2)
C(9)-N(4)-C(19)	113.7(2)	C(8)-N(4)-C(19)	112.6(2)
C(25)-N(5)-C(21)	118.9(3)	O(1)-C(1)-N(1)	123.8(3)
O(1)-C(1)-C(2)	119.6(3)	N(1)-C(1)-C(2)	116.6(2)
O(3)-C(2)-C(11)	111.6(2)	O(3)-C(2)-C(3)	99.8(2)
C(11)-C(2)-C(3)	113.8(2)	O(3)-C(2)-C(1)	109.7(2)
C(11)-C(2)-C(1)	109.2(2)	C(3)-C(2)-C(1)	112.4(2)
N(2)-C(3)-C(2)	117.0(2)	N(2)-C(4)-C(5)	115.7(2)
N(3)-C(5)-C(12)	112.5(2)	N(3)-C(5)-C(13)	110.1(2)
C(12)-C(5)-C(13)	109.3(3)	N(3)-C(5)-C(4)	106.1(2)
C(12)-C(5)-C(4)	112.9(3)	C(13)-C(5)-C(4)	105.6(3)
O(2)-C(6)-N(3)	123.7(3)	O(2)-C(6)-C(7)	120.6(3)
N(3)-C(6)-C(7)	115.7(3)	O(4)-C(7)-C(8)	104.9(2)
O(4)-C(7)-C(14)	110.8(3)	C(8)-C(7)-C(14)	108.1(3)
O(4)-C(7)-C(6)	111.4(2)	C(8)-C(7)-C(6)	112.5(3)
C(14)-C(7)-C(6)	109.0(3)	N(4)-C(8)-C(7)	116.0(2)
N(4)-C(9)-C(10)	115.9(2)	N(1)-C(10)-C(15)	111.5(2)
N(1)-C(10)-C(9)	106.6(2)	C(15)-C(10)-C(9)	112.6(3)
N(1)-C(10)-C(16)	110.5(3)	C(15)-C(10)-C(16)	109.3(3)
C(9)-C(10)-C(16)	106.0(2)	N(4)-C(19)-C(25)	113.3(2)
N(2)-C(20)-C(21)	112.8(2)	N(5)-C(21)-C(22)	121.9(3)
N(5)-C(21)-C(20)	115.8(3)	C(22)-C(21)-C(20)	122.3(3)
C(23)-C(22)-C(21)	118.7(3)	C(24)-C(23)-C(22)	119.1(3)
C(23)-C(24)-C(25)	119.3(3)	N(5)-C(25)-C(24)	121.8(3)
N(5)-C(25)-C(19)	115.9(3)	C(24)-C(25)-C(19)	122.3(3)

Symmetry transformations used to generate equivalent atoms:

Table A.4. Anisotropic displacement parameters [$Å^2$ x 10^3] for 6a.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
O(1)	48(1)	39(1)	67(2)	0(1)	-2(1)	-14(1)
O(2)	68(2)	46(1)	55(2)	-16(1)	-4(1)	15(1)
O(3)	32(1)	53(1)	38(1)	-2(1)	3(1)	3(1)
O(4)	46(1)	55(2)	45(1)	-3(1)	4(1)	-2(1)
N(1)	40(2)	28(1)	40(1)	4(1)	-1(1)	-3(1)
N(2)	32(1)	31(1)	38(1)	2(1)	1(1)	1(1)
N(3)	38(1)	38(1)	35(1)	-5(1)	-3(1)	7(1)
N(4)	39(1)	34(1)	35(1)	0(1)	-3(1)	4(1)
N(5)	34(1)	33(1)	42(1)	1(1)	-1(1)	0(1)
C(1)	39(2)	37(2)	34(2)	1(1)	3(1)	-3(1)
C(2)	32(2)	32(2)	36(2)	-4(1)	-1(1)	3(1)
C(3)	35(2)	35(2)	35(2)	3(1)	0(1)	2(1)
C(4)	40(2)	42(2)	35(2)	10(1)	4(1)	2(1)
C(5)	41(2)	41(2)	30(2)	2(1)	2(1)	8(1)
C(6)	43(2)	38(2)	38(2)	0(2)	4(1)	7(1)
C(7)	38(2)	40(2)	43(2)	-4(1)	0(1)	9(1)
C(8)	41(2)	40(2)	46(2)	4(2)	0(2)	12(1)
C(9)	47(2)	39(2)	39(2)	8(1)	-1(2)	7(2)
C(10)	46(2)	30(2)	41(2)	8(1)	2(1)	-1(1)
C(11)	48(2)	37(2)	42(2)	-5(1)	0(1)	2(1)
C(12)	47(2)	44(2)	40(2)	-4(2)	1(2)	-2(2)
C(13)	55(2)	67(2)	34(2)	2(2)	7(2)	10(2)
C(14)	52(2)	72(3)	57(2)	1(2)	7(2)	27(2)
C(15)	63(2)	33(2)	50(2)	-1(2)	3(2)	-1(2)
C(16)	68(2)	54(2)	49(2)	14(2)	12(2)	-7(2)
C(17)	46(2)	88(3)	51(2)	-4(2)	17(2)	-4(2)
C(18)	64(3)	70(3)	62(3)	3(2)	15(2)	-8(2)
C(19)	46(2)	43(2)	40(2)	-3(1)	-5(2)	3(1)
C(20)	45(2)	30(2)	50(2)	6(1)	3(2)	-2(1)
C(21)	39(2)	31(2)	43(2)	-1(1)	5(1)	0(1)
C(22)	48(2)	34(2)	62(2)	0(2)	4(2)	-9(2)
C(23)	47(2)	43(2)	90(3)	-6(2)	6(2)	-14(2)
C(24)	42(2)	48(2)	70(2)	-9(2)	-10(2)	-5(2)
C(25)	36(2)	37(2)	40(2)	-6(1)	-2(1)	4(1)

Table A.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 6a.

	x	y	z	U(eq)
H(1A)	4045(1)	2711(2)	8962(2)	44
H(3A)	4990(1)	2778(2)	7072(2)	46
H(3B)	2753(2)	3389(2)	5976(3)	43
H(3C)	2770(2)	4409(2)	6470(3)	43
H(4A)	4464(2)	3970(2)	5314(3)	48
H(4B)	3592(2)	3735(2)	4716(3)	48
H(8A)	5606(2)	766(2)	8918(3)	53
H(8B)	6348(2)	1264(2)	9714(3)	53
H(9A)	4787(2)	1904(2)	11080(3)	52
H(9B)	5053(2)	946(2)	10636(3)	52
H(11A)	2930(2)	3830(2)	9974(3)	65
H(11B)	2920(2)	4693(2)	9052(3)	65
H(11C)	3656(2)	4055(2)	9366(3)	65
H(12A)	3392(2)	1957(2)	6090(3)	67
H(12B)	3730(2)	1292(2)	5150(3)	67
H(12C)	3151(2)	2079(2)	4544(3)	67
H(13A)	4959(2)	2908(3)	4011(3)	79
H(13B)	4111(2)	2661(3)	3266(3)	79
H(13C)	4691(2)	1875(3)	3870(3)	79
H(14A)	6848(2)	1164(3)	6644(4)	91
H(14B)	6505(2)	372(3)	7387(4)	91
H(14C)	7156(2)	1019(3)	8175(4)	91
H(15A)	3465(2)	558(2)	7917(3)	75
H(15B)	4183(2)	64(2)	8809(3)	75
H(15C)	4312(2)	836(2)	7809(3)	75
H(16A)	3528(2)	1484(3)	11155(4)	85
H(16B)	3733(2)	460(3)	10875(4)	85
H(16C)	2991(2)	927(3)	10012(4)	85
H(17A)	941(2)	3525(3)	8201(4)	91
H(17B)	1640(2)	3882(3)	9293(4)	91
H(17C)	1565(2)	2828(3)	8948(4)	91
H(18A)	6882(2)	3598(3)	7228(4)	97
H(18B)	6292(2)	3035(3)	6167(4)	97
H(18C)	7116(2)	2625(3)	6774(4)	97
H(19A)	6373(2)	2580(2)	10616(3)	54
H(19B)	5653(2)	2828(2)	11227(3)	54
H(20A)	3844(2)	5051(2)	7693(3)	51
H(20B)	4242(2)	5120(2)	6469(3)	51
H(22A)	5498(2)	5767(2)	7658(4)	59
H(23A)	6657(2)	5535(3)	9208(4)	74
H(24A)	6810(2)	4201(2)	10465(4)	68

Table A.6. Crystal data and structure refinement for **18.

Identification code	taw1
Empirical formula	$C_{48.50}H_{76}N_{10}O_{18.20}$
Formula weight	1096.40
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P1
Unit cell dimensions	a = 9.6559(2) Å alpha = 90.2530(10)° b = 12.7467(3) Å beta = 108.4380(10)° c = 12.7602(3) Å gamma = 98.3950(10)°
Volume, Z	1471.81(6) $Å^3$, 1
Density (calculated)	1.237 Mg/m^3
Absorption coefficient	0.095 mm^{-1}
F(000)	586
Crystal size	0.20 x 0.20 x 0.40 mm
θ range for data collection	1.62 to 28.25°
Limiting indices	$-12 \le h \le 12$, $-16 \le k \le 16$, $-12 \le l \le 16$
Reflections collected	9808
Independent reflections	8008 (R_{int} = 0.0248)
Absorption correction	SADABS
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8002 / 3 / 687
Goodness-of-fit on F^2	0.983
Final R indices [I>2σ(I)]	R1 = 0.0676, wR2 = 0.1688
R indices (all data)	R1 = 0.1068, wR2 = 0.1971
Absolute structure parameter	-0.1(14)
Largest diff. peak and hole	0.784 and -0.241 $eÅ^{-3}$

Table A.7. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for +18. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(1)	-4786(5)	-774(3)	-1261(4)	50(1)
N(2)	-2245(5)	-474(3)	436(4)	45(1)
N(3)	-4767(4)	-2380(3)	1477(3)	38(1)
N(4)	-5870(5)	-471(3)	685(3)	42(1)
N(5)	-255(5)	3109(3)	6815(4)	46(1)
N(6)	543(5)	2698(3)	5044(3)	44(1)
N(7)	-1851(4)	4607(3)	4062(3)	39(1)
N(8)	-3133(5)	2845(3)	5005(3)	41(1)
N(9)	-1142(5)	1096(3)	2793(4)	54(1)
N(10)	-3959(5)	1173(3)	2829(4)	51(1)
O(1)	-6628(6)	-462(4)	-2771(4)	84(2)
O(2)	-2934(4)	-1333(3)	2811(3)	56(1)
O(3)	-6846(4)	-2270(2)	-796(3)	46(1)
O(4)	-3092(4)	-2721(3)	354(4)	55(1)
O(5)	-4184(8)	-1945(4)	-2855(5)	107(2)
O(6)	-2761(6)	-559(4)	-3215(4)	85(2)
O(7)	-7202(4)	-3796(3)	859(3)	50(1)
O(8)	-8643(4)	-2555(3)	855(4)	61(1)
O(9)	-610(5)	3075(4)	8498(3)	70(1)
O(10)	-1782(4)	3673(4)	2562(4)	69(1)
O(11)	-2066(4)	4692(2)	6441(3)	47(1)
O(12)	1055(4)	4964(3)	4973(3)	45(1)
O(13)	2293(6)	4380(3)	8155(5)	89(2)
O(14)	3282(5)	2933(3)	8726(4)	70(1)
O(15)	-4887(4)	5117(3)	4879(3)	51(1)
O(16)	-2878(4)	6216(3)	4815(3)	56(1)
C(1)	-7293(6)	-1302(4)	-1266(4)	48(1)
C(2)	-6211(7)	-811(4)	-1857(5)	54(1)
C(3)	-3523(7)	-358(4)	-1613(5)	53(1)
C(4)	-2125(6)	-579(4)	-677(5)	53(1)
C(5)	-1326(6)	-1139(4)	1233(5)	49(1)
C(6)	-2238(5)	-2188(4)	1388(5)	49(1)
C(7)	-3359(5)	-1902(4)	1968(5)	44(1)
C(8)	-6017(5)	-2116(4)	1774(4)	41(1)
C(9)	-6127(5)	-924(4)	1674(4)	42(1)
C(10)	-7233(6)	-570(4)	-274(5)	50(1)
C(11)	-8855(7)	-1500(5)	-2072(6)	66(2)
C(12)	-3507(8)	808(4)	-1917(6)	69(2)
C(13)	-1220(7)	-2865(6)	2167(7)	73(2)
C(14)	-5877(7)	-2392(5)	2981(5)	56(1)
C(15)	-3577(8)	-1056(5)	-2628(5)	62(2)
C(16)	-2654(12)	-1147(7)	-4160(7)	106(3)
C(17)	-7429(5)	-2816(4)	1085(5)	43(1)
C(18)	-8493(7)	-4541(5)	263(5)	63(2)
C(19)	-1881(7)	656(4)	823(5)	54(1)
C(20)	-5128(7)	659(4)	888(5)	55(2)
C(21)	-2453(9)	-3411(6)	-155(8)	91(3)

C(22)	-6777(7)	-3074(4)	-1563(5)	56(1)
C(23)	-2447(6)	3750(4)	6965(4)	45(1)
C(24)	-999(6)	3271(4)	7517(4)	48(1)
C(25)	1144(6)	2702(4)	7138(4)	45(1)
C(26)	1733(6)	2852(4)	6139(4)	48(1)
C(27)	1045(6)	3260(4)	4180(5)	48(1)
C(28)	538(5)	4344(4)	3927(4)	44(1)
C(29)	-1153(5)	4178(4)	3451(4)	44(1)
C(30)	-3464(5)	4492(4)	3857(4)	39(1)
C(31)	-4063(5)	3338(4)	4028(4)	44(1)
C(32)	-3556(6)	2995(4)	6010(4)	47(1)
C(33)	-3191(7)	3953(5)	7802(5)	63(2)
C(34)	968(8)	1554(4)	7523(5)	63(2)
C(35)	1215(6)	4827(5)	3058(5)	57(1)
C(36)	-4319(6)	4765(5)	2659(5)	52(1)
C(37)	2291(6)	3435(4)	8057(5)	52(1)
C(38)	4428(8)	3587(7)	9638(6)	88(2)
C(39)	-3663(6)	5361(4)	4588(5)	45(1)
C(40)	-5115(7)	5900(5)	5608(6)	62(2)
C(41)	-1036(7)	5508(4)	7177(6)	65(2)
C(42)	1113(7)	6093(4)	4922(6)	64(2)
C(43)	-5(7)	1565(4)	4737(5)	58(2)
C(44)	-3189(7)	1698(4)	4774(5)	53(1)
C(45)	-1372(6)	1361(4)	3733(5)	50(1)
C(46)	-2802(7)	1422(4)	3746(5)	53(1)
C(47)	-3731(6)	895(4)	1874(5)	51(1)
C(48)	-2308(7)	868(4)	1864(5)	53(2)
ME	2225(32)	-906(23)	4780(23)	260(17)
OH	3112(33)	220(23)	5075(23)	216(17)
H(20)	8048(12)	3281(9)	10398(10)	177(6)
O(19)	-8439(33)	-7330(21)	927(24)	309(18)

Table A.8. Bond lengths [Å] and angles [°] for +18.

N(1)-C(2)	1.339(7)	N(1)-C(3)	1.459(8)
N(2)-C(4)	1.468(7)	N(2)-C(19)	1.476(6)
N(2)-C(5)	1.482(7)	N(3)-C(7)	1.352(6)
N(3)-C(8)	1.456(6)	N(4)-C(9)	1.467(7)
N(4)-C(10)	1.475(6)	N(4)-C(20)	1.494(6)
N(5)-C(24)	1.345(7)	N(5)-C(25)	1.455(7)
N(6)-C(43)	1.470(6)	N(6)-C(27)	1.486(8)
N(6)-C(26)	1.493(7)	N(7)-C(29)	1.340(6)
N(7)-C(30)	1.481(6)	N(8)-C(44)	1.480(6)
N(8)-C(32)	1.483(7)	N(8)-C(31)	1.489(7)
N(9)-C(45)	1.337(7)	N(9)-C(48)	1.347(7)
N(10)-C(46)	1.336(7)	N(10)-C(47)	1.361(7)
O(1)-C(2)	1.217(7)	O(2)-C(7)	1.217(6)
O(3)-C(22)	1.436(6)	O(3)-C(1)	1.437(6)
O(4)-C(21)	1.408(7)	O(4)-C(6)	1.422(7)
O(5)-C(15)	1.186(7)	O(6)-C(15)	1.346(8)
O(6)-C(16)	1.457(8)	O(7)-C(17)	1.345(6)
O(7)-C(18)	1.443(6)	O(8)-C(17)	1.211(6)
O(9)-C(24)	1.226(7)	O(10)-C(29)	1.230(6)
O(11)-C(41)	1.431(6)	O(11)-C(23)	1.435(7)
O(12)-C(42)	1.435(7)	O(12)-C(28)	1.452(6)
O(13)-C(37)	1.209(7)	O(14)-C(37)	1.312(7)
O(14)-C(38)	1.476(7)	O(15)-C(39)	1.343(7)
O(15)-C(40)	1.448(6)	O(16)-C(39)	1.210(6)
C(1)-C(11)	1.517(8)	C(1)-C(2)	1.536(9)
C(1)-C(10)	1.551(7)	C(3)-C(12)	1.536(8)
C(3)-C(15)	1.551(8)	C(3)-C(4)	1.556(8)
C(5)-C(6)	1.540(8)	C(6)-C(13)	1.529(9)
C(6)-C(7)	1.572(8)	C(8)-C(17)	1.519(7)
C(8)-C(9)	1.541(7)	C(8)-C(14)	1.549(8)
C(19)-C(48)	1.545(8)	C(20)-C(47)	1.516(8)
C(23)-C(33)	1.504(8)	C(23)-C(32)	1.555(7)
C(23)-C(24)	1.567(8)	C(25)-C(37)	1.530(7)
C(25)-C(34)	1.549(8)	C(25)-C(26)	1.554(8)
C(27)-C(28)	1.535(8)	C(28)-C(29)	1.533(7)
C(28)-C(35)	1.543(8)	C(30)-C(39)	1.516(7)
C(30)-C(31)	1.543(7)	C(30)-C(36)	1.559(7)
C(43)-C(45)	1.509(8)	C(44)-C(46)	1.526(8)
C(45)-C(46)	1.400(8)	C(47)-C(48)	1.383(8)
ME-OH	1.54(3)		

C(2)-N(1)-C(3)	126.0(5)	C(4)-N(2)-C(19)	109.4(4)
C(4)-N(2)-C(5)	112.7(4)	C(19)-N(2)-C(5)	111.7(4)
C(7)-N(3)-C(8)	123.4(4)	C(9)-N(4)-C(10)	112.7(4)
C(9)-N(4)-C(20)	112.6(4)	C(10)-N(4)-C(20)	110.1(4)
C(24)-N(5)-C(25)	123.9(4)	C(43)-N(6)-C(27)	112.4(4)
C(43)-N(6)-C(26)	111.3(4)	C(27)-N(6)-C(26)	111.0(4)
C(29)-N(7)-C(30)	127.4(4)	C(44)-N(8)-C(32)	109.4(4)
C(44)-N(8)-C(31)	111.3(4)	C(32)-N(8)-C(31)	112.6(4)
C(45)-N(9)-C(48)	119.1(5)	C(46)-N(10)-C(47)	119.4(5)
C(22)-O(3)-C(1)	115.9(4)	C(21)-O(4)-C(6)	119.4(5)
C(15)-O(6)-C(16)	117.8(5)	C(17)-O(7)-C(18)	116.6(4)
C(41)-O(11)-C(23)	114.7(4)	C(42)-O(12)-C(28)	117.0(4)
C(37)-O(14)-C(38)	116.2(5)	C(39)-O(15)-C(40)	115.3(4)

