DISSERTATION

SYNTHESIS OF ALKYL- AND POLY(ETHYLENE)GLYCOL LINKED BIS-DIOXOCYCLAMS FROM BIS-CHROMIUM CARBENE COMPLEXES

Submitted by

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In partial fulfillment of the requirements

for the Degree of Doctor of Philosophy

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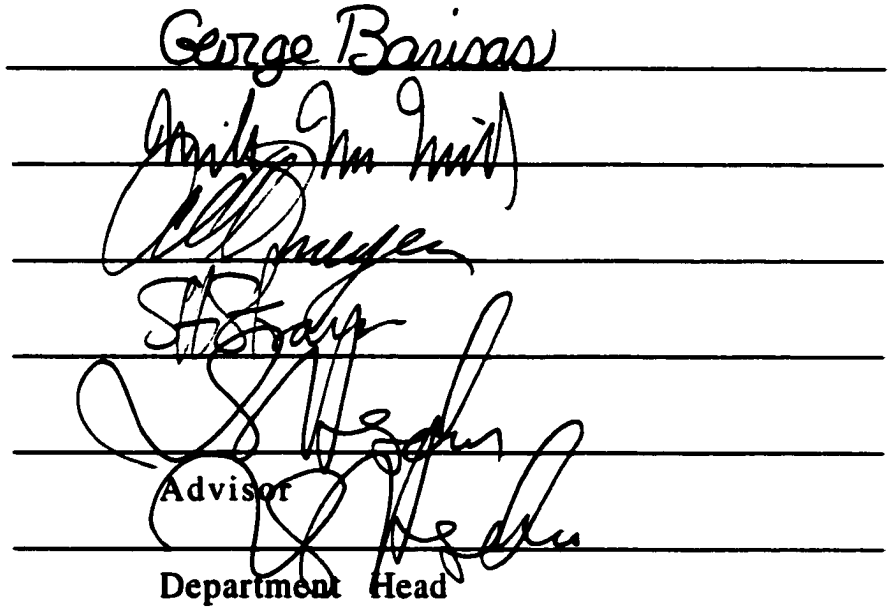
WE HEREBY RECOMMEND THAT THE DISSERTATION PREPARED UNDER OUR SUPERVISION BY ERIK M. KUESTER ENTITLED SYNTHESIS OF ALKYL- AND POLY(ETHYLENE GLYCOL) LINKED BIS-DIOXOCYCLAMS FROM BIS-CHROMIUM CARBENE COMPLEXES BE ACCEPTED AS FULFILLING IN PART THE REQUIREMENT FOR THE DEGREE OF DOCTOR OF PHILOSOPHY.

Committee on Graduate Work



ABSTRACT OF DISSERTATION

SYNTHESIS OF ALKYL- AND POLY(ETHYLENE GLYCOL) LINKED BIS-DIOXOCYCLAMS FROM BIS-CHROMIUM CARBENE COMPLEXES

Alkyl-linked bis-chromium carbene complexes have been prepared via deprotonation and α-alkylation of (methoxy)(methyl) chromium carbene complexes using 1,n-bis-triflates as electrophiles. These bis-carbene complexes were then photolyzed with N-protected imidazolines to give protected bis-azapenams. Azapenams are known to undergo a dimerization reaction to form 14-membered bis-imine bis-dioxocyclams. Unfortunately, all attempts to reduce the imine-cyclams to give the stable dioxocyclams were unsuccessful.

Both tri- and tetra(ethylene glycol) linked bis-chromium carbene complexes have been synthesized. These carbene complexes were photolyzed with imidazolines to give protected azapenams. The azapenams were transformed into polyether-linked basket dioxocyclams and bis-dioxocyclams. These compounds have cavities for the complexation of both "hard" and "soft" metal ions. The complexes of nickel, barium, and gadolinium were synthesized.

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For Sherie,
I love you more.

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Chapter One

Synthesis of Alkyl-Linked Bis-Dioxocyclams

1.1 Chromium Carbene Complexes

1.1.1 General Properties

Transition metal carbene complexes have been extensively developed since E. O. Fischer[1] discovered the Group 6 metal carbene complexes in 1964. Now, the reactivity of transition metal carbene complexes ranges from the nucleophilic olefination of carbonyl compounds with Petasis' reagent,[2] to the rhodium or copper-catalyzed decomposition of diazo compounds to accomplish cyclopropanation, C-H insertion,[3] and ylide chemistry. One of the most developed classes of transition metal carbene complexes are the electrophilic, Group 6 carbene complexes, known as Fischer carbenes. These carbene complexes are characterized by an electrophilic carbene-carbon-to-metal double bond. They also must have a heteroatom substituent on the carbene carbon to stabilize the complex. This heteroatom, typically an oxygen or a nitrogen, is aligned to have the best overlap of a lone pair on the heteroatom with the metal-carbon double bond. The resonance structure resulting from this overlap is stabilized because the electron density