O(3)-C(1)-C(11)	111.3(4)	O(3)-C(1)-C(2)	109.2(4)
C(11)-C(1)-C(2)	110.1(5)	O(3)-C(1)-C(10)	105.5(4)
C(11)-C(1)-C(10)	109.6(5)	C(2)-C(1)-C(10)	111.2(4)
O(1)-C(2)-N(1)	123.6(6)	O(1)-C(2)-C(1)	122.3(6)
N(1)-C(2)-C(1)	114.0(5)	N(1)-C(3)-C(12)	112.9(5)
N(1)-C(3)-C(15)	108.1(4)	C(12)-C(3)-C(15)	109.6(5)
N(1)-C(3)-C(4)	106.2(5)	C(12)-C(3)-C(4)	114.8(5)
C(15)-C(3)-C(4)	104.8(5)	N(2)-C(4)-C(3)	113.5(5)
N(2)-C(5)-C(6)	111.9(4)	O(4)-C(6)-C(13)	113.7(5)
O(4)-C(6)-C(5)	111.5(5)	C(13)-C(6)-C(5)	109.6(5)
O(4)-C(6)-C(7)	106.9(4)	C(13)-C(6)-C(7)	107.4(5)
C(5)-C(6)-C(7)	107.5(4)	O(2)-C(7)-N(3)	125.1(5)
O(2)-C(7)-C(6)	120.7(5)	N(3)-C(7)-C(6)	114.1(4)
N(3)-C(8)-C(17)	109.9(4)	N(3)-C(8)-C(9)	111.6(4)
C(17)-C(8)-C(9)	112.3(4)	N(3)-C(8)-C(14)	110.9(5)
C(17)-C(8)-C(14)	104.0(4)	C(9)-C(8)-C(14)	107.9(4)
N(4)-C(9)-C(8)	114.6(4)	N(4)-C(10)-C(1)	116.1(4)
O(5)-C(15)-O(6)	122.1(6)	O(5)-C(15)-C(3)	125.8(6)
O(6)-C(15)-C(3)	112.0(5)	O(8)-C(17)-O(7)	123.5(4)
O(8)-C(17)-C(8)	123.7(4)	O(7)-C(17)-C(8)	112.4(4)
N(2)-C(19)-C(48)	112.7(5)	N(4)-C(20)-C(47)	116.3(5)
O(11)-C(23)-C(33)	112.8(4)	O(11)-C(23)-C(32)	105.0(4)
C(33)-C(23)-C(32)	108.7(5)	O(11)-C(23)-C(24)	108.0(4)
C(33)-C(23)-C(24)	110.8(4)	C(32)-C(23)-C(24)	111.4(4)
O(9)-C(24)-N(5)	124.8(5)	O(9)-C(24)-C(23)	121.8(5)
N(5)-C(24)-C(23)	113.5(4)	N(5)-C(25)-C(37)	109.7(4)
N(5)-C(25)-C(34)	111.5(5)	C(37)-C(25)-C(34)	110.3(5)
N(5)-C(25)-C(26)	105.8(4)	C(37)-C(25)-C(26)	103.5(4)
C(34)-C(25)-C(26)	115.6(4)	N(6)-C(26)-C(25)	113.6(4)
N(6)-C(27)-C(28)	114.6(4)	O(12)-C(28)-C(29)	111.1(4)
O(12)-C(28)-C(27)	106.3(4)	C(29)-C(28)-C(27)	108.8(4)
O(12)-C(28)-C(35)	113.3(4)	C(29)-C(28)-C(35)	109.8(4)
C(27)-C(28)-C(35)	107.3(4)	O(10)-C(29)-N(7)	124.3(4)
O(10)-C(29)-C(28)	119.9(4)	N(7)-C(29)-C(28)	115.9(4)
N(7)-C(30)-C(39)	105.1(4)	N(7)-C(30)-C(31)	109.7(4)
C(39)-C(30)-C(31)	117.3(4)	N(7)-C(30)-C(36)	112.3(4)
C(39)-C(30)-C(36)	104.3(4)	C(31)-C(30)-C(36)	108.2(4)
N(8)-C(31)-C(30)	115.6(4)	N(8)-C(32)-C(23)	117.1(4)
O(13)-C(37)-O(14)	123.4(5)	O(13)-C(37)-C(25)	123.7(5)
O(14)-C(37)-C(25)	112.9(5)	O(16)-C(39)-O(15)	123.1(5)
O(16)-C(39)-C(30)	124.1(5)	O(15)-C(39)-C(30)	112.6(4)
N(6)-C(43)-C(45)	113.6(5)	N(8)-C(44)-C(46)	115.2(5)
N(9)-C(45)-C(46)	120.4(5)	N(9)-C(45)-C(43)	115.2(5)
C(46)-C(45)-C(43)	124.3(5)	N(10)-C(46)-C(45)	120.3(5)
N(10)-C(46)-C(44)	114.9(5)	C(45)-C(46)-C(44)	124.7(5)
N(10)-C(47)-C(48)	119.7(5)	N(10)-C(47)-C(20)	114.3(5)
C(48)-C(47)-C(20)	126.0(5)	N(9)-C(48)-C(47)	121.0(5)
N(9)-C(48)-C(19)	113.8(5)	C(47)-C(48)-C(19)	125.0(5)

Symmetry transformations used to generate equivalent atoms:

Table A.9. Anisotropic displacement parameters [$Å^2$ x 10^3] for +18.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
N(1)	57(3)	42(2)	42(3)	3(2)	8(2)	0(2)
N(2)	48(2)	35(2)	51(3)	-5(2)	16(2)	1(2)
N(3)	36(2)	35(2)	47(2)	1(2)	14(2)	10(2)
N(4)	44(2)	34(2)	39(2)	-8(2)	1(2)	6(2)
N(5)	52(2)	42(2)	38(2)	3(2)	3(2)	13(2)
N(6)	47(2)	35(2)	41(2)	-8(2)	4(2)	4(2)
N(7)	31(2)	41(2)	38(2)	-3(2)	4(2)	4(2)
N(8)	46(2)	33(2)	37(2)	-2(2)	6(2)	-1(2)
N(9)	64(3)	36(2)	51(3)	-14(2)	9(2)	2(2)
N(10)	57(3)	32(2)	53(3)	-16(2)	6(2)	-2(2)
O(1)	80(3)	93(4)	56(3)	20(2)	-5(2)	-4(3)
O(2)	45(2)	66(2)	46(2)	-9(2)	2(2)	0(2)
O(3)	55(2)	30(2)	46(2)	-2(1)	8(2)	3(2)
O(4)	46(2)	49(2)	73(3)	-15(2)	23(2)	7(2)
O(5)	160(6)	61(3)	105(4)	-35(3)	72(4)	-34(3)
O(6)	115(4)	74(3)	59(3)	-8(2)	35(3)	-23(3)
O(7)	41(2)	46(2)	58(2)	-4(2)	14(2)	2(2)
O(8)	34(2)	63(2)	85(3)	-15(2)	16(2)	8(2)
O(9)	84(3)	86(3)	37(2)	6(2)	11(2)	22(2)
O(10)	44(2)	96(3)	58(3)	-32(2)	5(2)	10(2)
O(11)	52(2)	33(2)	41(2)	-7(2)	-1(2)	-1(2)
O(12)	39(2)	41(2)	47(2)	-3(2)	4(2)	4(2)
O(13)	91(3)	49(3)	92(4)	-22(2)	-19(3)	10(2)
O(14)	65(3)	68(3)	58(3)	-6(2)	-8(2)	17(2)
O(15)	37(2)	56(2)	60(2)	-13(2)	14(2)	12(2)
O(16)	57(2)	38(2)	69(3)	-3(2)	17(2)	5(2)
C(1)	48(3)	37(3)	42(3)	-5(2)	-7(2)	4(2)
C(2)	66(4)	42(3)	35(3)	0(2)	-4(3)	1(3)
C(3)	67(4)	41(3)	43(3)	0(2)	13(3)	-7(3)
C(4)	56(3)	47(3)	49(3)	-5(2)	15(3)	-8(3)
C(5)	35(3)	50(3)	58(3)	4(3)	13(2)	2(2)
C(6)	32(3)	46(3)	67(4)	6(3)	12(3)	9(2)
C(7)	37(3)	41(3)	50(3)	15(2)	8(2)	10(2)
C(8)	36(3)	46(3)	42(3)	-4(2)	15(2)	3(2)
C(9)	39(3)	42(3)	42(3)	-7(2)	10(2)	8(2)
C(10)	51(3)	38(3)	50(3)	-5(2)	-1(3)	10(2)
C(11)	61(4)	65(4)	55(4)	-5(3)	-4(3)	9(3)
C(12)	92(5)	41(3)	60(4)	6(3)	15(4)	-11(3)
C(13)	50(3)	79(5)	96(5)	32(4)	25(4)	24(3)
C(14)	55(3)	64(4)	48(3)	3(3)	16(3)	4(3)
C(15)	76(4)	56(4)	46(3)	-10(3)	20(3)	-13(3)
C(16)	147(8)	97(6)	75(5)	-27(4)	57(6)	-15(5)
C(17)	40(3)	41(3)	52(3)	-4(2)	21(2)	4(2)
C(18)	61(4)	58(4)	60(4)	-15(3)	17(3)	-18(3)
C(19)	67(4)	42(3)	49(3)	-11(2)	19(3)	-7(3)
C(20)	65(4)	33(3)	56(4)	-7(2)	5(3)	5(2)
C(21)	77(5)	77(5)	129(7)	-25(5)	48(5)	17(4)

C(22)	64(4)	41(3)	59(4)	-11(3)	19(3)	2(3)
C(23)	54(3)	44(3)	33(3)	-3(2)	9(2)	8(2)
C(24)	56(3)	44(3)	36(3)	-5(2)	6(3)	4(2)
C(25)	50(3)	36(3)	42(3)	-3(2)	3(2)	11(2)
C(26)	42(3)	46(3)	48(3)	-14(2)	2(2)	8(2)
C(27)	41(3)	57(3)	44(3)	-9(3)	8(2)	14(2)
C(28)	32(2)	53(3)	43(3)	-7(2)	6(2)	7(2)
C(29)	35(3)	49(3)	40(3)	2(2)	4(2)	5(2)
C(30)	35(2)	38(3)	34(3)	0(2)	2(2)	2(2)
C(31)	36(3)	42(3)	46(3)	-8(2)	6(2)	-2(2)
C(32)	51(3)	44(3)	45(3)	-6(2)	19(3)	-5(2)
C(33)	78(4)	65(4)	46(3)	-1(3)	17(3)	17(3)
C(34)	79(4)	44(3)	54(4)	2(3)	2(3)	14(3)
C(35)	49(3)	69(4)	55(3)	4(3)	21(3)	5(3)
C(36)	46(3)	61(3)	43(3)	2(3)	6(2)	10(3)
C(37)	53(3)	51(3)	43(3)	-2(3)	5(3)	4(3)
C(38)	54(4)	125(6)	63(5)	-24(4)	-12(3)	7(4)
C(39)	38(3)	42(3)	50(3)	6(2)	6(2)	10(2)
C(40)	59(4)	66(4)	66(4)	-13(3)	24(3)	14(3)
C(41)	62(4)	43(3)	69(4)	-11(3)	-4(3)	-7(3)
C(42)	54(3)	49(3)	83(5)	-11(3)	16(3)	6(3)
C(43)	67(4)	39(3)	54(3)	-10(3)	0(3)	7(3)
C(44)	67(4)	37(3)	52(3)	-6(2)	15(3)	7(3)
C(45)	62(4)	36(3)	47(3)	-11(2)	9(3)	6(2)
C(46)	72(4)	32(3)	43(3)	-10(2)	9(3)	0(3)
C(47)	63(4)	28(2)	50(3)	-9(2)	8(3)	-2(2)
C(48)	61(4)	30(3)	60(4)	-11(2)	10(3)	-1(2)

Table A.10. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for +18.

	x	y	z	U(eq)
H(3A)	-4597(5)	-1017(3)	-612(4)	60
H(4A)	-4933(4)	-2865(3)	962(3)	46
H(2A)	-628(5)	3255(3)	6136(4)	55
H(6A)	-1299(4)	4993(3)	4638(3)	46
H(17A)	-1951(6)	-1292(4)	-801(5)	64
H(17B)	-1277(6)	-88(4)	-716(5)	64
H(19A)	-879(6)	-746(4)	1941(5)	58
H(19B)	-536(6)	-1296(4)	969(5)	58
H(25A)	-7102(5)	-819(4)	1673(4)	50
H(25B)	-5413(5)	-537(4)	2323(4)	50
H(35A)	-7365(6)	134(4)	-535(5)	60
H(35B)	-8063(6)	-834(4)	-24(5)	60
H(7A)	-9522(7)	-1807(5)	-1696(6)	99
H(7B)	-8900(7)	-1979(5)	-2669(6)	99
H(7C)	-9131(7)	-840(5)	-2361(6)	99
H(15A)	-3474(8)	1238(4)	-1288(6)	104
H(15B)	-4384(8)	870(4)	-2518(6)	104
H(15C)	-2653(8)	1043(4)	-2136(6)	104
H(4B)	-1791(7)	-3519(6)	2263(7)	110
H(4C)	-749(7)	-2486(6)	2871(7)	110
H(4D)	-482(7)	-3017(6)	1856(7)	110
H(20A)	-5001(7)	-1979(5)	3477(5)	84
H(20B)	-5816(7)	-3134(5)	3062(5)	84
H(20C)	-6727(7)	-2234(5)	3151(5)	84
H(3B)	-2046(12)	-707(7)	-4505(7)	158
H(3C)	-3623(12)	-1351(7)	-4684(7)	158
H(3D)	-2222(12)	-1771(7)	-3916(7)	158
H(5B)	-8203(7)	-5209(5)	147(5)	95
H(5C)	-8970(7)	-4271(5)	-440(5)	95
H(5D)	-9164(7)	-4637(5)	684(5)	95
H(14A)	-2395(7)	1076(4)	234(5)	65
H(14B)	-828(7)	885(4)	985(5)	65
H(32A)	-5830(7)	1093(4)	984(5)	66
H(32B)	-4889(7)	881(4)	231(5)	66
H(2B)	-3163(9)	-3707(6)	-842(8)	136
H(2C)	-2157(9)	-3973(6)	324(8)	136
H(2D)	-1605(9)	-3024(6)	-294(8)	136
H(12A)	-6470(7)	-3684(4)	-1170(5)	83
H(12B)	-6081(7)	-2802(4)	-1928(5)	83
H(12C)	-7736(7)	-3272(4)	-2102(5)	83
H(37A)	2286(6)	3562(4)	6203(4)	58
H(37B)	2408(6)	2351(4)	6169(4)	58
H(39A)	682(6)	2811(4)	3503(5)	57
H(39B)	2116(6)	3360(4)	4414(5)	57
H(41A)	-5036(5)	3322(4)	4099(4)	53
H(41B)	-4179(5)	2905(4)	3370(4)	53
H(23A)	-3722(6)	2304(4)	6302(4)	57
H(23B)	-4491(6)	3263(4)	5788(4)	57

H(8A)	-2515(7)	4419(5)	8396(5)	95
H(8B)	-3483(7)	3293(5)	8089(5)	95
H(8C)	-4047(7)	4278(5)	7456(5)	95
H(6B)	246(8)	1103(4)	6940(5)	94
H(6C)	650(8)	1548(4)	8164(5)	94
H(6D)	1898(8)	1298(4)	7704(5)	94
H(11A)	2273(6)	4929(5)	3360(5)	86
H(11B)	893(6)	5499(5)	2863(5)	86
H(11C)	899(6)	4355(5)	2410(5)	86
H(18A)	-4246(6)	4246(5)	2139(5)	78
H(18B)	-3898(6)	5456(5)	2511(5)	78
H(18C)	-5339(6)	4762(5)	2588(5)	78
H(1A)	5093(8)	3145(7)	10075(6)	133
H(1B)	3969(8)	3910(7)	10095(6)	133
H(1C)	4969(8)	4129(7)	9338(6)	133
H(10B)	-6011(7)	5660(5)	5771(6)	93
H(10C)	-5189(7)	6562(5)	5254(6)	93
H(10D)	-4297(7)	5998(5)	6283(6)	93
H(24A)	-840(7)	6108(4)	6765(6)	98
H(24B)	-132(7)	5242(4)	7535(6)	98
H(24C)	-1446(7)	5721(4)	7724(6)	98
H(9A)	1469(7)	6416(4)	5659(6)	96
H(9B)	142(7)	6253(4)	4551(6)	96
H(9C)	1768(7)	6366(4)	4523(6)	96
H(26A)	-224(7)	1225(4)	5358(5)	70
H(26B)	769(7)	1239(4)	4594(5)	70
H(30A)	-4176(7)	1337(4)	4693(5)	64
H(30B)	-2513(7)	1423(4)	5409(5)	64

Table A.11. Crystal data and structure refinement for 20.

Identification code	lsh23m
Empirical formula	$C_{44}H_{76}N_{10}O_8$
Formula weight	873.15
Temperature	298(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 9.3727(5) Å alpha = 65.237(3)° b = 12.0214(9) Å beta = 83.347(3)° c = 13.9041(10) Å gamma = 72.498(3)°
Volume, Z	1356.6(2) $Å^3$, 1
Density (calculated)	1.069 Mg/m^3
Absorption coefficient	0.074 mm^{-1}
F(000)	474
Crystal size	0.08 x 0.18 x 0.20 mm
θ range for data collection	1.61 to 28.34°
Limiting indices	$-12 \le h \le 11$, $-15 \le k \le 8$, $-18 \le l \le 18$
Reflections collected	8567
Independent reflections	6133 (R_{int} = 0.0817)
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6133 / 0 / 296
Goodness-of-fit on F^2	1.021
Final R indices [$I>2\sigma(I)$]	R1 = 0.1218, wR2 = 0.2780
R indices (all data)	R1 = 0.3820, wR2 = 0.4190
Largest diff. peak and hole	0.829 and -0.310 $eÅ^{-3}$

Table A.12. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 20. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
N(5)	9411(6)	7743(6)	2381(5)	49(2)
N(4)	13454(6)	3765(6)	6739(5)	49(2)
N(3)	11120(7)	5563(5)	4557(5)	55(2)
N(2)	7467(7)	7526(5)	1174(5)	50(2)
N(1)	13683(7)	1258(6)	6644(5)	58(2)
O(3)	6018(7)	7749(6)	-137(5)	86(2)
O(2)	12037(7)	-312(6)	7727(5)	80(2)
C(21)	8267(8)	8472(7)	545(6)	50(2)
C(20)	11069(8)	4934(7)	5614(6)	47(2)
O(1)	12216(7)	2173(6)	5180(5)	87(2)
O(4)	12829(7)	5061(5)	8266(5)	77(2)
C(18)	10080(8)	5647(6)	3947(6)	46(2)
C(17)	10233(8)	6376(7)	2776(5)	52(2)
C(16)	12494(10)	1439(8)	6114(7)	59(2)
C(15)	12237(9)	4980(7)	6236(6)	62(2)
C(14)	9542(9)	8352(8)	1212(6)	68(3)
C(13)	14067(9)	3943(8)	8429(7)	62(2)
C(12)	14267(8)	3334(7)	5925(6)	56(2)
C(11)	14492(9)	3955(7)	7315(6)	60(2)
C(10)	6460(9)	7224(8)	789(7)	58(2)
C(9)	14888(8)	1873(8)	6268(7)	59(2)
C(8)	7167(9)	9816(8)	200(7)	81(3)
C(21)	9890(8)	8400(8)	2919(6)	57(2)
C(7)	11369(10)	696(8)	6747(7)	67(3)
C(6)	8969(11)	8268(10)	-424(7)	99(3)
C(5)	16005(9)	1235(8)	7166(8)	88(3)
C(4)	15629(10)	1657(9)	5286(8)	92(3)
C(3)	10697(11)	244(10)	6084(8)	102(4)
C(2)	15398(10)	3998(9)	8913(7)	92(3)
C(1)	13068(12)	-1443(9)	7695(9)	119(4)
C(24)	12164(12)	5252(10)	9187(8)	107(4)
C(97)	19560(27)	7156(21)	6504(21)	103(14)
O(7)	18798(28)	7422(19)	7222(19)	324(17)
O(8)	17274(33)	6851(23)	7494(19)	416(22)

Table A.13. Bond lengths [Å] and angles [°] for 20.

N(5)-C(21)	1.473(10)	N(5)-C(14)	1.485(9)
N(5)-C(17)	1.475(8)	N(4)-C(12)	1.477(9)
N(4)-C(11)	1.452(9)	N(4)-C(15)	1.500(9)
N(3)-C(18)	1.319(9)	N(3)-C(20)	1.344(9)
N(2)-C(10)	1.339(9)	N(2)-C(21)	1.466(9)
N(1)-C(16)	1.320(9)	N(1)-C(9)	1.463(9)
O(3)-C(10)	1.231(9)	O(2)-C(1)	1.427(10)
O(2)-C(7)	1.441(9)	C(21)-C(6)	1.511(11)
C(21)-C(8)	1.538(10)	C(21)-C(14)	1.533(10)
C(20)-C(18)#1	1.402(10)	C(20)-C(15)	1.499(10)
O(1)-C(16)	1.230(9)	O(4)-C(24)	1.434(10)
O(4)-C(13)	1.440(9)	C(18)-C(20)#1	1.402(10)
C(18)-C(17)	1.505(9)	C(16)-C(7)	1.542(11)
C(13)-C(2)	1.514(11)	C(13)-C(11)	1.550(11)
C(13)-C(10)#1	1.552(11)	C(12)-C(9)	1.549(10)
C(10)-C(13)#1	1.552(11)	C(9)-C(5)	1.504(10)
C(9)-C(4)	1.544(11)	C(21)-C(7)#1	1.522(11)
C(7)-C(21)#1	1.522(11)	C(7)-C(3)	1.517(11)
C(97)-O(7)	1.25(3)		

C(21)-N(5)-C(14)	112.5(6)	C(21)-N(5)-C(17)	112.1(6)
C(14)-N(5)-C(17)	109.9(6)	C(12)-N(4)-C(11)	109.7(6)
C(12)-N(4)-C(15)	110.5(6)	C(11)-N(4)-C(15)	110.1(6)
C(18)-N(3)-C(20)	120.0(7)	C(10)-N(2)-C(21)	125.1(6)
C(16)-N(1)-C(9)	128.1(7)	C(1)-O(2)-C(7)	118.4(7)
N(2)-C(21)-C(6)	111.9(7)	N(2)-C(21)-C(8)	109.2(6)
C(6)-C(21)-C(8)	109.3(7)	N(2)-C(21)-C(14)	109.5(6)
C(6)-C(21)-C(14)	106.9(7)	C(8)-C(21)-C(14)	110.0(7)
N(3)-C(20)-C(18)#1	119.3(7)	N(3)-C(20)-C(15)	115.6(7)
C(18)#1-C(20)-C(15)	125.1(7)	C(24)-O(4)-C(13)	117.5(7)
N(3)-C(18)-C(20)#1	120.7(7)	N(3)-C(18)-C(17)	115.9(7)
C(20)#1-C(18)-C(17)	123.4(8)	N(5)-C(17)-C(18)	114.1(6)
O(1)-C(16)-N(1)	124.8(8)	O(1)-C(16)-C(7)	119.1(9)
N(1)-C(16)-C(7)	116.1(8)	N(4)-C(15)-C(20)	116.4(6)
N(5)-C(14)-C(21)	117.1(7)	O(4)-C(13)-C(2)	111.0(7)
O(4)-C(13)-C(11)	105.9(6)	C(2)-C(13)-C(11)	108.9(7)
O(4)-C(13)-C(10)#1	107.1(6)	C(2)-C(13)-C(10)#1	108.9(7)
C(11)-C(13)-C(10)#1	115.0(7)	N(4)-C(12)-C(9)	116.3(6)
N(4)-C(11)-C(13)	119.3(6)	O(3)-C(10)-N(2)	124.7(8)
O(3)-C(10)-C(13)#1	119.2(8)	N(2)-C(10)-C(13)#1	115.9(7)
N(1)-C(9)-C(5)	105.5(7)	N(1)-C(9)-C(12)	110.6(6)
C(5)-C(9)-C(12)	113.7(7)	N(1)-C(9)-C(4)	110.4(7)
C(5)-C(9)-C(4)	109.7(7)	C(12)-C(9)-C(4)	106.9(7)
N(5)-C(21)-C(7)#1	115.3(7)	O(2)-C(7)-C(21)#1	104.6(7)
O(2)-C(7)-C(3)	113.6(7)	C(21)#1-C(7)-C(3)	108.2(8)
O(2)-C(7)-C(16)	110.5(7)	C(21)#1-C(7)-C(16)	107.5(7)
C(3)-C(7)-C(16)	111.9(8)		

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,-y+1,-z+1

Table A.14. Anisotropic displacement parameters [$Å^2$ x 10^3] for 20.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
N(5)	51(4)	48(4)	39(4)	-5(3)	-3(3)	-18(3)
N(4)	42(4)	53(4)	48(4)	-14(3)	-7(3)	-16(3)
N(3)	50(4)	48(4)	52(5)	-9(3)	-11(4)	-5(3)
N(2)	54(4)	50(4)	41(4)	-7(3)	-14(3)	-18(3)
N(1)	54(4)	59(5)	51(4)	-12(3)	-11(4)	-11(4)
O(3)	108(5)	94(5)	51(4)	-8(3)	-23(4)	-44(4)
O(2)	90(5)	62(4)	79(5)	-17(3)	1(4)	-27(3)
C(21)	53(5)	55(5)	32(4)	-9(4)	3(4)	-14(4)
C(20)	49(5)	48(5)	37(5)	-9(4)	-10(4)	-12(4)
O(1)	99(5)	116(5)	44(4)	-15(4)	-8(4)	-50(4)
O(4)	97(5)	64(4)	71(4)	-29(3)	-9(4)	-18(4)
C(18)	39(5)	41(5)	45(5)	-10(4)	-5(4)	-2(4)
C(17)	51(5)	53(5)	36(5)	-4(4)	-3(4)	-12(4)
C(16)	73(6)	61(6)	40(5)	-16(5)	2(5)	-23(5)
C(15)	71(6)	55(5)	51(5)	-10(4)	-14(5)	-15(4)
C(14)	67(6)	79(6)	46(5)	-6(5)	-7(5)	-28(5)
C(13)	57(6)	61(6)	65(6)	-19(5)	-12(5)	-18(5)
C(12)	46(5)	61(6)	52(5)	-13(4)	4(4)	-15(4)
C(11)	50(5)	58(5)	68(6)	-15(4)	2(5)	-25(4)
C(10)	64(6)	57(6)	56(6)	-20(5)	-6(5)	-24(5)
C(9)	39(5)	76(6)	66(6)	-29(5)	-7(4)	-17(5)
C(8)	73(6)	58(6)	83(7)	3(5)	-26(5)	-15(5)
C(21)	49(5)	60(5)	53(5)	-7(4)	-4(4)	-21(4)
C(7)	80(7)	60(6)	57(6)	-11(5)	-8(5)	-29(5)
C(6)	122(9)	129(9)	74(7)	-52(7)	26(6)	-65(7)
C(5)	57(6)	74(6)	116(9)	-26(6)	-36(6)	-1(5)
C(4)	80(7)	98(8)	101(8)	-53(6)	26(6)	-20(6)
C(3)	104(8)	153(10)	102(9)	-77(8)	13(7)	-76(8)
C(2)	91(7)	108(8)	80(7)	-21(6)	-23(6)	-49(6)
C(1)	139(10)	59(7)	153(11)	-50(7)	7(8)	-9(7)
C(24)	135(10)	103(8)	99(9)	-58(7)	-8(8)	-26(7)

Table A.15. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 20.

	x	y	z	U(eq)
H(2A)	7659(7)	7133(5)	1843(5)	60
H(1A)	13758(7)	709(6)	7292(5)	70
H(17A)	11285(8)	6295(7)	2616(5)	62
H(17B)	9874(8)	5990(7)	2400(5)	62
H(15A)	12698(9)	5636(7)	5770(6)	75
H(15B)	11740(9)	5241(7)	6791(6)	75
H(14A)	10465(9)	7870(8)	1012(6)	82
H(14B)	9633(9)	9201(8)	1024(6)	82
H(12A)	15096(8)	3707(7)	5685(6)	68
H(12B)	13598(8)	3672(7)	5323(6)	68
H(11A)	14683(9)	4768(7)	6875(6)	72
H(11B)	15430(9)	3300(7)	7386(6)	72
H(8A)	6726(9)	9951(8)	814(7)	121
H(8B)	6396(9)	9895(8)	-242(7)	121
H(8C)	7694(9)	10441(8)	-189(7)	121
H(21A)	10545(8)	8880(8)	2449(6)	69
H(21B)	10471(8)	7761(8)	3544(6)	69
H(6A)	9649(11)	7427(10)	-210(7)	149
H(6B)	9503(11)	8889(10)	-804(7)	149
H(6C)	8200(11)	8357(10)	-873(7)	149
H(5A)	16350(9)	336(8)	7336(8)	132
H(5B)	15540(9)	1371(8)	7775(8)	132
H(5C)	16839(9)	1591(8)	6961(8)	132
H(4A)	14910(10)	2056(9)	4717(8)	138
H(4B)	15983(10)	758(9)	5457(8)	138
H(4C)	16456(10)	2021(9)	5073(8)	138
H(3B)	11475(11)	-332(10)	5868(8)	153
H(3C)	10212(11)	965(10)	5468(8)	153
H(3D)	9978(11)	-186(10)	6495(8)	153
H(2B)	15144(10)	3990(9)	9604(7)	137
H(2C)	15665(10)	4766(9)	8470(7)	137
H(2D)	16229(10)	3271(9)	8971(7)	137
H(1B)	13428(12)	-2025(9)	8399(9)	179
H(1C)	13895(12)	-1228(9)	7254(9)	179
H(1D)	12575(12)	-1835(9)	7411(9)	179
H(24A)	11363(12)	6029(10)	8974(8)	160
H(24B)	12905(12)	5308(10)	9574(8)	160
H(24C)	11778(12)	4548(10)	9629(8)	160

Table A.16. Crystal data and structure refinement for 22.

Identification code	lsh20m
Empirical formula	$C_{51}H_{84}N_{10}O_8$
Formula weight	965.28
Temperature	159(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 8.6399(7) Å alpha = 106.248(2)° b = 16.1523(13) Å beta = 93.178(2)° c = 20.212(2) Å gamma = 102.121(2)°
Volume, Z	2627.9(4) $Å^3$, 2
Density (calculated)	1.220 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	1048
Crystal size	0.05 x 0.10 x 0.40 mm
θ range for data collection	1.06 to 28.41°
Limiting indices	$-11 \le h \le 11$, $-21 \le k \le 9$, $-22 \le l \le 26$
Reflections collected	16826
Independent reflections	11772 (R_{int} = 0.1639)
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11770 / 0 / 623
Goodness-of-fit on F^2	0.912
Final R indices [$I>2\sigma(I)$]	R1 = 0.1559, wR2 = 0.2529
R indices (all data)	R1 = 0.4173, wR2 = 0.3454
Extinction coefficient	0.0021(9)
Largest diff. peak and hole	0.279 and -0.323 $eÅ^{-3}$

Table A.17. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 22. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(8)	276(6)	5920(4)	4646(3)	42(2)
N(9)	625(8)	3417(5)	1658(3)	34(2)
O(7)	5004(7)	3582(4)	-370(3)	41(2)
N(8)	4744(7)	4565(5)	2940(3)	28(2)
O(6)	155(7)	1440(4)	1845(3)	44(2)
O(5)	5750(7)	9139(4)	5603(3)	49(2)
N(7)	3452(8)	5977(4)	4243(3)	28(2)
O(4)	-1065(7)	6236(4)	3329(3)	54(2)
C(52)	4746(8)	4839(6)	1852(4)	24(2)
O(3)	7979(7)	8386(4)	4405(3)	42(2)
N(6)	4830(7)	7547(4)	3436(3)	28(2)
N(5)	5118(7)	5712(5)	2148(3)	31(2)
N(4)	3299(8)	2280(5)	351(3)	39(2)
N(3)	3176(8)	2637(4)	1777(3)	30(2)
N(2)	4992(8)	7721(5)	4904(3)	36(2)
N(1)	2788(8)	4032(5)	777(3)	33(2)
C(51)	4690(9)	4240(5)	2242(4)	23(2)
N(10)	1648(8)	6614(5)	3380(3)	39(2)
C(49)	586(11)	2326(6)	2304(4)	35(2)
O(2)	-1681(8)	2888(4)	2044(3)	54(2)
C(48)	6631(9)	8808(6)	4461(4)	33(2)
C(47)	5274(9)	6032(5)	2844(4)	25(2)
C(46)	2561(10)	3848(6)	14(4)	38(2)
O(1)	2918(8)	1581(4)	-812(3)	58(2)
C(45)	4064(10)	7294(6)	5359(4)	33(2)
C(44)	3319(11)	3175(6)	-455(4)	38(2)
C(43)	4959(9)	5433(6)	3240(4)	24(2)
C(42)	3699(10)	6288(5)	5016(4)	36(2)
C(41)	-859(10)	4564(6)	1635(4)	52(3)
C(40)	5718(10)	8564(7)	5040(5)	38(2)
C(39)	3599(10)	7482(6)	2876(4)	38(2)
C(38)	-873(9)	4658(6)	3624(4)	41(2)
C(37)	1582(10)	4511(6)	1085(4)	36(2)
C(36)	2388(10)	2606(6)	2396(4)	38(2)
C(35)	2033(9)	5241(5)	3952(4)	28(2)
C(34)	5974(9)	7030(5)	3149(4)	32(2)
C(33)	1642(10)	8179(6)	3632(4)	43(3)
C(32)	7(10)	2368(6)	3012(4)	49(3)
C(31)	3470(10)	1766(6)	1384(4)	36(2)
C(30)	303(12)	6153(6)	3507(4)	43(3)
C(29)	4932(9)	5720(6)	4020(4)	31(2)
C(28)	427(10)	5498(6)	3919(4)	31(2)
C(27)	-260(12)	2918(7)	1983(4)	46(3)
C(26)	5691(10)	8493(5)	3736(4)	36(2)
C(25)	4752(9)	3292(5)	1959(4)	31(2)
C(24)	3139(11)	2263(6)	-322(5)	42(3)
C(23)	5027(10)	7499(6)	6066(4)	50(3)

C(22)	4104(14)	882(7)	272(5)	82(4)
C(21)	5966(11)	3126(7)	-814(4)	57(3)
C(20)	1876(10)	7375(6)	3091(4)	36(2)
C(19)	4455(9)	4541(6)	1059(4)	38(2)
C(18)	2569(11)	3003(6)	-1207(4)	53(3)
C(17)	2595(20)	-893(8)	1312(6)	75(4)
C(16)	8939(10)	8542(7)	5053(4)	57(3)
C(15)	765(10)	7171(6)	2423(4)	51(3)
C(14)	2583(11)	7668(6)	5457(4)	53(3)
C(13)	3028(12)	1485(6)	584(4)	47(3)
C(12)	1277(12)	1002(7)	386(4)	74(4)
C(11)	77(10)	3935(6)	1241(4)	38(2)
C(10)	7242(11)	9804(6)	4637(4)	53(3)
C(9)	4032(17)	-559(9)	1695(8)	84(4)
C(8)	-1163(10)	6165(6)	4803(4)	49(3)
C(7)	-970(10)	3292(7)	584(4)	59(3)
C(6)	1346(17)	-399(8)	2309(7)	73(4)
C(5)	-1494(11)	1004(7)	1633(5)	72(4)
C(4)	4196(17)	-124(10)	2391(8)	90(5)
C(3)	1217(16)	-813(8)	1604(6)	72(4)
C(2)	2852(20)	-63(7)	2680(6)	78(4)
C(1)	-148(16)	-324(8)	2665(6)	113(5)

Table A.18. Bond lengths [Å] and angles [°] for 22.

O(8)-C(8)	1.408(9)	O(8)-C(28)	1.462(9)
N(9)-C(27)	1.326(10)	N(9)-C(11)	1.467(10)
O(7)-C(21)	1.416(9)	O(7)-C(44)	1.446(9)
N(8)-C(43)	1.330(9)	N(8)-C(51)	1.356(9)
O(6)-C(49)	1.428(9)	O(6)-C(5)	1.433(9)
O(5)-C(40)	1.246(9)	N(7)-C(35)	1.476(9)
N(7)-C(29)	1.480(9)	N(7)-C(42)	1.489(8)
O(4)-C(30)	1.260(10)	C(52)-N(5)	1.329(9)
C(52)-C(51)	1.403(10)	C(52)-C(19)	1.528(9)
O(3)-C(16)	1.440(8)	O(3)-C(48)	1.462(10)
N(6)-C(34)	1.466(10)	N(6)-C(39)	1.476(9)
N(6)-C(26)	1.487(9)	N(5)-C(47)	1.345(8)
N(4)-C(24)	1.352(9)	N(4)-C(13)	1.465(10)
N(3)-C(36)	1.465(8)	N(3)-C(31)	1.491(10)
N(3)-C(25)	1.493(9)	N(2)-C(40)	1.318(10)
N(2)-C(45)	1.471(9)	N(1)-C(46)	1.480(8)
N(1)-C(37)	1.487(10)	N(1)-C(19)	1.492(9)
C(51)-C(25)	1.490(10)	N(10)-C(30)	1.322(10)
N(10)-C(20)	1.485(10)	C(49)-C(36)	1.513(11)
C(49)-C(32)	1.530(10)	C(49)-C(27)	1.568(13)
O(2)-C(27)	1.232(10)	C(48)-C(10)	1.516(11)
C(48)-C(26)	1.532(10)	C(48)-C(40)	1.541(11)
C(47)-C(43)	1.414(10)	C(47)-C(34)	1.529(11)
C(46)-C(44)	1.516(11)	O(1)-C(24)	1.229(9)
C(45)-C(14)	1.526(12)	C(45)-C(23)	1.527(10)
C(45)-C(42)	1.532(11)	C(44)-C(18)	1.544(10)
C(44)-C(24)	1.548(12)	C(43)-C(29)	1.515(10)
C(41)-C(11)	1.511(11)	C(39)-C(20)	1.562(11)
C(38)-C(28)	1.514(11)	C(37)-C(11)	1.536(10)
C(35)-C(28)	1.533(11)	C(33)-C(20)	1.505(11)
C(31)-C(13)	1.552(10)	C(30)-C(28)	1.535(12)
C(22)-C(13)	1.522(12)	C(20)-C(15)	1.525(10)
C(17)-C(9)	1.346(14)	C(17)-C(3)	1.372(14)
C(13)-C(12)	1.523(12)	C(11)-C(7)	1.537(10)
C(9)-C(4)	1.370(14)	C(6)-C(3)	1.382(13)
C(6)-C(2)	1.384(15)	C(6)-C(1)	1.522(14)
C(4)-C(2)	1.339(15)		

C(8)-O(8)-C(28)	118.1(6)	C(27)-N(9)-C(11)	127.2(8)
C(21)-O(7)-C(44)	117.6(7)	C(43)-N(8)-C(51)	120.3(7)
C(49)-O(6)-C(5)	119.8(7)	C(35)-N(7)-C(29)	111.6(6)
C(35)-N(7)-C(42)	113.6(6)	C(29)-N(7)-C(42)	106.3(6)
N(5)-C(52)-C(51)	122.1(7)	N(5)-C(52)-C(19)	115.1(8)
C(51)-C(52)-C(19)	122.8(8)	C(16)-O(3)-C(48)	114.7(6)
C(34)-N(6)-C(39)	109.6(6)	C(34)-N(6)-C(26)	108.7(6)
C(39)-N(6)-C(26)	108.5(6)	C(52)-N(5)-C(47)	119.0(7)
C(24)-N(4)-C(13)	124.1(7)	C(36)-N(3)-C(31)	113.2(6)
C(36)-N(3)-C(25)	111.5(6)	C(31)-N(3)-C(25)	107.1(6)
C(40)-N(2)-C(45)	127.7(7)	C(46)-N(1)-C(37)	108.9(6)
C(46)-N(1)-C(19)	109.9(6)	C(37)-N(1)-C(19)	112.5(6)
N(8)-C(51)-C(52)	117.7(8)	N(8)-C(51)-C(25)	116.9(8)
C(52)-C(51)-C(25)	125.1(7)	C(30)-N(10)-C(20)	128.1(8)
O(6)-C(49)-C(36)	106.7(7)	O(6)-C(49)-C(32)	111.2(7)
C(36)-C(49)-C(32)	109.1(7)	O(6)-C(49)-C(27)	108.3(7)