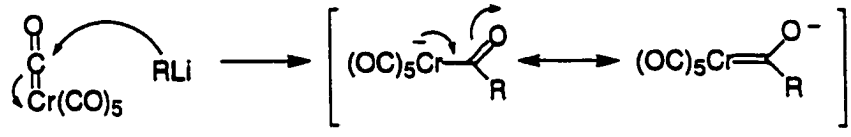
on the metal is delocalized throughout the pentacarbonyl moiety. The better the overlap, the more stable the carbene complex. Chromium carbene complexes are generally yellow to red solids that are relatively stable in the freezer and moderately unstable as solutions, particularly in the presence of light and air. The remaining five CO ligands form what is referred to as the "CO wall." This affects the conformation of the carbene fragment and hinders attack of large nucleophiles, especially those with α-branching.

The protons on the carbon alpha to the carbene carbon, called α-protons, are thermodynamically acidic. The α-protons of alkoxycarbene complexes have a pKa≈12,[4] whereas those of aminocarbene complexes have a pKa≈20.[5] This decrease in the acidity of the aminocarbene complexes is due to better overlap of the nitrogen lone pair into the metal carbon bond. The protons on both alkoxy- and aminocarbene complexes can be removed by a variety of strong bases to give "enolate" type anions, similar to those of esters and amides. The chromium carbene complex enolates are not very nucleophilic due to extensive delocalization of the electron density into the chromium pentacarbonyl fragment.

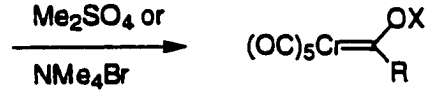
1.1.2 Synthesis of Chromium Carbene Complexes

The synthesis of chromium carbene complexes can be accomplished in a variety of ways. The most common approach is to treat $Cr(CO)_6$ with an alkyllithium. The alkyllithium attacks one of the carbonyl ligands to give a lithium "ate" complex. The tight lithium-oxygen ion pair is not very reactive and so is treated with a very reactive, hard alkylating agent, such as triethyloxonium

tetrafluoroborate, Et_3OBF_4, or dimethyl sulfate to alkylate the oxygen. Alternatively, the lithium "ate" complex can be treated with tetramethyl ammonium bromide under phase transfer conditions to form the more reactive, but isolable tetramethylammonium "ate" complex, **1**. A significant drawback to this method is only functional groups compatible with alkyllithiums can be incorporated into the carbene complex (equation 1.1).



(1.1)

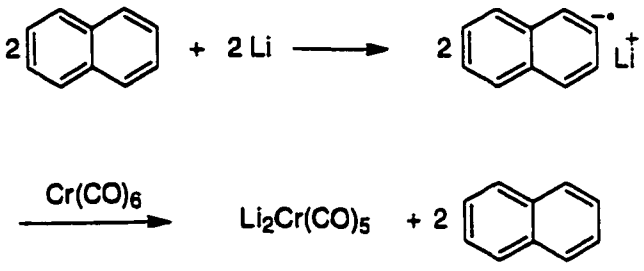


X = Me
1 X = NMe_4

Another method to synthesize chromium carbene complexes is to use a strong reducing agent to make a chromium pentacarbonyl dianion. This dianion is nucleophilic and reacts with a number of electrophiles, including acid chlorides and amides. One method to accomplish this reduction was developed by Semmelhack *et al.*[6] The use of lithium naphthalenide reduces chromium hexacarbonyl to the chromium pentacarbonyl dianion. However, it is stoichiometric in naphthalene (equation 1.2), and in practice, the naphthalene is difficult to completely remove from the desired product.

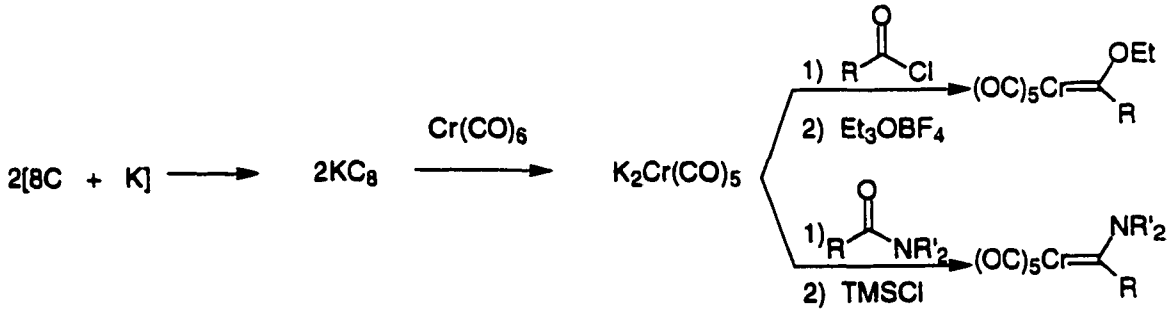
The Hegedus group developed a more efficient method of generating the chromium pentacarbonyl dianion, by using a

potassium-graphite laminate.[7] The potassium-graphite (KC_8) does a two electron reduction of the chromium to give a $Cr(CO)_5^{2-}$ species. The by-product of this reaction is graphite which can easily be



(1.2)

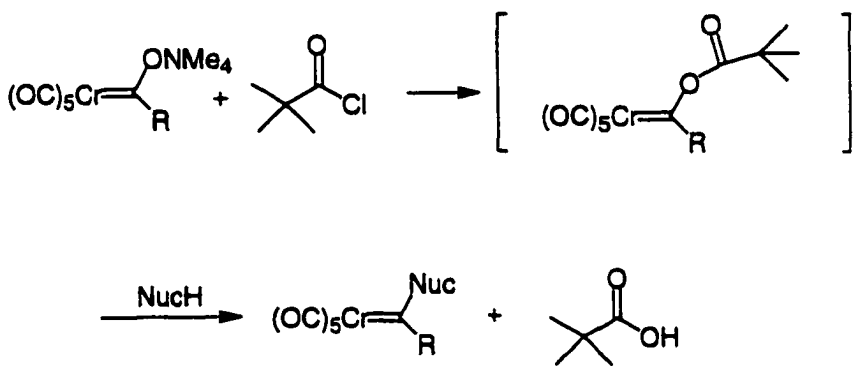
removed by filtration. The dianion attacks acid chlorides and, after alkylation of the oxygen, chromium carbene complexes are formed (Scheme 1.1). The dianion also attacks amides and after treatment with TMSCl, forms amino-carbene complexes.



Scheme 1.1

Since carbene complexes are electrophilic, elaborated carbene complexes can be made from the tetramethylammonium "ate" complexes or from other carbene complexes and the appropriate nucleophile. The tetramethylammonium "ate" complex can be treated with acetyl bromide or pivaloyl chloride to form a mixed anhydride. This anhydride is very reactive at the carbene carbon

and when treated with a nucleophile, the carboxylate is displaced to give a new carbene complex (equation 1.3). Using this method, one can synthesize a variety of carbene complexes with different alkoxy-groups (other than methoxy or ethoxy) or heteroatoms other than oxygen. Alternatively, amines will completely displace alkoxy-groups from carbene complexes to give aminocarbene complexes from alkoxycarbene complexes.



(1.3)

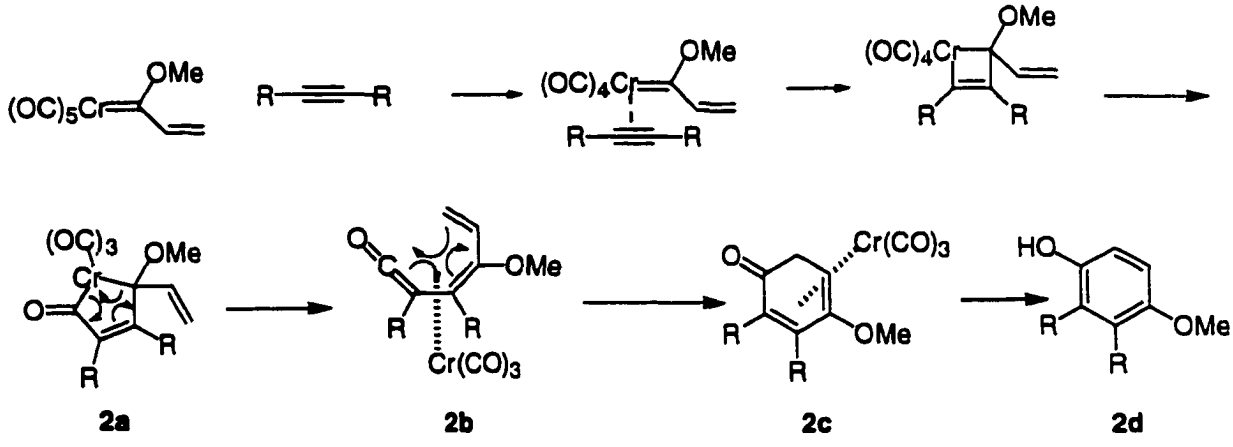
1.2 Reactions of Chromium Carbene Complexes