C(36)-C(49)-C(27)	114.3(7)	C(32)-C(49)-C(27)	107.4(8)
O(3)-C(48)-C(10)	109.5(7)	O(3)-C(48)-C(26)	106.4(7)
C(10)-C(48)-C(26)	106.6(7)	O(3)-C(48)-C(40)	107.3(7)
C(10)-C(48)-C(40)	110.9(7)	C(26)-C(48)-C(40)	115.9(7)
N(5)-C(47)-C(43)	119.2(8)	N(5)-C(47)-C(34)	115.8(7)
C(43)-C(47)-C(34)	124.7(7)	N(1)-C(46)-C(44)	120.8(7)
N(2)-C(45)-C(14)	107.3(7)	N(2)-C(45)-C(23)	111.0(7)
C(14)-C(45)-C(23)	109.1(7)	N(2)-C(45)-C(42)	107.8(6)
C(14)-C(45)-C(42)	113.9(7)	C(23)-C(45)-C(42)	107.8(7)
O(7)-C(44)-C(46)	106.3(7)	O(7)-C(44)-C(18)	110.7(6)
C(46)-C(44)-C(18)	107.2(7)	O(7)-C(44)-C(24)	107.6(7)
C(46)-C(44)-C(24)	117.5(7)	C(18)-C(44)-C(24)	107.4(7)
N(8)-C(43)-C(47)	120.4(7)	N(8)-C(43)-C(29)	115.9(7)
C(47)-C(43)-C(29)	123.7(8)	N(7)-C(42)-C(45)	116.5(7)
O(5)-C(40)-N(2)	124.1(9)	O(5)-C(40)-C(48)	120.3(8)
N(2)-C(40)-C(48)	115.6(8)	N(6)-C(39)-C(20)	113.7(6)
N(1)-C(37)-C(11)	115.8(7)	N(3)-C(36)-C(49)	117.5(7)
N(7)-C(35)-C(28)	116.4(7)	N(6)-C(34)-C(47)	114.9(6)
N(3)-C(31)-C(13)	115.8(7)	O(4)-C(30)-N(10)	124.3(9)
O(4)-C(30)-C(28)	118.2(8)	N(10)-C(30)-C(28)	117.5(9)
N(7)-C(29)-C(43)	114.5(6)	O(8)-C(28)-C(38)	110.4(7)
O(8)-C(28)-C(35)	103.7(6)	C(38)-C(28)-C(35)	108.4(7)
O(8)-C(28)-C(30)	108.6(7)	C(38)-C(28)-C(30)	110.0(7)
C(35)-C(28)-C(30)	115.5(7)	O(2)-C(27)-N(9)	124.6(10)
O(2)-C(27)-C(49)	118.8(9)	N(9)-C(27)-C(49)	116.6(9)
N(6)-C(26)-C(48)	119.7(7)	C(51)-C(25)-N(3)	115.6(7)
O(1)-C(24)-N(4)	123.7(9)	O(1)-C(24)-C(44)	120.3(8)
N(4)-C(24)-C(44)	115.9(8)	N(10)-C(20)-C(33)	109.2(6)
N(10)-C(20)-C(15)	112.0(7)	C(33)-C(20)-C(15)	111.1(8)
N(10)-C(20)-C(39)	105.0(7)	C(33)-C(20)-C(39)	113.6(7)
C(15)-C(20)-C(39)	105.7(6)	N(1)-C(19)-C(52)	113.3(6)
C(9)-C(17)-C(3)	121.2(12)	N(4)-C(13)-C(22)	111.2(7)
N(4)-C(13)-C(12)	108.7(8)	C(22)-C(13)-C(12)	111.0(9)
N(4)-C(13)-C(31)	109.2(7)	C(22)-C(13)-C(31)	106.4(8)
C(12)-C(13)-C(31)	110.4(7)	N(9)-C(11)-C(41)	112.3(7)
N(9)-C(11)-C(37)	106.5(7)	C(41)-C(11)-C(37)	106.7(8)
N(9)-C(11)-C(7)	108.7(8)	C(41)-C(11)-C(7)	109.5(8)
C(37)-C(11)-C(7)	113.2(7)	C(17)-C(9)-C(4)	122.0(13)
C(3)-C(6)-C(2)	118.7(12)	C(3)-C(6)-C(1)	120.1(14)
C(2)-C(6)-C(1)	121.2(13)	C(2)-C(4)-C(9)	116.9(13)
C(17)-C(3)-C(6)	117.9(11)	C(4)-C(2)-C(6)	123.2(12)

Symmetry transformations used to generate equivalent atoms:

Table A.19. Anisotropic displacement parameters [$Å^2$ x 10^3] for 22.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
O(8)	33(4)	53(4)	48(4)	14(3)	10(3)	29(3)
N(9)	17(4)	40(5)	48(5)	20(4)	0(3)	5(4)
O(7)	41(4)	52(4)	32(3)	11(3)	8(3)	15(4)
N(8)	21(4)	36(5)	32(4)	13(4)	-3(3)	19(4)
O(6)	37(4)	39(4)	53(4)	8(3)	6(3)	8(3)
O(5)	53(4)	44(4)	41(4)	0(4)	6(3)	13(4)
N(7)	29(4)	35(5)	25(4)	11(4)	0(3)	17(4)
O(4)	35(4)	70(5)	67(4)	32(4)	-5(3)	21(4)
C(52)	12(5)	31(6)	32(5)	8(5)	5(4)	10(4)
O(3)	36(4)	48(4)	43(4)	12(3)	-1(3)	16(3)
N(6)	26(4)	32(5)	32(4)	12(4)	4(3)	14(4)
N(5)	23(4)	30(5)	37(4)	4(4)	5(3)	11(4)
N(4)	48(5)	34(5)	29(4)	5(4)	-2(4)	-1(4)
N(3)	32(5)	30(5)	30(4)	9(4)	6(3)	12(4)
N(2)	39(5)	29(5)	39(4)	5(4)	3(4)	10(4)
N(1)	30(5)	43(5)	24(4)	10(4)	-1(3)	4(4)
C(51)	18(5)	24(5)	28(5)	5(4)	-3(4)	11(4)
N(10)	23(5)	49(5)	53(5)	29(4)	5(4)	12(4)
C(49)	44(6)	34(6)	33(5)	12(5)	9(4)	16(5)
O(2)	39(4)	58(5)	74(5)	29(4)	20(4)	11(4)
C(48)	15(5)	36(6)	48(6)	7(5)	-2(4)	13(5)
C(47)	24(5)	30(6)	22(5)	2(4)	-2(4)	19(4)
C(46)	48(6)	39(6)	34(5)	12(5)	2(4)	24(5)
O(1)	93(6)	39(5)	39(4)	8(4)	10(4)	11(4)
C(45)	36(6)	42(6)	22(5)	12(5)	3(4)	7(5)
C(44)	40(6)	41(6)	34(5)	22(5)	-2(4)	1(5)
C(43)	16(5)	34(6)	37(5)	22(5)	6(4)	18(4)
C(42)	37(6)	37(6)	39(5)	16(5)	1(4)	16(5)
C(41)	36(6)	64(8)	72(7)	29(6)	16(5)	32(6)
C(40)	34(6)	44(7)	41(6)	12(6)	0(5)	20(5)
C(39)	45(6)	50(7)	27(5)	20(5)	3(4)	14(5)
C(38)	26(6)	45(6)	60(6)	22(5)	7(4)	18(5)
C(37)	33(6)	47(6)	33(5)	18(5)	0(4)	12(5)
C(36)	43(6)	39(6)	43(6)	27(5)	10(4)	10(5)
C(35)	28(5)	31(6)	31(5)	21(4)	8(4)	8(5)
C(34)	31(6)	34(6)	31(5)	9(5)	4(4)	9(5)
C(33)	48(6)	39(6)	44(5)	10(5)	8(5)	21(5)
C(32)	48(6)	62(7)	56(6)	35(6)	22(5)	25(6)
C(31)	36(6)	32(6)	37(5)	11(5)	6(4)	-4(5)
C(30)	41(7)	44(7)	37(6)	2(5)	1(5)	13(6)
C(29)	24(5)	42(6)	31(5)	18(5)	5(4)	8(5)
C(28)	28(5)	43(6)	31(5)	17(5)	9(4)	16(5)
C(27)	36(7)	42(7)	43(6)	-4(5)	10(5)	-9(6)
C(26)	37(6)	32(6)	42(5)	11(5)	-7(4)	22(5)
C(25)	24(5)	32(6)	42(5)	15(5)	9(4)	11(5)
C(24)	49(7)	34(7)	37(6)	1(5)	0(5)	8(5)
C(23)	58(7)	49(7)	39(5)	13(5)	-11(5)	10(6)

C(22)	153(12)	74(9)	52(7)	26(7)	45(7)	81(9)
C(21)	51(7)	83(9)	43(6)	22(6)	6(5)	23(6)
C(20)	41(6)	44(7)	25(5)	13(5)	1(4)	14(5)
C(19)	33(6)	43(6)	32(5)	8(5)	6(4)	2(5)
C(18)	67(7)	62(7)	26(5)	17(5)	2(5)	2(6)
C(17)	117(12)	53(8)	55(8)	21(7)	10(9)	15(9)
C(16)	46(6)	74(8)	46(6)	4(6)	-13(5)	27(6)
C(15)	53(7)	54(7)	60(6)	32(6)	4(5)	23(6)
C(14)	56(7)	59(7)	52(6)	19(6)	23(5)	20(6)
C(13)	65(8)	31(6)	45(6)	9(5)	26(5)	10(6)
C(12)	77(8)	77(9)	51(6)	26(6)	-9(6)	-28(7)
C(11)	29(6)	50(7)	39(5)	19(5)	3(4)	11(5)
C(10)	53(7)	46(7)	49(6)	3(5)	-1(5)	5(6)
C(9)	75(11)	84(11)	115(12)	52(10)	39(9)	26(9)
C(8)	48(7)	53(7)	51(6)	16(5)	8(5)	25(6)
C(7)	42(6)	77(8)	54(6)	24(6)	-17(5)	7(6)
C(6)	98(11)	65(9)	71(9)	32(8)	36(8)	29(8)
C(5)	46(7)	57(8)	91(8)	4(7)	2(6)	-11(6)
C(4)	74(11)	95(12)	111(12)	65(11)	3(9)	-5(9)
C(3)	84(10)	61(9)	71(9)	37(8)	-10(7)	2(8)
C(2)	113(12)	43(8)	62(8)	12(7)	-5(9)	-6(9)
C(1)	163(14)	96(12)	123(11)	64(10)	52(10)	73(11)

Table A.20. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 22.

	x	y	z	U(eq)
H(9A)	1654(8)	3440(5)	1697(3)	41
H(4A)	3585(8)	2800(5)	670(3)	47
H(2A)	5071(8)	7371(5)	4493(3)	44
H(10A)	2518(8)	6448(5)	3479(3)	46
H(46A)	2944(10)	4419(6)	-83(4)	46
H(46B)	1398(10)	3659(6)	-135(4)	46
H(42A)	4588(10)	6064(5)	5175(4)	43
H(42B)	2727(10)	6015(5)	5187(4)	43
H(41A)	-1835(10)	4223(6)	1746(4)	78
H(41B)	-1140(10)	4922(6)	1348(4)	78
H(41C)	-210(10)	4954(6)	2066(4)	78
H(39A)	3618(10)	6968(6)	2474(4)	46
H(39B)	3867(10)	8022(6)	2725(4)	46
H(38A)	-1910(9)	4810(6)	3599(4)	62
H(38B)	-872(9)	4276(6)	3924(4)	62
H(38C)	-678(9)	4344(6)	3157(4)	62
H(37A)	1253(10)	4823(6)	763(4)	44
H(37B)	2098(10)	4969(6)	1522(4)	44
H(36A)	2714(10)	3203(6)	2739(4)	46
H(36B)	2803(10)	2194(6)	2601(4)	46
H(35A)	1974(9)	4825(5)	4234(4)	33
H(35B)	2187(9)	4916(5)	3476(4)	33
H(34A)	6848(9)	7128(5)	3521(4)	38
H(34B)	6446(9)	7258(5)	2781(4)	38
H(33A)	2368(10)	8295(6)	4055(4)	64
H(33B)	537(10)	8073(6)	3738(4)	64
H(33C)	1867(10)	8694(6)	3456(4)	64
H(32A)	-1160(10)	2187(6)	2955(4)	74
H(32B)	360(10)	2976(6)	3323(4)	74
H(32C)	451(10)	1968(6)	3212(4)	74
H(31A)	2856(10)	1301(6)	1562(4)	43
H(31B)	4615(10)	1786(6)	1482(4)	43
H(29A)	5077(9)	5228(6)	4200(4)	37
H(29B)	5849(9)	6230(6)	4232(4)	37
H(26A)	4897(10)	8856(5)	3743(4)	43
H(26B)	6444(10)	8636(5)	3410(4)	43
H(25A)	5407(9)	3141(5)	2305(4)	37
H(25B)	5303(9)	3226(5)	1537(4)	37
H(23A)	5981(10)	7260(6)	6005(4)	75
H(23B)	4373(10)	7225(6)	6364(4)	75
H(23C)	5347(10)	8143(6)	6282(4)	75
H(22A)	5222(14)	1206(7)	406(5)	123
H(22B)	3870(14)	687(7)	-235(5)	123
H(22C)	3913(14)	363(7)	443(5)	123
H(21A)	7076(11)	3470(7)	-704(4)	86
H(21B)	5588(11)	3051(7)	-1298(4)	86
H(21C)	5900(11)	2543(7)	-746(4)	86
H(19A)	4697(9)	5070(6)	894(4)	45

H(19B)	5198(9)	4166(6)	875(4)	45
H(18A)	3033(11)	2569(6)	-1525(4)	79
H(18B)	2784(11)	3559(6)	-1328(4)	79
H(18C)	1414(11)	2771(6)	-1244(4)	79
H(17A)	2533(20)	-1190(8)	830(6)	90
H(16A)	9811(10)	8238(7)	4969(4)	86
H(16B)	8278(10)	8314(7)	5371(4)	86
H(16C)	9382(10)	9181(7)	5260(4)	86
H(15A)	942(10)	6646(6)	2080(4)	77
H(15B)	985(10)	7679(6)	2239(4)	77
H(15C)	-345(10)	7058(6)	2521(4)	77
H(14A)	1961(11)	7538(6)	5005(4)	80
H(14B)	2906(11)	8311(6)	5674(4)	80
H(14C)	1931(11)	7394(6)	5756(4)	80
H(12A)	609(12)	1403(7)	593(4)	111
H(12B)	1069(12)	484(7)	558(4)	111
H(12C)	1027(12)	808(7)	-120(4)	111
H(10B)	7854(11)	10035(6)	5099(4)	80
H(10C)	6337(11)	10081(6)	4631(4)	80
H(10D)	7929(11)	9940(6)	4293(4)	80
H(9B)	4962(17)	-628(9)	1476(8)	101
H(8B)	-1101(10)	6439(6)	5305(4)	73
H(8C)	-2048(10)	5637(6)	4654(4)	73
H(8D)	-1340(10)	6590(6)	4560(4)	73
H(7A)	-363(10)	2884(7)	329(4)	88
H(7B)	-1297(10)	3629(7)	289(4)	88
H(7C)	-1919(10)	2952(7)	716(4)	88
H(5B)	-1584(11)	406(7)	1322(5)	109
H(5C)	-2002(11)	1343(7)	1391(5)	109
H(5D)	-2026(11)	965(7)	2043(5)	109
H(4B)	5216(17)	124(10)	2655(8)	108
H(3A)	206(16)	-1036(8)	1329(6)	86
H(2B)	2935(20)	226(7)	3164(6)	93
H(1A)	157(16)	-14(8)	3161(6)	169
H(1B)	-808(16)	-919(8)	2604(6)	169
H(1C)	-754(16)	10(8)	2458(6)	169

Table A.21. Crystal data and structure refinement for 23a.

Identification code	lshlla
Empirical formula	$C_{38}H_{47}Cl_2CuN_5O_4$
Formula weight	772.25
Temperature	163(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 11.0870(3) Å alpha = 79.9970(10)° b = 12.68930(10) Å beta = 75.7280(10)° c = 13.6631(3) Å gamma = 85.1800(10)°
Volume, Z	1832.86(7) $Å^3$, 2
Density (calculated)	1.399 Mg/m^3
Absorption coefficient	0.789 mm^{-1}
F(000)	810
Crystal size	0.20 x 0.20 x 0.38 mm
θ range for data collection	1.56 to 23.24°
Limiting indices	$-12 \le h \le 12$, $-14 \le k \le 7$, $-15 \le l \le 14$
Reflections collected	8434
Independent reflections	5184 (R_{int} = 0.0318)
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5184 / 0 / 451
Goodness-of-fit on F^2	1.052
Final R indices [$I>2\sigma(I)$]	R1 = 0.0431, wR2 = 0.0958
R indices (all data)	R1 = 0.0666, wR2 = 0.1073
Largest diff. peak and hole	0.624 and -0.461 $eÅ^{-3}$

Table A.22. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 23a. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Cu(1)	6610(1)	8044(1)	7446(1)	17(1)
N(1)	6478(3)	7898(2)	6090(2)	16(1)
N(2)	5885(3)	9633(2)	7356(2)	15(1)
N(3)	7382(3)	8325(2)	8505(2)	15(1)
N(4)	6590(3)	6367(2)	7793(2)	19(1)
N(5)	4706(3)	7819(2)	8189(2)	18(1)
O(1)	5969(2)	8801(2)	4605(2)	24(1)
O(2)	9100(2)	7930(2)	9207(2)	23(1)
O(3)	8303(2)	9347(2)	5701(2)	22(1)
O(4)	6832(2)	6279(2)	9959(2)	21(1)
Cl(1)	8273(1)	8423(1)	12319(1)	47(1)
Cl(2)	9967(1)	6582(1)	11945(1)	57(1)
C(1)	6424(3)	8745(3)	5366(3)	20(1)
C(2)	7112(3)	9735(3)	5482(3)	22(1)
C(3)	6458(3)	10330(3)	6374(3)	21(1)
C(4)	6145(3)	9960(3)	8280(3)	19(1)
C(5)	7370(3)	9496(3)	8556(3)	19(1)
C(6)	8199(3)	7666(3)	8899(3)	17(1)
C(7)	7933(3)	6440(3)	9113(3)	18(1)
C(8)	7679(3)	5944(3)	8232(3)	19(1)
C(9)	6779(3)	6053(3)	6753(3)	21(1)
C(10)	6165(3)	6815(3)	5983(3)	21(1)
C(11)	7300(4)	10572(3)	4507(3)	28(1)
C(12)	8519(3)	10052(3)	7853(3)	25(1)
C(13)	7240(4)	9699(3)	9662(3)	27(1)
C(14)	9042(3)	5777(3)	9419(3)	24(1)
C(15)	6811(4)	6514(3)	4923(3)	29(1)
C(16)	4757(3)	6692(3)	6134(3)	27(1)
C(17)	9087(3)	8784(3)	4937(3)	26(1)
C(18)	9791(3)	7837(3)	5413(3)	24(1)
C(19)	10083(3)	7796(3)	6350(3)	26(1)
C(20)	10806(4)	6951(4)	6728(3)	33(1)
C(21)	11228(4)	6119(4)	6181(3)	40(1)
C(22)	10926(4)	6134(4)	5247(4)	46(1)
C(23)	10227(4)	6988(4)	4870(3)	37(1)
C(24)	6875(4)	6678(4)	10866(3)	30(1)
C(25)	5571(3)	6795(3)	11504(3)	23(1)
C(26)	4564(4)	7051(3)	11044(3)	28(1)
C(27)	3359(4)	7150(3)	11641(3)	31(1)
C(28)	3149(4)	7025(3)	12699(3)	35(1)
C(29)	4131(4)	6814(3)	13161(3)	36(1)
C(30)	5338(4)	6682(3)	12565(3)	31(1)
C(31)	5385(3)	5971(3)	8498(3)	23(1)
C(32)	4499(3)	9668(3)	7474(3)	21(1)
C(33)	3902(3)	8654(3)	8097(3)	18(1)
C(34)	2627(3)	8516(3)	8468(3)	26(1)
C(35)	2224(4)	7498(3)	8915(3)	27(1)

C(36)	3075(3)	6632(3)	8956(3)	24(1)
C(37)	4344(3)	6830(3)	8566(3)	20(1)
C(50)	9572(4)	7915(4)	11445(3)	37(1)

Table A.23. Bond lengths [Å] and angles [°] for 23a.