1.2.1 Thermal Reactions

1.2.1a Dötz Reaction

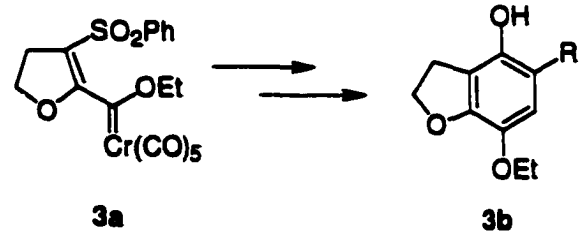
A very useful thermal reaction of chromium carbene complexes is the Dötz reaction.[8] Treatment of an α,β-unsaturated chromium carbene complex with an alkyne under thermal conditions results in hydroquinones being produced. The mechanism of this reaction has been well-studied. The first step is believed to be a thermal dissociation of a carbonyl ligand to give a 16-electron coordinatively unsaturated species, followed by alkyne coordination. The coordinated alkyne and the carbene complex undergo a [2+2]

cycloaddition followed by CO insertion to give chromium species **2a**. This is converted to a chromium-bound vinyl ketene, **2b**, which undergoes an electrocyclic reaction to produce a chromium-bound hydroquinone, **2c**. The chromium tricarbonyl can then be removed under mild oxidative conditions (Scheme1.2).[9]



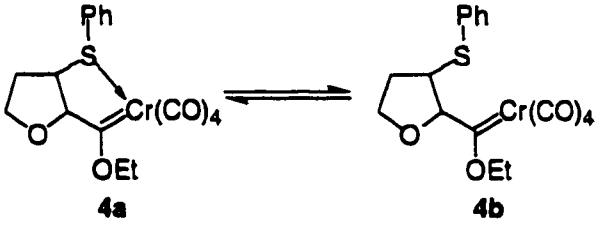
Scheme 1.2

In 1993, Kerr *et al.* developed dry state adsorption conditions for the Dötz reaction.[10] Adsorption of the reactants onto silica gel increased the yields while simultaneously decreasing the reaction times. These solid state conditions were used with dihydrofuranchromium carbene complexes in the Dötz reaction.[11] Although the free dihydrofuranchromium carbene complex proved to be unstable, the benzenesulfonyl analog, **3a**, gave the desired product, **3b**, in moderate yield (equation 1.4). The use of thioethers,



(1.4)

like **4**, increased the rate of the reaction. It was postulated the sulfur atom was coordinated to the chromium as shown in equation 1.5. Under thermal conditions, the sulfur atom dissociated from the chromium to give a 16-electron coordinatively unsaturated species

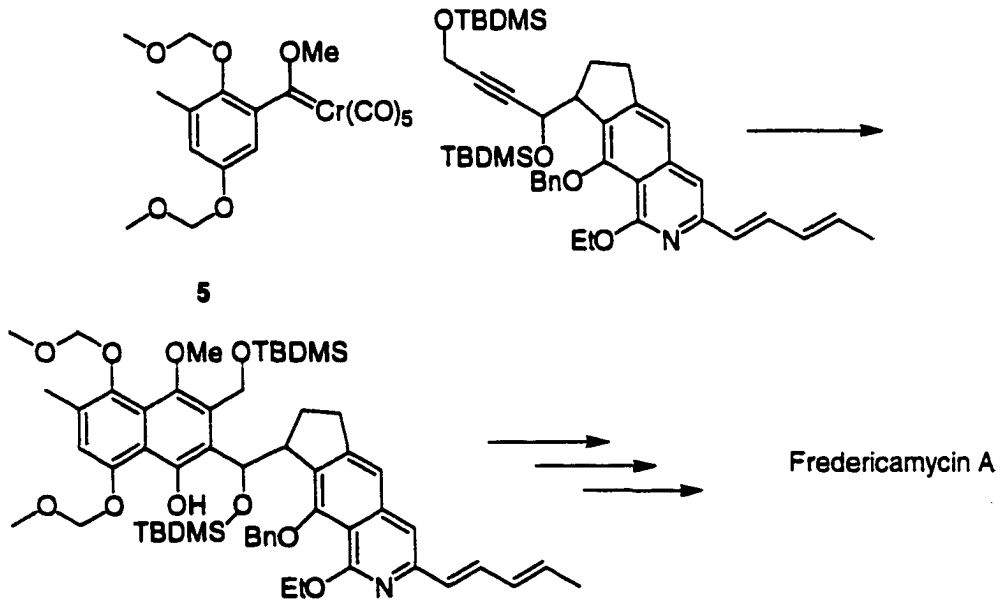


(1.5)

4b. Since the rate-limiting step of the Dötz reaction was the dissociation of a ligand to produce a 16-electron coordinatively unsaturated species, this intramolecular version was able to proceed under much milder conditions.

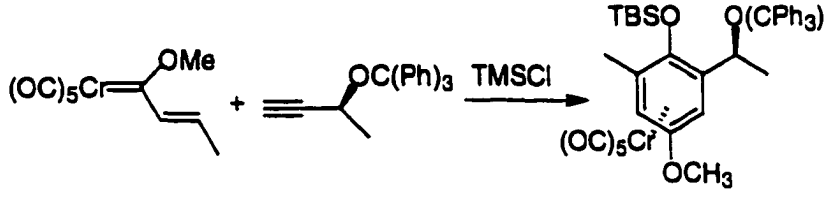
The Dötz reaction has been used in the total synthesis of natural products. Boger *et al.* used chromium carbene complex **5** in his synthesis of Fredericamycin A (Scheme 1.3).[12] Deoxyfrenolicin has also been prepared via a Dötz reaction.[13]