Cu(1)-N(1)	1.936(3)	Cu(1)-N(3)	1.948(3)
Cu(1)-N(4)	2.100(3)	Cu(1)-N(2)	2.102(3)
Cu(1)-N(5)	2.125(3)	N(1)-C(1)	1.336(5)
N(1)-C(10)	1.484(4)	N(2)-C(4)	1.493(4)
N(2)-C(3)	1.499(4)	N(2)-C(32)	1.502(4)
N(3)-C(6)	1.329(4)	N(3)-C(5)	1.498(5)
N(4)-C(8)	1.497(4)	N(4)-C(9)	1.502(4)
N(4)-C(31)	1.508(4)	N(5)-C(37)	1.326(5)
N(5)-C(33)	1.337(5)	O(1)-C(1)	1.252(4)
O(2)-C(6)	1.266(4)	O(3)-C(17)	1.436(4)
O(3)-C(2)	1.453(4)	O(4)-C(24)	1.431(4)
O(4)-C(7)	1.459(4)	Cl(1)-C(50)	1.783(4)
Cl(2)-C(50)	1.773(5)	C(1)-C(2)	1.574(5)
C(2)-C(3)	1.541(5)	C(2)-C(11)	1.535(5)
C(4)-C(5)	1.541(5)	C(5)-C(12)	1.536(5)
C(5)-C(13)	1.546(5)	C(6)-C(7)	1.571(5)
C(7)-C(14)	1.534(5)	C(7)-C(8)	1.545(5)
C(9)-C(10)	1.547(5)	C(10)-C(16)	1.542(5)
C(10)-C(15)	1.546(5)	C(17)-C(18)	1.516(5)
C(18)-C(19)	1.388(5)	C(18)-C(23)	1.399(6)
C(19)-C(20)	1.388(6)	C(20)-C(21)	1.382(6)
C(21)-C(22)	1.394(6)	C(22)-C(23)	1.380(6)
C(24)-C(25)	1.503(5)	C(25)-C(30)	1.391(5)
C(25)-C(26)	1.400(5)	C(26)-C(27)	1.392(5)
C(27)-C(28)	1.388(5)	C(28)-C(29)	1.374(6)
C(29)-C(30)	1.398(6)	C(31)-C(37)	1.516(5)
C(32)-C(33)	1.518(5)	C(33)-C(34)	1.394(5)
C(34)-C(35)	1.388(5)	C(35)-C(36)	1.390(5)
C(36)-C(37)	1.403(5)		

N(1)-Cu(1)-N(3)	157.98(12)	N(1)-Cu(1)-N(4)	87.05(11)
N(3)-Cu(1)-N(4)	99.29(11)	N(1)-Cu(1)-N(2)	94.42(11)
N(3)-Cu(1)-N(2)	87.75(11)	N(4)-Cu(1)-N(2)	157.37(11)
N(1)-Cu(1)-N(5)	96.93(11)	N(3)-Cu(1)-N(5)	104.97(11)
N(4)-Cu(1)-N(5)	78.80(11)	N(2)-Cu(1)-N(5)	78.60(11)
C(1)-N(1)-C(10)	121.7(3)	C(1)-N(1)-Cu(1)	122.2(2)
C(10)-N(1)-Cu(1)	114.9(2)	C(4)-N(2)-C(3)	113.7(3)
C(4)-N(2)-C(32)	108.7(3)	C(3)-N(2)-C(32)	108.6(3)
C(4)-N(2)-Cu(1)	101.8(2)	C(3)-N(2)-Cu(1)	113.2(2)
C(32)-N(2)-Cu(1)	110.6(2)	C(6)-N(3)-C(5)	118.9(3)
C(6)-N(3)-Cu(1)	124.9(2)	C(5)-N(3)-Cu(1)	112.5(2)
C(8)-N(4)-C(9)	109.1(3)	C(8)-N(4)-C(31)	111.0(3)
C(9)-N(4)-C(31)	111.8(3)	C(8)-N(4)-Cu(1)	109.6(2)
C(9)-N(4)-Cu(1)	102.0(2)	C(31)-N(4)-Cu(1)	113.0(2)
C(37)-N(5)-C(33)	122.7(3)	C(37)-N(5)-Cu(1)	118.6(2)
C(33)-N(5)-Cu(1)	117.7(2)	C(17)-O(3)-C(2)	114.0(3)
C(24)-O(4)-C(7)	116.0(3)	O(1)-C(1)-N(1)	127.6(3)
O(1)-C(1)-C(2)	118.8(3)	N(1)-C(1)-C(2)	113.4(3)
O(3)-C(2)-C(3)	104.8(3)	O(3)-C(2)-C(11)	110.7(3)
C(3)-C(2)-C(11)	106.5(3)	O(3)-C(2)-C(1)	107.9(3)
C(3)-C(2)-C(1)	115.6(3)	C(11)-C(2)-C(1)	111.1(3)
N(2)-C(3)-C(2)	115.6(3)	N(2)-C(4)-C(5)	115.9(3)
N(3)-C(5)-C(12)	113.2(3)	N(3)-C(5)-C(4)	104.6(3)
C(12)-C(5)-C(4)	112.6(3)	N(3)-C(5)-C(13)	111.8(3)

C(12)-C(5)-C(13)	109.3(3)	C(4)-C(5)-C(13)	105.0(3)
O(2)-C(6)-N(3)	126.6(3)	O(2)-C(6)-C(7)	116.5(3)
N(3)-C(6)-C(7)	116.5(3)	O(4)-C(7)-C(14)	109.3(3)
O(4)-C(7)-C(8)	106.8(3)	C(14)-C(7)-C(8)	105.4(3)
O(4)-C(7)-C(6)	107.4(3)	C(14)-C(7)-C(6)	110.1(3)
C(8)-C(7)-C(6)	117.6(3)	N(4)-C(8)-C(7)	119.2(3)
N(4)-C(9)-C(10)	116.2(3)	N(1)-C(10)-C(16)	113.2(3)
N(1)-C(10)-C(15)	112.3(3)	C(16)-C(10)-C(15)	107.0(3)
N(1)-C(10)-C(9)	103.8(3)	C(16)-C(10)-C(9)	115.1(3)
C(15)-C(10)-C(9)	105.3(3)	O(3)-C(17)-C(18)	111.6(3)
C(19)-C(18)-C(23)	118.0(4)	C(19)-C(18)-C(17)	122.6(4)
C(23)-C(18)-C(17)	119.3(3)	C(20)-C(19)-C(18)	121.1(4)
C(19)-C(20)-C(21)	120.2(4)	C(20)-C(21)-C(22)	119.7(4)
C(23)-C(22)-C(21)	119.6(4)	C(22)-C(23)-C(18)	121.5(4)
O(4)-C(24)-C(25)	109.1(3)	C(30)-C(25)-C(26)	118.3(4)
C(30)-C(25)-C(24)	120.9(3)	C(26)-C(25)-C(24)	120.8(3)
C(27)-C(26)-C(25)	120.4(4)	C(28)-C(27)-C(26)	120.2(4)
C(29)-C(28)-C(27)	120.2(4)	C(28)-C(29)-C(30)	119.7(4)
C(25)-C(30)-C(29)	121.1(4)	N(4)-C(31)-C(37)	112.7(3)
N(2)-C(32)-C(33)	112.8(3)	N(5)-C(33)-C(34)	119.9(3)
N(5)-C(33)-C(32)	114.0(3)	C(34)-C(33)-C(32)	125.8(3)
C(35)-C(34)-C(33)	118.6(4)	C(34)-C(35)-C(36)	120.4(4)
C(35)-C(36)-C(37)	117.9(4)	N(5)-C(37)-C(36)	120.4(4)
N(5)-C(37)-C(31)	115.0(3)	C(36)-C(37)-C(31)	124.6(3)
Cl(2)-C(50)-Cl(1)	109.7(2)		

Symmetry transformations used to generate equivalent atoms:

Table A.24. Anisotropic displacement parameters [$Å^2$ x 10^3] for 23a.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
Cu(1)	19(1)	15(1)	17(1)	-2(1)	-6(1)	0(1)
N(1)	21(2)	13(2)	15(2)	0(1)	-5(1)	-1(1)
N(2)	16(2)	13(2)	16(2)	1(1)	-7(1)	-1(1)
N(3)	17(2)	11(2)	19(2)	-4(1)	-7(1)	3(1)
N(4)	19(2)	16(2)	21(2)	-2(1)	-7(1)	-1(1)
N(5)	23(2)	16(2)	16(2)	-1(1)	-6(1)	0(2)
O(1)	30(2)	26(2)	20(1)	-1(1)	-14(1)	0(1)
O(2)	21(1)	24(2)	27(2)	-2(1)	-11(1)	-1(1)
O(3)	18(1)	27(2)	22(1)	-7(1)	-5(1)	2(1)
O(4)	22(1)	25(2)	16(1)	-4(1)	-3(1)	-4(1)
Cl(1)	49(1)	47(1)	47(1)	-18(1)	-15(1)	17(1)
Cl(2)	61(1)	52(1)	71(1)	-27(1)	-34(1)	24(1)
C(1)	14(2)	24(2)	21(2)	-9(2)	-1(2)	1(2)
C(2)	21(2)	24(2)	21(2)	2(2)	-6(2)	-5(2)
C(3)	22(2)	16(2)	26(2)	1(2)	-10(2)	-1(2)
C(4)	24(2)	15(2)	18(2)	-3(2)	-5(2)	1(2)
C(5)	22(2)	16(2)	22(2)	-5(2)	-9(2)	0(2)
C(6)	17(2)	20(2)	13(2)	-2(2)	0(2)	-2(2)
C(7)	15(2)	18(2)	18(2)	2(2)	-5(2)	1(2)
C(8)	19(2)	16(2)	21(2)	0(2)	-6(2)	1(2)
C(9)	29(2)	16(2)	19(2)	-8(2)	-7(2)	1(2)
C(10)	26(2)	15(2)	24(2)	-6(2)	-10(2)	0(2)
C(11)	31(2)	25(2)	25(2)	6(2)	-8(2)	-7(2)
C(12)	28(2)	19(2)	31(2)	-3(2)	-11(2)	-3(2)
C(13)	33(2)	27(2)	26(2)	-14(2)	-13(2)	7(2)
C(14)	28(2)	20(2)	26(2)	-2(2)	-10(2)	1(2)
C(15)	38(2)	28(2)	24(2)	-8(2)	-12(2)	1(2)
C(16)	34(2)	24(2)	27(2)	-4(2)	-14(2)	-5(2)
C(17)	24(2)	32(3)	22(2)	-6(2)	0(2)	-7(2)
C(18)	15(2)	29(2)	25(2)	-1(2)	-1(2)	-2(2)
C(19)	23(2)	29(3)	23(2)	-3(2)	1(2)	-6(2)
C(20)	25(2)	39(3)	32(2)	4(2)	-4(2)	-4(2)
C(21)	27(2)	40(3)	47(3)	1(2)	-5(2)	9(2)
C(22)	35(3)	46(3)	54(3)	-21(3)	-3(2)	14(2)
C(23)	31(2)	49(3)	33(2)	-21(2)	-4(2)	6(2)
C(24)	31(2)	39(3)	21(2)	-3(2)	-11(2)	-8(2)
C(25)	33(2)	14(2)	22(2)	-2(2)	-5(2)	-7(2)
C(26)	35(2)	22(2)	26(2)	-6(2)	-5(2)	-1(2)
C(27)	29(2)	24(2)	40(3)	-8(2)	-6(2)	5(2)
C(28)	40(3)	20(2)	39(3)	-9(2)	8(2)	-3(2)
C(29)	54(3)	32(3)	18(2)	-7(2)	6(2)	-11(2)
C(30)	41(3)	28(3)	26(2)	-6(2)	-9(2)	-6(2)
C(31)	26(2)	20(2)	24(2)	3(2)	-12(2)	-4(2)
C(32)	21(2)	19(2)	22(2)	-2(2)	-7(2)	2(2)
C(33)	22(2)	20(2)	15(2)	-7(2)	-6(2)	0(2)
C(34)	23(2)	33(3)	25(2)	-11(2)	-6(2)	5(2)
C(35)	20(2)	37(3)	21(2)	-5(2)	-1(2)	-4(2)

C(36)	27(2)	27(2)	19(2)	1(2)	-5(2)	-10(2)
C(37)	24(2)	21(2)	16(2)	-2(2)	-8(2)	-1(2)
C(50)	36(3)	39(3)	37(3)	-13(2)	-10(2)	8(2)

Table A.25. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 23a.

	x	y	z	U(eq)
H(3A)	7073(3)	10776(3)	6508(3)	25
H(3B)	5797(3)	10821(3)	6156(3)	25
H(4A)	5446(3)	9742(3)	8872(3)	23
H(4B)	6158(3)	10751(3)	8173(3)	23
H(8A)	8436(3)	6017(3)	7665(3)	23
H(8B)	7577(3)	5167(3)	8476(3)	23
H(9A)	6452(3)	5332(3)	6840(3)	25
H(9B)	7686(3)	5997(3)	6450(3)	25
H(11A)	7715(4)	10228(3)	3915(3)	41
H(11B)	7816(4)	11137(3)	4566(3)	41
H(11C)	6489(4)	10885(3)	4416(3)	41
H(12A)	9271(3)	9729(3)	8059(3)	37
H(12B)	8448(3)	10816(3)	7906(3)	37
H(12C)	8572(3)	9966(3)	7144(3)	37
H(13A)	6506(4)	9346(3)	10113(3)	40
H(13B)	7146(4)	10471(3)	9678(3)	40
H(13C)	7986(4)	9408(3)	9895(3)	40
H(14A)	9252(3)	6055(3)	9980(3)	36
H(14B)	9761(3)	5827(3)	8830(3)	36
H(14C)	8822(3)	5027(3)	9643(3)	36
H(15A)	7713(4)	6583(3)	4799(3)	43
H(15B)	6493(4)	6996(3)	4392(3)	43
H(15C)	6638(4)	5773(3)	4907(3)	43
H(16A)	4313(3)	6878(3)	6800(3)	41
H(16B)	4604(3)	5949(3)	6107(3)	41
H(16C)	4459(3)	7171(3)	5590(3)	41
H(17A)	9690(3)	9281(3)	4461(3)	32
H(17B)	8569(3)	8529(3)	4538(3)	32
H(19A)	9784(3)	8356(3)	6740(3)	31
H(20A)	11012(4)	6944(4)	7365(3)	40
H(21A)	11722(4)	5540(4)	6441(3)	48
H(22A)	11201(4)	5559(4)	4872(4)	55
H(23A)	10036(4)	7000(4)	4227(3)	44
H(24A)	7267(4)	7380(4)	10682(3)	36
H(24B)	7380(4)	6175(4)	11261(3)	36
H(26A)	4705(4)	7158(3)	10320(3)	34
H(27A)	2678(4)	7304(3)	11324(3)	37
H(28A)	2324(4)	7086(3)	13104(3)	42
H(29A)	3991(4)	6758(3)	13882(3)	43
H(30A)	6011(4)	6513(3)	12889(3)	37
H(31A)	5524(3)	5715(3)	9190(3)	28
H(31B)	5128(3)	5357(3)	8251(3)	28
H(32A)	4320(3)	9777(3)	6787(3)	25
H(32B)	4121(3)	10288(3)	7810(3)	25
H(34A)	2046(3)	9105(3)	8416(3)	32
H(35A)	1361(4)	7393(3)	9195(3)	32
H(36A)	2807(3)	5929(3)	9238(3)	29

Table A.26. Crystal data and structure refinement for 23b.

Identification code	lsh12m
Empirical formula	$C_{37}H_{47}CuN_5O_4$
Formula weight	689.34
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 11.6459(3) Å alpha = 72.1220(10)° b = 12.15910(10) Å beta = 85.2210(10)° c = 12.8298(3) Å gamma = 71.9050(10)°
Volume, Z	1643.36(6) $Å^3$, 2
Density (calculated)	1.393 Mg/m^3
Absorption coefficient	0.714 mm^{-1}
F(000)	730
Crystal size	0.10 x 0.25 x 0.38 mm
θ range for data collection	1.67 to 23.22°
Limiting indices	$-9 \le h \le 12$, $-13 \le k \le 13$, $-12 \le l \le 14$
Reflections collected	7579
Independent reflections	4647 (R_{int} = 0.0294)
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4646 / 0 / 424
Goodness-of-fit on F^2	1.030
Final R indices [$I>2\sigma(I)$]	R1 = 0.0410, wR2 = 0.0905
R indices (all data)	R1 = 0.0598, wR2 = 0.1013
Largest diff. peak and hole	0.363 and -0.381 $eÅ^{-3}$

Table A.27. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 23b. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Cu(1)	6679(1)	6794(1)	6995(1)	17(1)
N(1)	5293(2)	7965(2)	7414(2)	17(1)
N(2)	6241(2)	7099(2)	5340(2)	16(1)
N(3)	7346(2)	5078(2)	7082(2)	17(1)
N(4)	7624(2)	6858(2)	8323(2)	18(1)
N(5)	7960(2)	7659(2)	6158(2)	18(1)
O(1)	3526(2)	9541(2)	6854(2)	27(1)
O(2)	8914(2)	3332(2)	7844(2)	29(1)
O(3)	4035(2)	6741(2)	6447(2)	21(1)
O(4)	8653(2)	3586(2)	9860(2)	22(1)
C(1)	4294(3)	8564(3)	6808(3)	19(1)
C(2)	4038(3)	7986(3)	5943(3)	19(1)
C(3)	4991(3)	7945(3)	5042(3)	18(1)
C(4)	6343(3)	5837(3)	5321(3)	19(1)
C(5)	7415(3)	4843(3)	6002(3)	19(1)
C(6)	8091(3)	4261(3)	7899(3)	21(1)
C(7)	7854(3)	4545(3)	9031(3)	18(1)
C(8)	8321(3)	5607(3)	9015(3)	21(1)
C(9)	6628(3)	7456(3)	8971(3)	19(1)
C(10)	5563(3)	8451(3)	8269(3)	19(1)
C(11)	2832(3)	8750(3)	5358(3)	26(1)
C(12)	7181(3)	3636(3)	6092(3)	26(1)
C(13)	8653(3)	4823(3)	5467(3)	25(1)
C(14)	6533(3)	4698(3)	9364(3)	24(1)
C(15)	4514(3)	8650(3)	9077(3)	28(1)
C(16)	5841(3)	9667(3)	7731(3)	26(1)
C(17)	3252(3)	6550(3)	7364(3)	27(1)
C(18)	3156(3)	5283(3)	7612(3)	24(1)
C(19)	2030(3)	5079(3)	7679(3)	31(1)
C(20)	1938(4)	3914(4)	7900(3)	40(1)
C(21)	2979(4)	2938(4)	8047(3)	38(1)
C(22)	4101(4)	3119(3)	7977(3)	36(1)
C(23)	4187(4)	4295(3)	7765(3)	30(1)
C(24)	8409(3)	2439(3)	10180(3)	24(1)
C(25)	9559(3)	1445(3)	10612(3)	20(1)
C(26)	10607(3)	1359(3)	9987(3)	23(1)
C(27)	11659(3)	420(3)	10362(3)	25(1)
C(28)	11669(3)	-450(3)	11357(3)	27(1)
C(29)	10647(3)	-387(3)	11980(3)	29(1)
C(30)	9582(3)	562(3)	11615(3)	23(1)
C(31)	8490(3)	7596(3)	7950(3)	21(1)
C(32)	7115(3)	7600(3)	4540(3)	21(1)
C(33)	8060(3)	7862(3)	5071(3)	19(1)
C(34)	8983(3)	8277(3)	4503(3)	25(1)
C(35)	9802(3)	8475(3)	5086(3)	26(1)
C(36)	9700(3)	8257(3)	6217(3)	25(1)
C(37)	8755(3)	7834(3)	6735(3)	18(1)

Table A.28. Bond lengths [Å] and angles [°] for 23b.