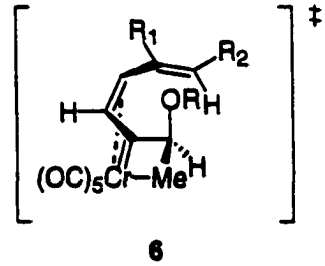
In recent years, the stereoselectivity of the Dötz reaction has become a major focus.[14] The use of a chiral carbene complex or a chiral alkyne should give diastereomers in which the $Cr(CO)_3$ moiety is on one side of the arene ring. The first attempts were made using chiral alkynes.[15] Although good diastereoselectivity was observed (equation 1.6), the authors postulated that the selectivity was due more to a stereoelectronic effect, then due to a pure steric effect. The propargylic oxygen did not coordinate to the chromium



Scheme 1.3

as first believed, but rather preferred to be positioned anti to the chromium-carbene bond as in **6**.

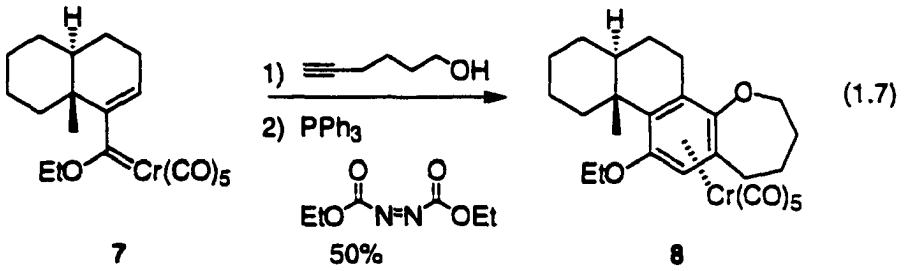




6

Attempts to use a bulky chiral cyclohexenylchromium carbene complex were also tried.[16] Treatment of **7** with 5-hexyn-1-ol, under thermal conditions, followed by Mitsunobu-type alcohol activation

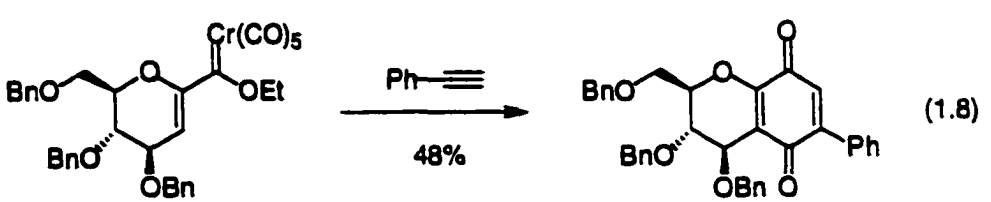
conditions to close the seven-membered ring, produced the anti-diastereomer, **8**, in good yield (equation 1.7). Other optically active



7 8 (1.7)

chromium carbene complexes have also been studied.[17] Using (+) and (-)-menthyl derivatives, high diastereoselectivities were obtained. It was found, however, that increasing the steric bulk or rigidity of the carbene complexes did not enhance the diastereoselectivities.

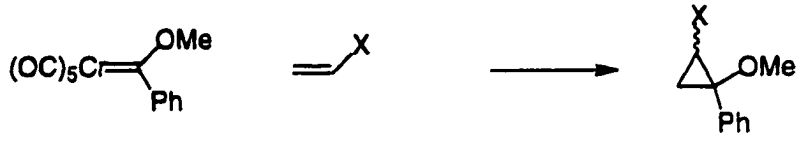
C-Arylglycosides are an important class of compounds which show broad antibiotic and anti-tumor activity.[18] The key glycosidic bond was formed via the Dötz reaction from two complementary approaches.[19] The use of an alkynyl sugar and an α,β–unsaturated chromium carbene complex afforded the desired linkage as did the use of an alkyne and an a sugar substituted α,β–unsaturated chromium carbene complex. α,β–Unsaturated sugar chromium carbene complexes have been used to synthesize benzopyrans (equation 1.8).[20]



9 10 (1.8)

1.2.1b Cyclopropanation

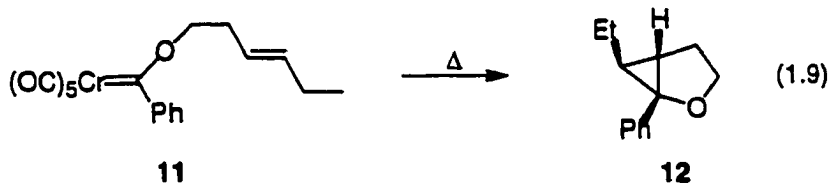
Since the first reported examples of cyclopropanation of olefins by chromium carbene complexes,[21] the scope of this reaction has been well-studied.[22] The first examples of cyclopropanation using chromium carbene complexes were reported with electron-deficient olefins.[21] This reaction was not limited to α,β-unsaturated esters, but other electron-deficient olefins, including acrylonitrile, N,N-dimethyl acrylamide, dimethyl vinylphosphonate and phenylvinyl sulfone, were also cyclopropanated in reasonable yields, with a cis/trans ratio near 1:1 (Figure 1.1).[23] Electron-deficient 1,3-dienes underwent cyclopropanation exclusively at the olefin more distant from the electron-withdrawing group.[24]