Cu(1)-N(1)	1.954(3)	Cu(1)-N(3)	1.957(2)
Cu(1)-N(2)	2.118(3)	Cu(1)-N(5)	2.121(3)
Cu(1)-N(4)	2.138(3)	N(1)-C(1)	1.328(4)
N(1)-C(10)	1.492(4)	N(2)-C(3)	1.499(4)
N(2)-C(4)	1.510(4)	N(2)-C(32)	1.512(4)
N(3)-C(6)	1.347(4)	N(3)-C(5)	1.490(4)
N(4)-C(9)	1.500(4)	N(4)-C(31)	1.506(4)
N(4)-C(8)	1.511(4)	N(5)-C(37)	1.336(4)
N(5)-C(33)	1.341(4)	O(1)-C(1)	1.261(4)
O(2)-C(6)	1.251(4)	O(3)-C(17)	1.432(4)
O(3)-C(2)	1.453(4)	O(4)-C(24)	1.438(4)
O(4)-C(7)	1.445(4)	C(1)-C(2)	1.573(5)
C(2)-C(11)	1.529(4)	C(2)-C(3)	1.535(4)
C(4)-C(5)	1.542(4)	C(5)-C(13)	1.541(4)
C(5)-C(12)	1.544(4)	C(6)-C(7)	1.576(5)
C(7)-C(14)	1.531(5)	C(7)-C(8)	1.544(4)
C(9)-C(10)	1.549(4)	C(10)-C(15)	1.544(4)
C(10)-C(16)	1.550(4)	C(17)-C(18)	1.512(5)
C(18)-C(23)	1.386(5)	C(18)-C(19)	1.399(5)
C(19)-C(20)	1.394(5)	C(20)-C(21)	1.387(5)
C(21)-C(22)	1.383(6)	C(22)-C(23)	1.404(5)
C(24)-C(25)	1.507(4)	C(25)-C(30)	1.396(4)
C(25)-C(26)	1.397(5)	C(26)-C(27)	1.389(5)
C(27)-C(28)	1.383(5)	C(28)-C(29)	1.373(5)
C(29)-C(30)	1.402(4)	C(31)-C(37)	1.519(4)
C(32)-C(33)	1.501(5)	C(33)-C(34)	1.386(5)
C(34)-C(35)	1.377(5)	C(35)-C(36)	1.395(5)
C(36)-C(37)	1.391(5)		

N(1)-Cu(1)-N(3)	142.84(11)	N(1)-Cu(1)-N(2)	101.22(10)
N(3)-Cu(1)-N(2)	86.66(10)	N(1)-Cu(1)-N(5)	110.33(10)
N(3)-Cu(1)-N(5)	106.82(10)	N(2)-Cu(1)-N(5)	78.58(10)
N(1)-Cu(1)-N(4)	86.23(10)	N(3)-Cu(1)-N(4)	100.73(10)
N(2)-Cu(1)-N(4)	156.76(10)	N(5)-Cu(1)-N(4)	78.19(10)
C(1)-N(1)-C(10)	118.7(3)	C(1)-N(1)-Cu(1)	124.0(2)
C(10)-N(1)-Cu(1)	114.5(2)	C(3)-N(2)-C(4)	111.8(2)
C(3)-N(2)-C(32)	108.4(2)	C(4)-N(2)-C(32)	110.2(2)
C(3)-N(2)-Cu(1)	111.5(2)	C(4)-N(2)-Cu(1)	101.8(2)
C(32)-N(2)-Cu(1)	113.1(2)	C(6)-N(3)-C(5)	118.7(3)
C(6)-N(3)-Cu(1)	122.9(2)	C(5)-N(3)-Cu(1)	113.7(2)
C(9)-N(4)-C(31)	110.0(2)	C(9)-N(4)-C(8)	110.6(2)
C(31)-N(4)-C(8)	108.2(2)	C(9)-N(4)-Cu(1)	103.1(2)
C(31)-N(4)-Cu(1)	112.9(2)	C(8)-N(4)-Cu(1)	112.0(2)
C(37)-N(5)-C(33)	121.2(3)	C(37)-N(5)-Cu(1)	119.3(2)
C(33)-N(5)-Cu(1)	118.7(2)	C(17)-O(3)-C(2)	115.7(2)
C(24)-O(4)-C(7)	115.8(2)	O(1)-C(1)-N(1)	127.1(3)
O(1)-C(1)-C(2)	116.5(3)	N(1)-C(1)-C(2)	116.4(3)
O(3)-C(2)-C(11)	110.2(3)	O(3)-C(2)-C(3)	105.9(2)
C(11)-C(2)-C(3)	106.0(3)	O(3)-C(2)-C(1)	111.8(3)
C(11)-C(2)-C(1)	109.7(3)	C(3)-C(2)-C(1)	113.0(3)
N(2)-C(3)-C(2)	118.7(2)	N(2)-C(4)-C(5)	113.9(3)
N(3)-C(5)-C(13)	111.6(3)	N(3)-C(5)-C(4)	105.3(2)
C(13)-C(5)-C(4)	113.9(3)	N(3)-C(5)-C(12)	112.2(3)
C(13)-C(5)-C(12)	108.5(3)	C(4)-C(5)-C(12)	105.1(3)

O(2)-C(6)-N(3)	127.1(3)	O(2)-C(6)-C(7)	118.8(3)
N(3)-C(6)-C(7)	114.1(3)	O(4)-C(7)-C(14)	110.6(3)
O(4)-C(7)-C(8)	99.5(2)	C(14)-C(7)-C(8)	115.1(3)
O(4)-C(7)-C(6)	109.6(2)	C(14)-C(7)-C(6)	110.9(3)
C(8)-C(7)-C(6)	110.5(3)	N(4)-C(8)-C(7)	117.4(3)
N(4)-C(9)-C(10)	114.5(3)	N(1)-C(10)-C(15)	112.5(3)
N(1)-C(10)-C(9)	106.7(2)	C(15)-C(10)-C(9)	105.2(3)
N(1)-C(10)-C(16)	110.5(3)	C(15)-C(10)-C(16)	108.8(3)
C(9)-C(10)-C(16)	113.1(3)	O(3)-C(17)-C(18)	107.9(3)
C(23)-C(18)-C(19)	118.4(3)	C(23)-C(18)-C(17)	120.6(3)
C(19)-C(18)-C(17)	121.0(3)	C(20)-C(19)-C(18)	121.2(4)
C(21)-C(20)-C(19)	119.5(4)	C(22)-C(21)-C(20)	120.2(4)
C(21)-C(22)-C(23)	119.9(4)	C(18)-C(23)-C(22)	120.7(4)
O(4)-C(24)-C(25)	108.9(3)	C(30)-C(25)-C(26)	118.9(3)
C(30)-C(25)-C(24)	120.7(3)	C(26)-C(25)-C(24)	120.3(3)
C(27)-C(26)-C(25)	120.6(3)	C(28)-C(27)-C(26)	119.8(3)
C(29)-C(28)-C(27)	120.4(3)	C(28)-C(29)-C(30)	120.3(3)
C(25)-C(30)-C(29)	119.9(3)	N(4)-C(31)-C(37)	112.6(3)
C(33)-C(32)-N(2)	113.8(3)	N(5)-C(33)-C(34)	121.2(3)
N(5)-C(33)-C(32)	115.1(3)	C(34)-C(33)-C(32)	123.7(3)
C(35)-C(34)-C(33)	118.2(3)	C(34)-C(35)-C(36)	120.5(3)
C(37)-C(36)-C(35)	118.2(3)	N(5)-C(37)-C(36)	120.6(3)
N(5)-C(37)-C(31)	114.5(3)	C(36)-C(37)-C(31)	124.8(3)

Symmetry transformations used to generate equivalent atoms:

Table A.29. Anisotropic displacement parameters [$Å^2 \times 10^3$] for 23b.

The anisotropic displacement factor exponent takes the form:

$-2\pi^2 [(ha^*)^2 U_{11} + \ldots + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
Cu(1)	19(1)	16(1)	16(1)	-5(1)	-4(1)	-2(1)
N(1)	18(2)	15(1)	18(2)	-5(1)	-3(1)	-4(1)
N(2)	16(2)	15(1)	17(2)	-4(1)	-2(1)	-4(1)
N(3)	21(2)	14(1)	13(2)	0(1)	-4(1)	-3(1)
N(4)	19(2)	14(1)	20(2)	-6(1)	-1(1)	-4(1)
N(5)	18(2)	16(2)	17(2)	-3(1)	-2(1)	-6(1)
O(1)	25(1)	20(1)	33(2)	-11(1)	-10(1)	5(1)
O(2)	31(2)	22(1)	25(1)	-9(1)	-5(1)	8(1)
O(3)	22(1)	16(1)	24(1)	-5(1)	3(1)	-6(1)
O(4)	27(1)	15(1)	20(1)	-2(1)	-9(1)	-2(1)
C(1)	20(2)	18(2)	18(2)	-1(2)	0(2)	-7(2)
C(2)	19(2)	14(2)	22(2)	-2(2)	-6(2)	-1(2)
C(3)	19(2)	12(2)	17(2)	0(1)	-9(1)	0(2)
C(4)	21(2)	18(2)	20(2)	-7(2)	-3(2)	-6(2)
C(5)	22(2)	17(2)	18(2)	-8(2)	-1(2)	-2(2)
C(6)	22(2)	18(2)	22(2)	-4(2)	0(2)	-8(2)
C(7)	19(2)	15(2)	16(2)	-2(1)	-6(1)	0(2)
C(8)	22(2)	19(2)	18(2)	-5(2)	-4(2)	-2(2)
C(9)	26(2)	18(2)	13(2)	-6(2)	1(2)	-6(2)
C(10)	21(2)	18(2)	17(2)	-6(2)	-2(2)	-2(2)
C(11)	21(2)	25(2)	30(2)	-8(2)	-8(2)	-3(2)
C(12)	31(2)	19(2)	26(2)	-9(2)	-5(2)	-3(2)
C(13)	24(2)	25(2)	22(2)	-8(2)	0(2)	-2(2)
C(14)	26(2)	21(2)	21(2)	-3(2)	-7(2)	-5(2)
C(15)	28(2)	34(2)	22(2)	-14(2)	0(2)	-2(2)
C(16)	29(2)	19(2)	25(2)	-3(2)	-9(2)	-3(2)
C(17)	26(2)	24(2)	30(2)	-8(2)	8(2)	-8(2)
C(18)	30(2)	24(2)	19(2)	-5(2)	2(2)	-9(2)
C(19)	32(2)	36(2)	24(2)	-7(2)	5(2)	-14(2)
C(20)	50(3)	50(3)	30(2)	-11(2)	5(2)	-33(2)
C(21)	71(3)	30(2)	20(2)	-3(2)	4(2)	-28(2)
C(22)	57(3)	24(2)	21(2)	-2(2)	-6(2)	-5(2)
C(23)	40(2)	32(2)	18(2)	-7(2)	-2(2)	-12(2)
C(24)	27(2)	20(2)	23(2)	-2(2)	-3(2)	-5(2)
C(25)	22(2)	18(2)	20(2)	-6(2)	-6(2)	-3(2)
C(26)	30(2)	21(2)	17(2)	-5(2)	-3(2)	-7(2)
C(27)	24(2)	28(2)	26(2)	-13(2)	1(2)	-6(2)
C(28)	26(2)	20(2)	33(2)	-9(2)	-8(2)	1(2)
C(29)	37(2)	18(2)	24(2)	4(2)	-8(2)	-6(2)
C(30)	28(2)	19(2)	20(2)	-3(2)	-5(2)	-5(2)
C(31)	22(2)	19(2)	22(2)	-6(2)	-3(2)	-7(2)
C(32)	22(2)	23(2)	16(2)	-2(2)	-1(2)	-7(2)
C(33)	22(2)	13(2)	18(2)	-4(1)	-4(2)	-1(2)
C(34)	24(2)	28(2)	18(2)	-4(2)	2(2)	-6(2)
C(35)	18(2)	34(2)	28(2)	-4(2)	4(2)	-13(2)
C(36)	23(2)	28(2)	25(2)	-7(2)	-3(2)	-9(2)
C(37)	15(2)	12(2)	24(2)	-4(2)	-2(2)	0(2)

Table A.30. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 23b.

	x	y	z	U(eq)
H(3A)	4677(3)	7737(3)	4458(3)	21
H(3B)	5057(3)	8774(3)	4721(3)	21
H(4A)	6427(3)	5816(3)	4553(3)	23
H(4B)	5585(3)	5652(3)	5604(3)	23
H(8A)	8341(3)	5628(3)	9778(3)	25
H(8B)	9165(3)	5428(3)	8756(3)	25
H(9A)	6970(3)	7821(3)	9413(3)	23
H(9B)	6312(3)	6827(3)	9485(3)	23
H(11A)	2187(3)	8807(3)	5899(3)	39
H(11B)	2660(3)	8369(3)	4842(3)	39
H(11C)	2875(3)	9565(3)	4959(3)	39
H(12A)	6395(3)	3635(3)	6431(3)	39
H(12B)	7818(3)	2961(3)	6543(3)	39
H(12C)	7180(3)	3545(3)	5359(3)	39
H(13A)	9290(3)	4173(3)	5941(3)	37
H(13B)	8795(3)	5603(3)	5364(3)	37
H(13C)	8663(3)	4680(3)	4754(3)	37
H(14A)	6315(3)	3986(3)	9351(3)	35
H(14B)	6012(3)	5424(3)	8849(3)	35
H(14C)	6428(3)	4782(3)	10104(3)	35
H(15A)	3804(3)	9275(3)	8683(3)	43
H(15B)	4757(3)	8911(3)	9653(3)	43
H(15C)	4317(3)	7891(3)	9408(3)	43
H(16A)	6506(3)	9550(3)	7216(3)	38
H(16B)	6072(3)	9946(3)	8300(3)	38
H(16C)	5121(3)	10274(3)	7337(3)	38
H(17A)	2444(3)	7153(3)	7188(3)	32
H(17B)	3586(3)	6639(3)	8007(3)	32
H(19A)	1315(3)	5748(3)	7573(3)	37
H(20A)	1166(4)	3790(4)	7949(3)	48
H(21A)	2922(4)	2142(4)	8197(3)	46
H(22A)	4814(4)	2450(3)	8072(3)	44
H(23A)	4960(4)	4414(3)	7726(3)	36
H(24A)	8101(3)	2313(3)	9543(3)	29
H(24B)	7786(3)	2428(3)	10754(3)	29
H(26A)	10599(3)	1948(3)	9298(3)	27
H(27A)	12371(3)	375(3)	9937(3)	30
H(28A)	12387(3)	-1095(3)	11610(3)	32
H(29A)	10661(3)	-990(3)	12661(3)	35
H(30A)	8877(3)	605(3)	12050(3)	28
H(31A)	9256(3)	7162(3)	8371(3)	25
H(31B)	8144(3)	8381(3)	8109(3)	25
H(32A)	7521(3)	7011(3)	4137(3)	25
H(32B)	6653(3)	8357(3)	3999(3)	25
H(34A)	9050(3)	8420(3)	3733(3)	30
H(35A)	10440(3)	8762(3)	4714(3)	32
H(36A)	10260(3)	8394(3)	6623(3)	30

Table A.31. Crystal data and structure refinement for (S)35.

Identification code	lsh15
Empirical formula	$C_{36}H_{54.86}Cu_{1.71}N_{6.86}O_{13.71}$
Formula weight	912.08
Temperature	165(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12$
Unit cell dimensions	a = 17.9475(3) Å alpha = 90° b = 34.3790(7) Å beta = 90° c = 14.28450(10) Å gamma = 90°
Volume, Z	8813.8(2) $Å^3$, 7
Density (calculated)	1.203 Mg/m^3
Absorption coefficient	0.787 mm^{-1}
F(000)	3348
Crystal size	0.12 x 0.36 x 0.40 mm
θ range for data collection	1.18 to 23.26°
Limiting indices	$-19 \le h \le 19$, $-38 \le k \le 36$, $-13 \le l \le 15$
Reflections collected	40394
Independent reflections	12617 (R_{int} = 0.0836)
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12617 / 0 / 919
Goodness-of-fit on F^2	1.093
Final R indices [I>2σ(I)]	R1 = 0.0738, wR2 = 0.1991
R indices (all data)	R1 = 0.1075, wR2 = 0.2263
Absolute structure parameter	-0.01(2)
Largest diff. peak and hole	2.356 and -0.631 $eÅ^{-3}$

Table A.32. Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for (S)35. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Cu(1)	9369(1)	8419(1)	4824(1)	27(1)
Cu(2)	9585(1)	7042(1)	679(1)	21(1)
Cu(3)	8217(1)	5575(1)	-3116(1)	25(1)
O(1)	7739(4)	7702(2)	5761(5)	36(2)
O(2)	11256(4)	8917(2)	3667(5)	34(2)
O(3)	8003(4)	7667(2)	3535(5)	38(2)
O(4)	6829(4)	7859(2)	3849(5)	39(2)
O(5)	11707(4)	8274(2)	4866(5)	38(2)
O(6)	12120(4)	8791(2)	5630(6)	51(2)
O(7)	9643(4)	7694(2)	5676(5)	32(2)
O(8)	9508(4)	7000(2)	3244(4)	33(2)
O(9)	10190(3)	8240(2)	2686(5)	30(2)
O(10)	10688(3)	7556(2)	351(4)	26(2)
O(11)	10299(4)	6221(2)	2566(5)	38(2)
O(12)	9297(4)	8055(2)	-754(5)	34(2)
O(13)	11514(4)	6745(2)	1961(5)	35(2)
O(14)	11865(4)	6160(2)	1412(5)	44(2)
O(15)	8711(4)	8063(2)	1441(5)	34(2)
O(16)	7843(4)	8220(2)	367(5)	32(2)
O(17)	7284(4)	4606(2)	-4217(6)	47(2)
O(18)	9423(4)	6383(2)	-1593(5)	35(2)
O(19)	8138(4)	6382(2)	-13(5)	50(2)
O(20)	8644(4)	5791(2)	-257(6)	44(2)
O(21)	8514(4)	4660(2)	-5895(5)	46(2)
O(22)	9137(5)	4723(2)	-4535(6)	45(2)
O(23)	7837(4)	4948(2)	-2096(5)	32(2)
O(24)	10138(4)	5626(2)	-2657(5)	32(2)
N(1)	8433(4)	8181(2)	5089(6)	26(2)
N(2)	8940(4)	8451(3)	3528(6)	32(2)
N(3)	10326(5)	8633(2)	4563(6)	32(2)
N(4)	9656(4)	8460(3)	6202(6)	34(2)
N(5)	10074(4)	6631(2)	1340(5)	17(2)
N(6)	10245(4)	6892(2)	-413(5)	22(2)
N(7)	9131(4)	7473(2)	30(6)	25(2)
N(8)	8768(4)	7147(2)	1623(5)	24(2)
N(9)	7861(5)	5197(2)	-3987(6)	28(2)
N(10)	9087(5)	5581(3)	-3992(6)	30(2)
N(11)	8589(4)	5944(2)	-2214(6)	27(2)
N(12)	7218(5)	5651(2)	-2471(6)	33(2)
C(1)	8330(6)	7895(3)	5676(7)	31(3)
C(2)	7816(6)	8267(3)	4408(8)	38(3)
C(3)	8168(6)	8549(3)	3670(7)	39(3)
C(4)	9343(6)	8751(3)	2946(7)	30(2)
C(5)	10162(6)	8652(3)	2840(7)	34(3)
C(6)	10615(6)	8748(3)	3759(8)	33(3)
C(8)	10485(6)	8442(4)	6184(7)	41(3)
C(9)	9308(6)	8158(3)	6809(7)	38(3)

C(10)	9030(6)	7800(3)	6284(7)	32(3)
C(11)	8855(6)	7468(3)	6980(7)	35(3)
C(12)	7155(6)	8478(4)	4907(8)	42(3)
C(14)	10689(7)	9149(3)	5693(8)	48(3)
C(15)	7577(6)	7892(3)	3899(7)	28(2)
C(16)	6571(6)	7519(4)	3373(8)	48(3)
C(17)	11615(6)	8605(3)	5314(8)	32(3)
C(18)	12482(7)	8171(4)	4691(10)	56(4)
C(19)	9529(6)	7358(3)	5085(7)	34(3)
C(20)	10194(6)	7341(4)	4415(8)	40(3)
C(21)	10161(6)	6980(3)	3804(7)	37(3)
C(22)	10931(6)	8061(3)	2666(7)	35(3)
C(22)	10469(7)	8875(4)	2030(8)	46(3)
C(23)	10874(5)	7728(3)	1930(7)	27(2)
C(24)	10690(6)	7885(3)	970(7)	31(3)
C(25)	9938(6)	6484(3)	2180(7)	28(2)
C(26)	10713(5)	6451(3)	850(6)	23(2)
C(27)	10934(5)	6721(3)	27(7)	28(2)
C(28)	10423(6)	7224(3)	-1029(7)	29(2)
C(29)	10361(5)	7619(3)	-563(6)	24(2)
C(30)	9530(5)	7730(3)	-435(6)	24(2)
C(31)	8351(5)	7573(3)	299(7)	24(2)
C(32)	8130(5)	7273(3)	1051(7)	24(2)
C(33)	8604(5)	6795(3)	2184(7)	28(2)
C(34)	9268(5)	6659(3)	2779(7)	26(2)
C(35)	8991(7)	6353(3)	3454(8)	43(3)
C(36)	10795(6)	7921(3)	-1115(8)	38(3)
C(37)	11424(6)	6418(3)	1456(7)	28(2)
C(38)	12170(7)	6758(4)	2506(8)	51(3)
C(39)	8342(5)	7973(3)	762(7)	26(2)
C(40)	7823(7)	8612(3)	743(10)	49(3)
C(41)	10501(6)	6048(3)	485(8)	36(3)
C(42)	7831(5)	7543(3)	-547(7)	26(2)
C(42)	10775(6)	8712(3)	5426(7)	35(3)
C(43)	7433(5)	4897(3)	-3727(8)	30(3)
C(44)	8205(6)	5196(3)	-4919(8)	33(3)
C(45)	8728(6)	5543(3)	-4924(7)	33(3)
C(46)	9554(6)	5942(3)	-3908(7)	29(2)
C(47)	9849(6)	6004(3)	-2922(8)	33(3)
C(48)	9248(6)	6127(3)	-2193(8)	30(3)
C(49)	8021(6)	6084(3)	-1557(7)	29(2)
C(50)	7410(6)	5770(3)	-1524(7)	31(3)
C(51)	6739(6)	5292(3)	-2496(8)	31(2)
C(52)	7180(5)	4916(3)	-2681(8)	32(3)
C(53)	6694(6)	4572(3)	-2416(9)	45(3)
C(54)	10481(6)	6307(4)	-2949(9)	47(3)
C(55)	7600(7)	5268(3)	-5691(8)	47(3)
C(56)	7719(6)	6481(3)	-1876(9)	39(3)
C(57)	8659(6)	4826(3)	-5068(8)	31(3)
C(58)	8961(8)	4312(4)	-6117(10)	60(4)
C(59)	8287(6)	6119(3)	-528(8)	35(3)
C(60)	8706(8)	5751(5)	784(8)	65(4)
C(61)	8363(6)	4631(3)	-2149(8)	35(3)
C(62)	9066(5)	4747(3)	-1703(7)	29(2)
C(63)	10366(6)	5581(3)	-1727(7)	35(3)

Table A.33. Bond lengths [Å] and angles [°] for (S)35.