X = CN, SO_2Ph, $PO(OMe)_2$, $CONMe_2$

Figure 1.1

Electron-neutral olefins have also been cyclopropanated with chromium carbene complexes. Unactivated 1,3-dienes selectively cyclopropanate at the less sterically-hindered olefin,[25] as long as the diene can attain an s-*cis* conformation. Intramolecular cyclopropanations are facile. Alkoxychromium carbene complex **11** underwent an intramolecular cyclopropanation to give **12** (equation 1.9).[26]



11 12 (1.9)

Electron-rich olefins were first successfully cyclopropanated in 1972.[27] A competing process under these condition was olefin metathesis. High CO pressure inhibited this, as was shown in a model study in a total synthesis of (±)-prostaglandin E_2-methyl ester, **14** (Scheme 1.4).[28] Also, Danishefski's diene was selectively mono-cyclopropanated with (methoxy)(phenyl)chromium carbene complex[29] at the less electron-rich olefin.

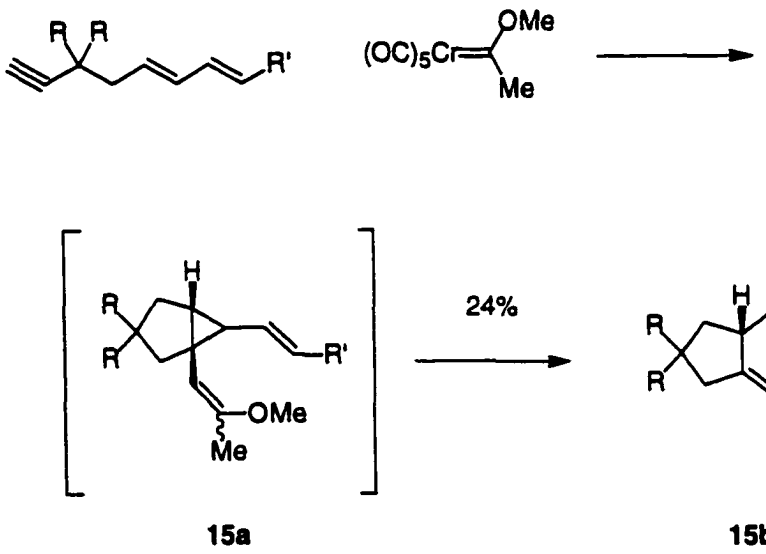
13 14

Scheme 1.4

1.2.1c Metathesis Reactions

Chromium carbene complexes undergo a metathesis reaction with alkynes.[30] This reaction proceeds both by an intra- and intermolecular route. Yndienes participated in a reaction with (methoxy)(methyl)chromium carbene complex to give a [5.3.0] bicyclic system, **15b**.[31] These molecules came from an alkyne metathesis, followed by a cyclopropanation to give intermediate **15a**.

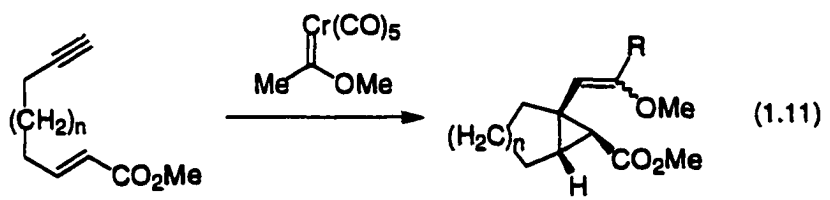
This then, underwent a Cope rearrangement to give the product **15b** in 24% yield (equation 1.10).



(1.10)

15a **15b**

1,6- and 1,7-enynes **16a,b** also reacted with (methoxy) (methyl)chromium carbene complexes.[32] The olefins were electron-deficient, having an ester group in conjugation with the olefin. The yields of this reaction, again, were only moderate (equation 1.11).