Cu(1)-N(3)	1.905(9)	Cu(1)-N(1)	1.907(8)
Cu(1)-N(2)	2.007(8)	Cu(1)-N(4)	2.039(8)
Cu(2)-N(5)	1.914(7)	Cu(2)-N(7)	1.928(8)
Cu(2)-N(8)	2.024(8)	Cu(2)-N(6)	2.028(7)
Cu(3)-N(9)	1.909(8)	Cu(3)-N(11)	1.930(8)
Cu(3)-N(10)	2.001(8)	Cu(3)-N(12)	2.032(8)
O(1)-C(1)	1.257(12)	O(2)-C(6)	1.296(12)
O(3)-C(15)	1.204(12)	O(4)-C(15)	1.349(12)
O(4)-C(16)	1.429(13)	O(5)-C(17)	1.316(13)
O(5)-C(18)	1.457(14)	O(6)-C(17)	1.197(12)
O(7)-C(19)	1.445(12)	O(7)-C(10)	1.448(12)
O(8)-C(34)	1.416(12)	O(8)-C(21)	1.421(12)
O(9)-C(5)	1.432(12)	O(9)-C(22)	1.466(12)
O(10)-C(24)	1.435(12)	O(10)-C(29)	1.449(11)
O(11)-C(25)	1.240(12)	O(12)-C(30)	1.277(11)
O(13)-C(37)	1.344(13)	O(13)-C(38)	1.412(13)
O(14)-C(37)	1.192(12)	O(15)-C(39)	1.214(12)
O(16)-C(39)	1.356(11)	O(16)-C(40)	1.454(13)
O(17)-C(43)	1.250(12)	O(18)-C(48)	1.267(12)
O(19)-C(59)	1.195(12)	O(20)-C(59)	1.354(13)
O(20)-C(60)	1.496(14)	O(21)-C(57)	1.338(12)
O(21)-C(58)	1.476(13)	O(22)-C(57)	1.200(12)
O(23)-C(61)	1.446(12)	O(23)-C(52)	1.449(12)
O(24)-C(63)	1.399(12)	O(24)-C(47)	1.451(13)
N(1)-C(1)	1.306(13)	N(1)-C(2)	1.504(13)
N(2)-C(3)	1.442(14)	N(2)-C(4)	1.508(13)
N(3)-C(6)	1.321(14)	N(3)-C(42)	1.499(13)
N(4)-C(9)	1.489(14)	N(4)-C(8)	1.489(13)
N(5)-C(25)	1.324(13)	N(5)-C(26)	1.481(11)
N(6)-C(28)	1.477(13)	N(6)-C(27)	1.505(12)
N(7)-C(30)	1.317(12)	N(7)-C(31)	1.492(12)
N(8)-C(32)	1.471(12)	N(8)-C(33)	1.483(13)
N(9)-C(43)	1.338(13)	N(9)-C(44)	1.468(14)
N(10)-C(45)	1.484(13)	N(10)-C(46)	1.501(13)
N(11)-C(48)	1.339(13)	N(11)-C(49)	1.466(12)
N(12)-C(50)	1.455(13)	N(12)-C(51)	1.504(13)
C(1)-C(10)	1.561(14)	C(2)-C(15)	1.54(2)
C(2)-C(12)	1.563(14)	C(2)-C(3)	1.57(2)
C(4)-C(5)	1.515(15)	C(5)-C(22)	1.495(15)
C(5)-C(6)	1.580(15)	C(8)-C(42)	1.52(2)
C(9)-C(10)	1.527(15)	C(10)-C(11)	1.547(15)
C(14)-C(42)	1.56(2)	C(17)-C(42)	1.561(15)
C(19)-C(20)	1.532(14)	C(20)-C(21)	1.52(2)
C(22)-C(23)	1.557(15)	C(23)-C(24)	1.510(14)
C(25)-C(34)	1.595(14)	C(26)-C(41)	1.526(14)
C(26)-C(37)	1.547(13)	C(26)-C(27)	1.550(14)
C(28)-C(29)	1.518(14)	C(29)-C(36)	1.517(14)
C(29)-C(30)	1.551(13)	C(31)-C(39)	1.525(14)
C(31)-C(42)	1.531(13)	C(31)-C(32)	1.543(13)
C(33)-C(34)	1.537(13)	C(34)-C(35)	1.509(14)
C(43)-C(52)	1.56(2)	C(44)-C(45)	1.518(15)
C(44)-C(57)	1.526(14)	C(44)-C(55)	1.568(14)
C(46)-C(47)	1.521(14)	C(47)-C(54)	1.540(15)
C(47)-C(48)	1.558(15)	C(49)-C(50)	1.538(15)

C(49)-C(56)	1.539(15)	C(49)-C(59)	1.550(15)
C(51)-C(52)	1.540(14)	C(52)-C(53)	1.515(15)
C(61)-C(62)	1.468(14)	C(62)-C(63)#1	1.520(14)
C(63)-C(62)#1	1.520(14)		

N(3)-Cu(1)-N(1)	177.3(4)	N(3)-Cu(1)-N(2)	98.3(3)
N(1)-Cu(1)-N(2)	82.5(3)	N(3)-Cu(1)-N(4)	86.2(3)
N(1)-Cu(1)-N(4)	93.5(3)	N(2)-Cu(1)-N(4)	169.3(4)
N(5)-Cu(2)-N(7)	177.3(3)	N(5)-Cu(2)-N(8)	97.8(3)
N(7)-Cu(2)-N(8)	83.0(3)	N(5)-Cu(2)-N(6)	85.6(3)
N(7)-Cu(2)-N(6)	94.2(3)	N(8)-Cu(2)-N(6)	169.1(3)
N(9)-Cu(3)-N(11)	178.3(4)	N(9)-Cu(3)-N(10)	82.0(3)
N(11)-Cu(3)-N(10)	98.1(3)	N(9)-Cu(3)-N(12)	95.0(3)
N(11)-Cu(3)-N(12)	85.3(3)	N(10)-Cu(3)-N(12)	166.0(4)
C(15)-O(4)-C(16)	114.6(9)	C(17)-O(5)-C(18)	114.4(9)
C(19)-O(7)-C(10)	116.3(8)	C(34)-O(8)-C(21)	118.4(8)
C(5)-O(9)-C(22)	116.8(8)	C(24)-O(10)-C(29)	116.0(7)
C(37)-O(13)-C(38)	115.0(9)	C(39)-O(16)-C(40)	116.3(8)
C(59)-O(20)-C(60)	113.3(10)	C(57)-O(21)-C(58)	115.4(9)
C(61)-O(23)-C(52)	116.3(7)	C(63)-O(24)-C(47)	116.8(8)
C(1)-N(1)-C(2)	117.3(8)	C(1)-N(1)-Cu(1)	125.2(7)
C(2)-N(1)-Cu(1)	115.9(7)	C(3)-N(2)-C(4)	112.3(8)
C(3)-N(2)-Cu(1)	104.6(6)	C(4)-N(2)-Cu(1)	111.2(6)
C(6)-N(3)-C(42)	116.7(8)	C(6)-N(3)-Cu(1)	129.8(7)
C(42)-N(3)-Cu(1)	113.2(6)	C(9)-N(4)-C(8)	113.5(9)
C(9)-N(4)-Cu(1)	114.1(6)	C(8)-N(4)-Cu(1)	103.5(6)
C(25)-N(5)-C(26)	114.3(8)	C(25)-N(5)-Cu(2)	130.2(6)
C(26)-N(5)-Cu(2)	115.5(6)	C(28)-N(6)-C(27)	111.9(7)
C(28)-N(6)-Cu(2)	112.7(6)	C(27)-N(6)-Cu(2)	105.0(5)
C(30)-N(7)-C(31)	119.0(8)	C(30)-N(7)-Cu(2)	121.9(6)
C(31)-N(7)-Cu(2)	116.7(6)	C(32)-N(8)-C(33)	112.6(7)
C(32)-N(8)-Cu(2)	104.3(6)	C(33)-N(8)-Cu(2)	111.0(6)
C(43)-N(9)-C(44)	119.4(9)	C(43)-N(9)-Cu(3)	122.4(7)
C(44)-N(9)-Cu(3)	116.9(7)	C(45)-N(10)-C(46)	112.8(8)
C(45)-N(10)-Cu(3)	102.8(6)	C(46)-N(10)-Cu(3)	113.2(6)
C(48)-N(11)-C(49)	116.6(8)	C(48)-N(11)-Cu(3)	129.0(7)
C(49)-N(11)-Cu(3)	113.7(6)	C(50)-N(12)-C(51)	112.9(8)
C(50)-N(12)-Cu(3)	104.4(6)	C(51)-N(12)-Cu(3)	112.8(6)
O(1)-C(1)-N(1)	125.4(9)	O(1)-C(1)-C(10)	121.0(10)
N(1)-C(1)-C(10)	113.6(9)	N(1)-C(2)-C(15)	110.2(8)
N(1)-C(2)-C(12)	110.9(9)	C(15)-C(2)-C(12)	113.1(9)
N(1)-C(2)-C(3)	105.1(8)	C(15)-C(2)-C(3)	108.3(9)
C(12)-C(2)-C(3)	108.9(9)	N(2)-C(3)-C(2)	109.7(9)
N(2)-C(4)-C(5)	111.5(8)	O(9)-C(5)-C(22)	112.2(9)
O(9)-C(5)-C(4)	105.8(8)	C(22)-C(5)-C(4)	108.6(9)
O(9)-C(5)-C(6)	108.4(8)	C(22)-C(5)-C(6)	110.2(9)
C(4)-C(5)-C(6)	111.6(9)	O(2)-C(6)-N(3)	124.9(9)
O(2)-C(6)-C(5)	117.8(10)	N(3)-C(6)-C(5)	117.2(9)
N(4)-C(8)-C(42)	109.2(9)	N(4)-C(9)-C(10)	114.4(8)
O(7)-C(10)-C(9)	104.4(8)	O(7)-C(10)-C(11)	110.8(8)
C(9)-C(10)-C(11)	110.3(9)	O(7)-C(10)-C(1)	109.2(8)
C(9)-C(10)-C(1)	111.6(9)	C(11)-C(10)-C(1)	110.4(9)
O(3)-C(15)-O(4)	123.7(10)	O(3)-C(15)-C(2)	124.3(9)
O(4)-C(15)-C(2)	111.8(9)	O(6)-C(17)-O(5)	123.5(10)
O(6)-C(17)-C(42)	124.5(10)	O(5)-C(17)-C(42)	111.9(9)
O(7)-C(19)-C(20)	106.6(8)	C(21)-C(20)-C(19)	111.1(9)
O(8)-C(21)-C(20)	108.5(9)	O(9)-C(22)-C(23)	105.2(8)
C(24)-C(23)-C(22)	111.4(8)	O(10)-C(24)-C(23)	106.2(8)

C(10)	29(6)	46(7)	21(6)	-1(5)	0(5)	4(5)
C(11)	28(6)	55(7)	22(6)	7(5)	-1(5)	4(5)
C(12)	36(6)	55(8)	36(7)	-15(6)	-7(5)	20(6)
C(14)	67(8)	39(7)	39(7)	-16(6)	-18(7)	13(6)
C(15)	27(6)	42(7)	15(5)	4(5)	-6(4)	1(5)
C(16)	34(7)	65(9)	45(8)	-7(6)	-2(6)	-19(6)
C(17)	24(6)	33(6)	41(7)	3(5)	-8(5)	-10(5)
C(18)	48(8)	56(9)	65(9)	-3(7)	9(7)	10(7)
C(19)	38(6)	41(6)	22(5)	-12(5)	-1(5)	7(5)
C(20)	35(6)	54(8)	32(6)	-2(6)	4(5)	-1(6)
C(21)	33(6)	52(8)	27(6)	-6(5)	-2(5)	13(6)
C(22)	31(6)	50(7)	24(6)	0(5)	7(5)	0(5)
C(22)	48(7)	55(8)	34(6)	15(6)	-15(6)	-12(6)
C(23)	22(5)	27(6)	33(6)	-3(5)	-3(5)	5(4)
C(24)	35(6)	31(6)	28(6)	-2(5)	-11(5)	4(5)
C(25)	29(6)	21(6)	34(6)	-2(5)	-8(5)	8(5)
C(26)	19(5)	31(6)	18(5)	-6(4)	-2(4)	7(4)
C(27)	19(5)	44(7)	22(6)	-1(5)	2(4)	0(5)
C(28)	23(5)	48(7)	17(5)	-10(5)	3(4)	2(5)
C(29)	22(5)	30(6)	20(5)	-2(4)	9(4)	7(4)
C(30)	24(5)	30(6)	19(5)	2(4)	-7(4)	11(5)
C(31)	14(5)	29(6)	29(6)	2(5)	2(4)	-1(4)
C(32)	20(5)	20(5)	33(6)	-3(4)	4(4)	-4(4)
C(33)	16(5)	39(6)	30(6)	-2(5)	-1(4)	2(5)
C(34)	22(5)	35(6)	21(5)	3(5)	1(4)	7(5)
C(35)	44(7)	42(7)	42(7)	18(6)	14(6)	17(6)
C(36)	21(5)	46(7)	48(7)	12(6)	11(5)	-3(5)
C(37)	28(6)	34(6)	24(5)	2(5)	-9(5)	6(5)
C(38)	54(8)	67(9)	32(7)	3(6)	-15(6)	-16(7)
C(39)	18(5)	27(5)	32(6)	9(5)	4(5)	9(5)
C(40)	49(7)	28(7)	71(9)	2(6)	-15(7)	2(6)
C(41)	37(6)	30(6)	40(7)	-5(5)	-2(5)	15(5)
C(42)	24(5)	25(6)	31(6)	-2(5)	-4(5)	7(4)
C(42)	33(6)	47(7)	27(6)	-3(5)	-3(5)	-4(5)
C(43)	23(6)	14(6)	52(7)	-10(5)	-17(5)	-2(5)
C(44)	36(6)	26(6)	37(7)	-11(5)	-15(5)	11(5)
C(45)	43(6)	38(6)	17(5)	-6(5)	0(5)	0(5)
C(46)	24(5)	35(6)	26(6)	-2(5)	-4(5)	3(5)
C(47)	32(6)	29(6)	36(7)	-9(5)	3(5)	-13(5)
C(48)	28(6)	22(6)	41(7)	-1(5)	1(5)	6(5)
C(49)	30(6)	35(6)	21(5)	-20(5)	-1(4)	4(5)
C(50)	33(6)	31(6)	30(6)	-1(5)	1(5)	8(5)
C(51)	22(5)	24(5)	48(7)	-3(5)	4(5)	-3(5)
C(52)	19(5)	21(6)	56(7)	-10(5)	-2(5)	-10(4)
C(53)	34(6)	26(6)	73(9)	-10(6)	6(6)	3(5)
C(54)	35(7)	51(8)	56(8)	-10(6)	8(6)	-7(6)
C(55)	58(8)	44(7)	38(7)	-23(6)	-27(6)	16(6)
C(56)	34(6)	40(7)	44(7)	1(6)	0(6)	8(5)
C(57)	42(6)	22(6)	29(6)	-4(5)	-3(5)	3(5)
C(58)	65(9)	43(8)	72(10)	-34(7)	8(8)	17(7)
C(59)	26(6)	44(7)	35(7)	-5(6)	1(5)	6(5)
C(60)	77(10)	96(11)	23(7)	5(7)	-26(7)	-3(9)
C(61)	35(6)	25(6)	45(7)	5(5)	1(5)	4(5)
C(62)	30(6)	28(6)	30(6)	2(5)	-7(5)	-8(5)
C(63)	31(6)	41(6)	32(6)	0(5)	-5(5)	11(5)

Table A.34. Anisotropic displacement parameters [$Å^2 \times 10^3$] for (S)35. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [(ha^*)^2 U_{11} + ... + 2hka^*b^* U_{12}]$