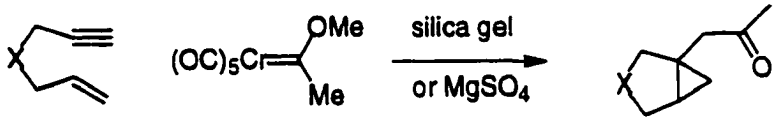
(1.11)

16a n = 1
16b n = 2

17a n = 1 33%
17b n = 2 34%

An improvement in the yields of these metathesis reactions was developed by Katz, *et al.*[33] He discovered that the yields were significantly increased upon adsorption of the starting material onto silica gel or magnesium sulfate (equation 1.12). It was observed the

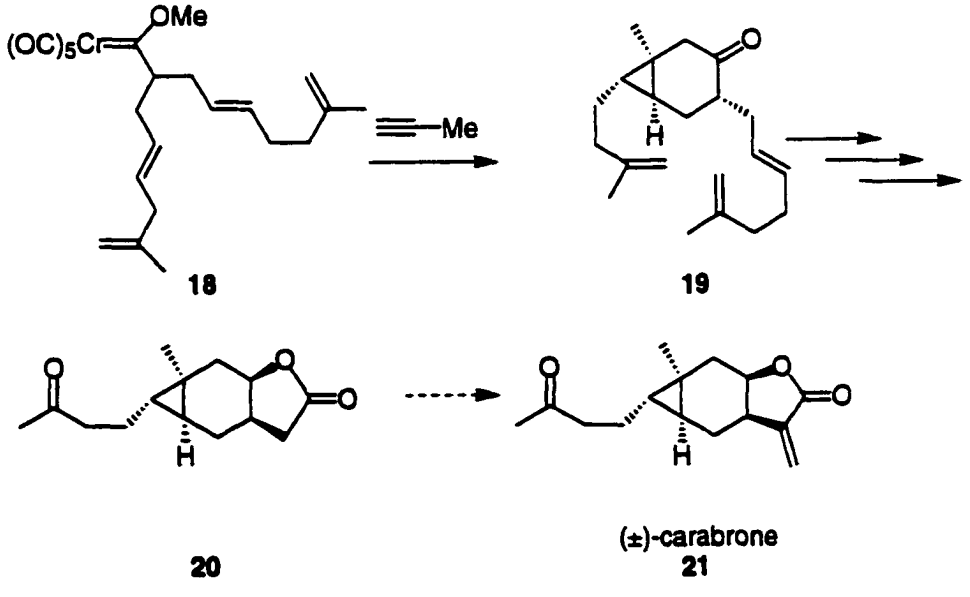
solid support did not simply displace a CO ligand but was postulated to bring the chromium carbene complex and the olefin within close proximity to each other.



(1.12)

X =	
$[(MeO_2C)_2CH-]$	94%
O	85%
$PhCH_2N-$	51%
Me_2CH-	54%

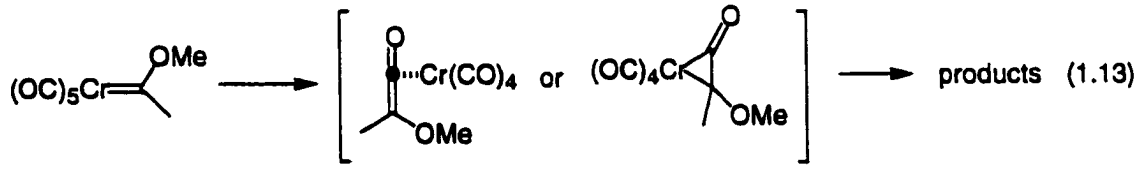
This reaction was also utilized in a formal synthesis of (±)-carabrone.[34] In this example, intermolecular alkyne metathesis followed by cyclopropanation gave intermediate **19**. This was further transformed into **20**, which completed the formal synthesis of (±)-carabrone (Scheme 1.5).



Scheme 1.5

1.2.2 Photoreactions

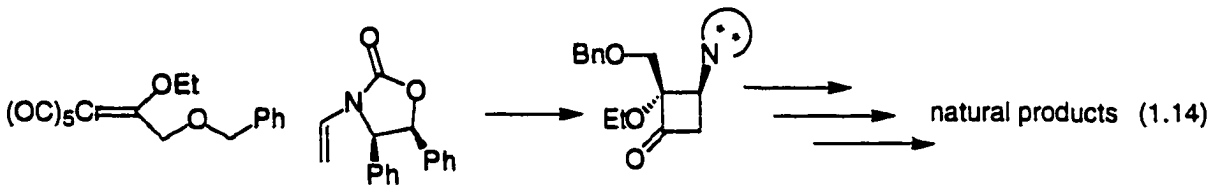
Although chromium carbene complexes are efficient in thermal reactions, their photochemistry has also been developed extensively.[35] Chromium carbene complexes absorb visible light and are yellow to red. This visible absorption corresponds to a spin-allowed metal-to-ligand charge-transfer band (MLCT). The molecular orbital diagram of the (methoxy)(phenyl)tungsten carbene complex has been published.[36] Irradiation of this compound into its MLCT band corresponds to a one electron promotion from a metal-centered HOMO to a ligand-centered LUMO. This promotion can be considered to be a formal one-electron oxidation of the metal and is believed to drive a CO insertion.[37] The short-lived intermediate is believed to be either a metallocyclopropanone or a metal-bound ketene (equation 1.13). Although neither of these species has been observed, when photolysis of chromium carbene complexes is carried out in the presence of ketene traps, products derived from ketenes are formed.