	U11	U22	U33	U23	U13	U12
Cu(1)	24(1)	33(1)	24(1)	-3(1)	-6(1)	0(1)
Cu(2)	18(1)	25(1)	21(1)	1(1)	0(1)	4(1)
Cu(3)	26(1)	22(1)	26(1)	-7(1)	0(1)	2(1)
O(1)	20(4)	51(5)	35(4)	-5(4)	0(3)	2(4)
O(2)	33(4)	31(4)	36(4)	2(4)	-5(4)	-10(4)
O(3)	32(4)	41(5)	39(4)	-5(4)	-3(4)	5(4)
O(4)	26(4)	59(5)	33(4)	-7(4)	-5(3)	-6(4)
O(5)	31(4)	33(4)	49(5)	-13(4)	-14(4)	8(3)
O(6)	35(5)	47(5)	71(6)	-8(5)	-12(5)	-8(4)
O(7)	25(4)	46(5)	24(4)	-1(3)	-1(3)	1(3)
O(8)	38(4)	38(4)	23(4)	-4(3)	-2(3)	10(4)
O(9)	21(4)	31(4)	38(4)	-7(3)	1(3)	-6(3)
O(10)	21(3)	36(4)	21(4)	-1(3)	-2(3)	2(3)
O(11)	36(4)	40(5)	40(4)	4(4)	14(4)	15(4)
O(12)	32(4)	36(4)	35(4)	12(3)	-2(3)	4(3)
O(13)	30(4)	49(5)	26(4)	-6(4)	-11(3)	3(3)
O(14)	35(4)	55(5)	42(5)	-4(4)	-9(4)	28(4)
O(15)	34(4)	35(4)	33(4)	-7(3)	-16(4)	5(3)
O(16)	31(4)	21(4)	43(5)	-1(3)	-14(3)	5(3)
O(17)	51(5)	30(4)	60(5)	-16(4)	-6(4)	-3(4)
O(18)	28(4)	32(4)	44(4)	-14(4)	-10(3)	6(3)
O(19)	53(5)	55(5)	41(5)	-27(4)	-1(4)	3(4)
O(20)	40(4)	49(5)	42(5)	4(4)	-8(4)	-1(4)
O(21)	55(5)	43(5)	41(5)	-26(4)	-2(4)	20(4)
O(22)	51(5)	41(5)	42(5)	-2(4)	-3(4)	23(4)
O(23)	33(4)	27(4)	37(4)	-7(3)	4(3)	2(3)
O(24)	32(4)	33(4)	31(4)	-11(3)	-3(3)	11(3)
N(1)	23(4)	30(5)	25(5)	0(4)	-6(4)	6(4)
N(2)	25(5)	39(5)	32(5)	11(4)	-12(4)	4(4)
N(3)	32(5)	36(5)	27(5)	-3(4)	-1(4)	-4(4)
N(4)	21(4)	55(6)	27(5)	-2(4)	-2(4)	-2(4)
N(5)	13(4)	27(5)	11(4)	-3(3)	-1(3)	6(3)
N(6)	8(4)	38(5)	20(4)	3(4)	2(3)	10(3)
N(7)	22(4)	33(5)	21(5)	5(4)	5(4)	2(4)
N(8)	14(4)	28(5)	28(5)	5(4)	-3(3)	0(3)
N(9)	26(5)	34(5)	24(5)	-9(4)	2(4)	11(4)
N(10)	39(5)	29(5)	23(5)	-3(4)	1(4)	-1(4)
N(11)	23(5)	24(5)	34(5)	-7(4)	-1(4)	-5(4)
N(12)	29(5)	26(5)	43(6)	-10(4)	-2(4)	-1(4)
C(1)	26(6)	49(7)	17(5)	-13(5)	-3(5)	8(5)
C(2)	34(6)	49(7)	31(6)	7(6)	-5(5)	13(5)
C(3)	37(6)	51(7)	29(6)	-1(5)	-16(5)	10(6)
C(4)	38(6)	25(6)	27(6)	5(4)	-7(5)	-3(5)
C(5)	44(7)	30(6)	28(6)	11(5)	-3(5)	-1(5)
C(6)	30(6)	27(6)	41(7)	-7(5)	-18(6)	3(5)
C(8)	35(6)	53(8)	34(6)	-6(6)	-9(5)	-8(6)
C(9)	37(6)	56(8)	21(6)	-12(6)	-3(5)	3(6)

O(11)-C(25)-N(5)	125.8(9)	O(11)-C(25)-C(34)	115.5(9)
N(5)-C(25)-C(34)	118.7(8)	N(5)-C(26)-C(41)	110.3(8)
N(5)-C(26)-C(37)	113.8(7)	C(41)-C(26)-C(37)	109.4(8)
N(5)-C(26)-C(27)	107.9(7)	C(41)-C(26)-C(27)	110.4(8)
C(37)-C(26)-C(27)	104.9(7)	N(6)-C(27)-C(26)	109.9(7)
N(6)-C(28)-C(29)	114.6(7)	O(10)-C(29)-C(36)	111.3(8)
O(10)-C(29)-C(28)	103.4(7)	C(36)-C(29)-C(28)	110.3(8)
O(10)-C(29)-C(30)	108.7(7)	C(36)-C(29)-C(30)	112.8(8)
C(28)-C(29)-C(30)	110.0(8)	O(12)-C(30)-N(7)	126.1(9)
O(12)-C(30)-C(29)	119.2(9)	N(7)-C(30)-C(29)	114.7(8)
N(7)-C(31)-C(39)	109.2(7)	N(7)-C(31)-C(42)	110.7(8)
C(39)-C(31)-C(42)	113.4(8)	N(7)-C(31)-C(32)	105.5(7)
C(39)-C(31)-C(32)	107.4(8)	C(42)-C(31)-C(32)	110.3(8)
N(8)-C(32)-C(31)	112.5(7)	N(8)-C(33)-C(34)	113.2(8)
O(8)-C(34)-C(35)	112.1(8)	O(8)-C(34)-C(33)	104.1(8)
C(35)-C(34)-C(33)	108.1(8)	O(8)-C(34)-C(25)	109.5(7)
C(35)-C(34)-C(25)	109.2(8)	C(33)-C(34)-C(25)	113.8(8)
O(14)-C(37)-O(13)	124.9(9)	O(14)-C(37)-C(26)	124.8(9)
O(13)-C(37)-C(26)	109.8(8)	O(15)-C(39)-O(16)	122.2(9)
O(15)-C(39)-C(31)	124.7(8)	O(16)-C(39)-C(31)	113.0(8)
N(3)-C(42)-C(8)	106.9(8)	N(3)-C(42)-C(14)	108.9(9)
C(8)-C(42)-C(14)	112.4(9)	N(3)-C(42)-C(17)	113.1(8)
C(8)-C(42)-C(17)	105.1(9)	C(14)-C(42)-C(17)	110.4(9)
O(17)-C(43)-N(9)	125.8(11)	O(17)-C(43)-C(52)	120.3(10)
N(9)-C(43)-C(52)	113.7(8)	N(9)-C(44)-C(45)	105.2(8)
N(9)-C(44)-C(57)	110.7(9)	C(45)-C(44)-C(57)	109.0(9)
N(9)-C(44)-C(55)	110.2(9)	C(45)-C(44)-C(55)	107.5(9)
C(57)-C(44)-C(55)	113.8(9)	N(10)-C(45)-C(44)	109.5(8)
N(10)-C(46)-C(47)	112.6(8)	O(24)-C(47)-C(46)	103.9(8)
O(24)-C(47)-C(54)	110.5(9)	C(46)-C(47)-C(54)	109.2(9)
O(24)-C(47)-C(48)	108.5(8)	C(46)-C(47)-C(48)	114.5(9)
C(54)-C(47)-C(48)	110.0(8)	O(18)-C(48)-N(11)	124.0(9)
O(18)-C(48)-C(47)	118.0(9)	N(11)-C(48)-C(47)	118.0(9)
N(11)-C(49)-C(50)	106.7(8)	N(11)-C(49)-C(56)	110.2(9)
C(50)-C(49)-C(56)	112.2(8)	N(11)-C(49)-C(59)	114.8(8)
C(50)-C(49)-C(59)	104.2(9)	C(56)-C(49)-C(59)	108.6(8)
N(12)-C(50)-C(49)	109.8(8)	N(12)-C(51)-C(52)	113.6(8)
O(23)-C(52)-C(53)	112.6(9)	O(23)-C(52)-C(51)	104.7(8)
C(53)-C(52)-C(51)	108.4(8)	O(23)-C(52)-C(43)	108.6(8)
C(53)-C(52)-C(43)	112.0(9)	C(51)-C(52)-C(43)	110.3(9)
O(22)-C(57)-O(21)	125.1(10)	O(22)-C(57)-C(44)	122.6(9)
O(21)-C(57)-C(44)	112.0(9)	O(19)-C(59)-O(20)	124.0(10)
O(19)-C(59)-C(49)	125.0(10)	O(20)-C(59)-C(49)	110.6(9)
O(23)-C(61)-C(62)	109.5(8)	C(61)-C(62)-C(63)#1	111.5(9)
O(24)-C(63)-C(62)#1	107.4(8)		

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,-y+1,z

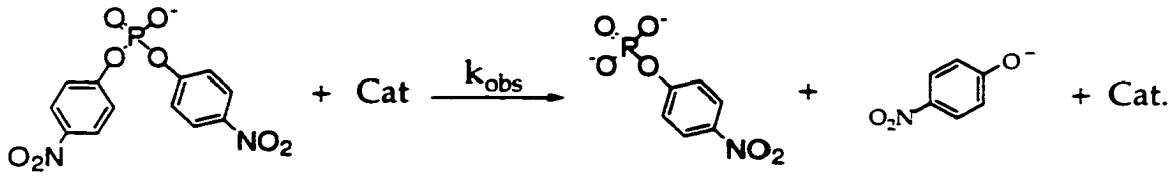
Table A.35. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for (S)35.

	x	y	z	U(eq)
H(3A)	7894(6)	8528(3)	3070(7)	47
H(3B)	8127(6)	8821(3)	3894(7)	47
H(4A)	9294(6)	9009(3)	3247(7)	36
H(4B)	9110(6)	8766(3)	2319(7)	36
H(8A)	10649(6)	8172(4)	6055(7)	49
H(8B)	10687(6)	8521(4)	6800(7)	49
H(9A)	8884(6)	8277(3)	7147(7)	46
H(9B)	9678(6)	8075(3)	7282(7)	46
H(11A)	8677(6)	7240(3)	6635(7)	53
H(11B)	8470(6)	7553(3)	7420(7)	53
H(11C)	9308(6)	7400(3)	7327(7)	53
H(12A)	7339(6)	8713(4)	5218(8)	63
H(12B)	6934(6)	8303(4)	5374(8)	63
H(12C)	6777(6)	8549(4)	4443(8)	63
H(14A)	10883(7)	9311(3)	5185(8)	73
H(14B)	10968(7)	9201(3)	6268(8)	73
H(14C)	10161(7)	9208(3)	5793(8)	73
H(16A)	6025(6)	7517(4)	3367(8)	72
H(16B)	6754(6)	7287(4)	3698(8)	72
H(16C)	6758(6)	7520(4)	2728(8)	72
H(18A)	12503(7)	7922(4)	4358(10)	85
H(18B)	12746(7)	8148(4)	5289(10)	85
H(18C)	12717(7)	8374(4)	4310(10)	85
H(19A)	9058(6)	7384(3)	4729(7)	40
H(19B)	9503(6)	7119(3)	5468(7)	40
H(20A)	10195(6)	7576(4)	4013(8)	48
H(20B)	10663(6)	7340(4)	4781(8)	48
H(21A)	10608(6)	6967(3)	3400(7)	45
H(21B)	10148(6)	6744(3)	4201(7)	45
H(22A)	11064(6)	7956(3)	3289(7)	42
H(22B)	11314(6)	8253(3)	2478(7)	42
H(22C)	10998(7)	8814(4)	1953(8)	69
H(22D)	10410(7)	9155(4)	2147(8)	69
H(22E)	10198(7)	8804(4)	1459(8)	69
H(23A)	11353(5)	7586(3)	1904(7)	33
H(23B)	10482(5)	7543(3)	2125(7)	33
H(24A)	10196(6)	8013(3)	973(7)	37
H(24B)	11069(6)	8078(3)	770(7)	37
H(27A)	11259(5)	6932(3)	259(7)	34
H(27B)	11216(5)	6571(3)	-447(7)	34
H(28A)	10083(6)	7218(3)	-1575(7)	35
H(28B)	10937(6)	7192(3)	-1268(7)	35
H(32A)	7746(5)	7388(3)	1465(7)	29
H(32B)	7908(5)	7043(3)	742(7)	29
H(33A)	8455(5)	6582(3)	1757(7)	34
H(33B)	8177(5)	6850(3)	2603(7)	34
H(35A)	9407(7)	6262(3)	3841(8)	64
H(35B)	8783(7)	6134(3)	3103(8)	64

H(35C)	8605(7)	6466(3)	3857(8)	64
H(36A)	10750(6)	8175(3)	-807(8)	58
H(36B)	10593(6)	7938(3)	-1751(8)	58
H(36C)	11320(6)	7845(3)	-1143(8)	58
H(38A)	12190(7)	7005(4)	2849(8)	77
H(38B)	12606(7)	6737(4)	2096(8)	77
H(38C)	12169(7)	6541(4)	2952(8)	77
H(40A)	7445(7)	8765(3)	409(10)	74
H(40B)	8312(7)	8735(3)	663(10)	74
H(40C)	7697(7)	8603(3)	1410(10)	74
H(41A)	10050(6)	6068(3)	101(8)	54
H(41B)	10407(6)	5874(3)	1015(8)	54
H(41C)	10910(6)	5944(3)	106(8)	54
H(42A)	7862(5)	7280(3)	-812(7)	40
H(42B)	7980(5)	7733(3)	-1021(7)	40
H(42C)	7317(5)	7595(3)	-349(7)	40
H(45A)	9115(6)	5507(3)	-5412(7)	39
H(45B)	8446(6)	5783(3)	-5071(7)	39
H(46A)	9251(6)	6170(3)	-4092(7)	34
H(46B)	9979(6)	5923(3)	-4347(7)	34
H(50A)	7589(6)	5543(3)	-1164(7)	37
H(50B)	6963(6)	5875(3)	-1206(7)	37
H(51A)	6359(6)	5323(3)	-2992(8)	37
H(51B)	6476(6)	5267(3)	-1891(8)	37
H(53A)	6967(6)	4330(3)	-2530(9)	67
H(53B)	6240(6)	4575(3)	-2796(9)	67
H(53C)	6562(6)	4590(3)	-1752(9)	67
H(54A)	10673(6)	6348(4)	-2314(9)	71
H(54B)	10288(6)	6553(4)	-3196(9)	71
H(54C)	10883(6)	6213(4)	-3354(9)	71
H(55A)	7253(7)	5049(3)	-5706(8)	70
H(55B)	7843(7)	5294(3)	-6303(8)	70
H(55C)	7327(7)	5508(3)	-5548(8)	70
H(56A)	8126(6)	6671(3)	-1886(9)	59
H(56B)	7332(6)	6568(3)	-1440(9)	59
H(56C)	7506(6)	6456(3)	-2505(9)	59
H(58A)	8816(8)	4212(4)	-6733(10)	90
H(58B)	8873(8)	4112(4)	-5641(10)	90
H(58C)	9491(8)	4381(4)	-6124(10)	90
H(60A)	8968(8)	5509(5)	936(8)	98
H(60B)	8206(8)	5746(5)	1059(8)	98
H(60C)	8984(8)	5973(5)	1037(8)	98
H(61A)	8454(6)	4562(3)	-2812(8)	42
H(61B)	8157(6)	4399(3)	-1828(8)	42
H(62A)	8968(5)	4821(3)	-1045(7)	35
H(62B)	9271(5)	4977(3)	-2031(7)	35
H(63A)	9933(6)	5516(3)	-1326(7)	42
H(63B)	10591(6)	5825(3)	-1493(7)	42

APPENDIX B: RATE CONSTANT CALCULATIONS FOR PHOSPHATE DIESTER HYDROLYSIS STUDIES

Calculations for ethylene glycol-linked bis-dioxocyclam **25**



BPNPP . PNP PNPA

$dA/dt = 2.1502 \times 10^{-7}\ As^{-1}$

BPNPP $\varepsilon(400, 25^{\circ}\ C, pH\ 7) = 6.76 \times 10^{+3}$

$A = \varepsilon bc,\ (dA/dt) = \varepsilon b(dc/dt),\ b = 1,\ (dA/dt) = \varepsilon b(d[PNPA]/dt)$

$(d[PNPA]/dt) = -(d[BPNPP]/dt)$, rate of hydrolysis of BPNPP

$2.1502 \times 10^{-7} = 6.76 \times 10^{+3} * (d[PNPA]/dt)$

$(d[PNPA]/dt) = 3.19 \times 10^{-11}$

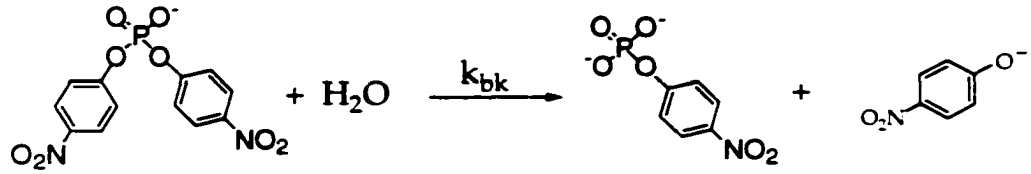
$d[PNPA]/dt = k_{obs}[BPNPP]$

$3.19 \times 10^{-11} = k_{obs}[5.68 \times 10^{-4}]$

$k_{obs} = 5.62 \times 10^{-8}$ rate of hydrolysis in the presence of **25**

$k_{bk} = 1.16 \times 10^{-8}$ rate of background hydrolysis 5 fold rate increase

Background Hydrolysis



BPNPP . PNP PNPA

$A/dt = 4.477 \times 10^{-8}\ As^{-1}$

BPNPP $\varepsilon(400, 25^\circ C, pH\ 7) = 6.76 \times 10^{+3}$

$A = \varepsilon bc,\ (dA/dt) = \varepsilon b(dc/dt),\ b = 1,\ (dA/dt) = \varepsilon b(d[PNPA]/dt)$

$(d[PNPA]/dt) = -(d[BPNPP]/dt)$, rate of hydrolysis of BPNPP

$4.477 \times 10^{-8} = 6.76 \times 10^{+3} * (d[PNPA]/dt)$

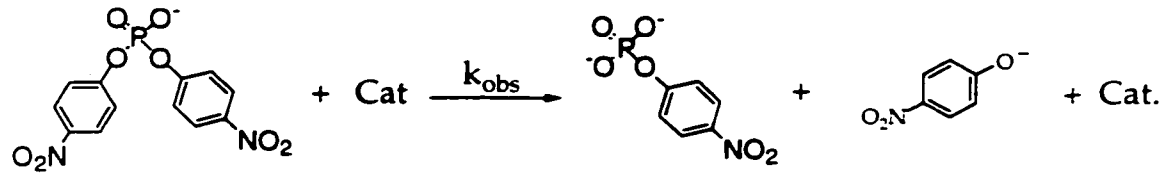
$(d[PNPA]/dt) = 6.62 \times 10^{-12}$

$d[PNPA]/dt = k_{bk}[BPNPP]$

$6.62 \times 10^{-12} = k_{bk}[5.68 \times 10^{-4}]$

$k_{bk} = 1.16 \times 10^{-8}$ rate of background hydrolysis

Calculations for ethylene 1,3-propane diol linked bis-dioxocyclam **26**



BPNPP . PNP PNPA

$dA/dt = 2.844 \times 10^{-7}\ As^{-1}$

BPNPP $\varepsilon(400, 25°\ C, pH\ 7) = 6.76 \times 10^{+3}$

$A = \varepsilon bc,\ (dA/dt) = \varepsilon b(dc/dt),\ b = 1,\ (dA/dt) = \varepsilon b(d[PNPA]/dt)$

$(d[PNPA]/dt) = -(d[BPNPP]/dt)$, rate of hydrolysis of BPNPP

$2.844 \times 10^{-7} = 6.76 \times 10^{+3} * (d[PNPA]/dt)$

$(d[PNPA]/dt) = 4.21 \times 10^{-11}$

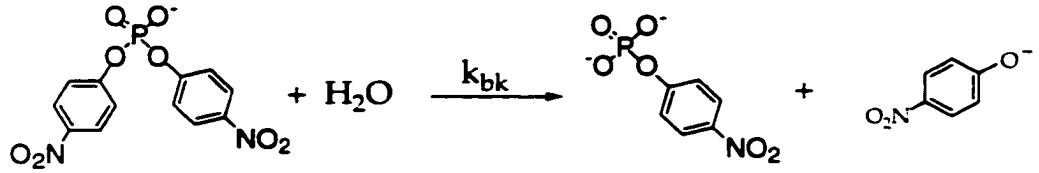
$d[PNPA]/dt = k_{obs}[BPNPP]$

$4.21 \times 10^{-11} = k_{obs}[5.54 \times 10^{-4}]$

$k_{obs} = 7.6 \times 10^{-8}$ rate of hydrolysis in the presence of **26**

$k_{bk} = 6.03 \times 10^{-9}$ rate of background hydrolysis 13 fold rate increase

Background Hydrolysis



BPNPP . PNP PNPA

$A/dt = 2.261 \times 10^{-8}\ As^{-1}$ A = Absorbance

BPNPP $\varepsilon(400, 25^\circ C, pH\ 7) = 6.76 \times 10^{+3}$

$A = \varepsilon bc$, $(dA/dt) = \varepsilon b(dc/dt)$, $b = 1$, $(dA/dt) = \varepsilon b(d[PNPA]/dt)$

$(d[PNPA]/dt) = -(d[BPNPP]/dt)$, rate of hydrolysis of BPNPP

$2.261 \times 10^{-8} = 6.76 \times 10^{+3} * (d[PNPA]/dt)$

$(d[PNPA]/dt) = 3.34 \times 10^{-12}$

$d[PNPA]/dt = k_{bk}[BPNPP]$

$3.34 \times 10^{-12} = k_{bk}[5.54 \times 10^{-4}]$

$k_{bk} = 6.03 \times 10^{-9}$ rate of background hydrolysis