(1.13)

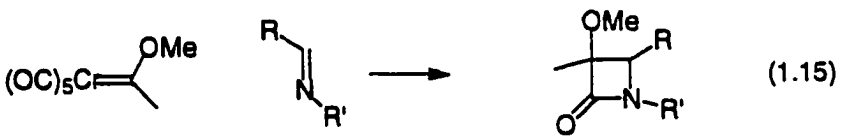
When classically-generated ketenes (from acid chlorides) were treated with olefins, cyclobutanones were produced.[38] When chromium carbene complexes were photolyzed in the presence of electron-rich olefins, they too produced cyclobutanones in similar yields and with similar stereoselectivities.[39] When optically active

ene carbamates were used, one diastereomer of the cyclobutanone was formed (equation 1.14).[40] These cyclobutanones have been elaborated into a variety of natural products.[41]



(1.14)

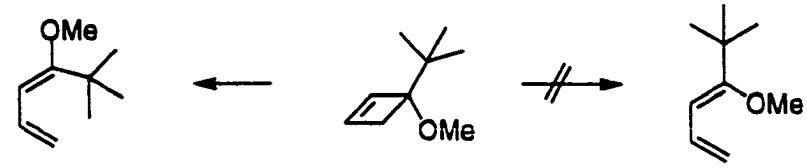
Photolysis of chromium carbene complexes with imines gave β-lactams.[42] This reaction was very clean, high yielding and highly diastereoselective (equation 1.15). A variety of imines underwent reaction, including aromatic imines and imidazolines. The stereo-



(1.15)

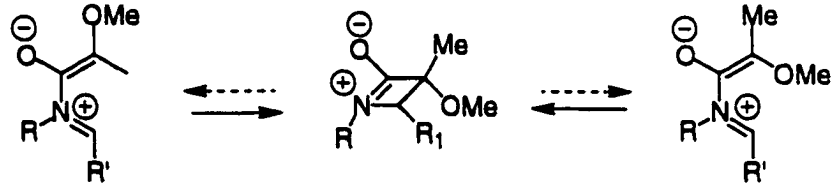
chemistry of these photoreactions is believed to be controlled by torquoselectivity.[43] Torquoselectivity, as put forth by Houk,[44] deals with ring opening of cyclobutenes that have attached donor groups on the ring. When these compounds are heated, conrotary ring opening occurs so the donor atom rotates out, regardless of sterics. For example, cyclobutene **22a** only ring opens to give **22c** even though **22b** is less sterically hindered (equation 1.16). To use the concept of torquoselectivity in the explanation of the stereochemistry of the β-lactams, one must think in reverse. Imine attack on the ketene intermediate is believed to give zwitterionic species **22c'** or **22b'**. The intermediate resulting from attack of the imine anti- to

the donor group (**22c'**) has a barrier to conrotary ring closure which is 10-12 kcal/mole lower that resulting from attack of the imine syn to the donor group (equation 1.17).



(1.16)

22c **22a** **22b**



(1.17)

22c' **22a'** **22b'**

Chromium carbene complexes undergo a variety of other photoreactions, although they have been developed less than the reactions already mentioned. The Dötz reaction, as stated above, goes with formation of a vinyl ketene intermediate and proceeds under photochemical conditions[45] as well as thermal conditions. Also, treatment of aminocarbene complexes with methanol under photolysis condition yields α-amino acid methyl esters.[46] Photolysis of alkoxycarbene complexes with tertiary allylic amines forms intermediates which readily undergo a [3+3] sigmatropic rearrangement to form amides.[47]

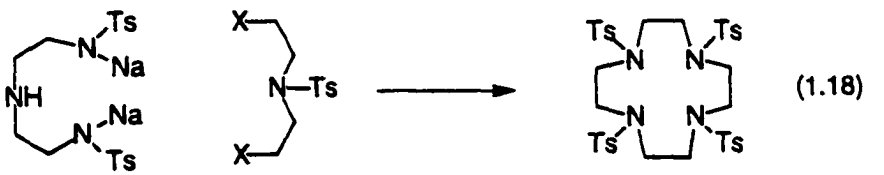
1.3 Tetraazamacrocycles

1.3.1 Cyclams

1.3.1a Non-Template Synthesis of Cyclams

Polyazamacrocycles have been studied for many years. One of the most common polyazamacrocycle is the 1,4,8,11-tetraazacyclotetradecane, or cyclam. There are two general methods used to synthesize cyclams and their derivatives: template cyclization and non-template cyclization. The template version uses a metal ion, usually a transition metal, to pre-organize the starting materials which facilitates macrocyclic ring closure. The non-template method typically uses high dilution conditions to help close the macrocyclic ring.

One of the first macrocyclic polyamines synthesized via the non-template method was tetraazacyclododecane, **23** (equation 1.18).[48] The yield of this reaction was only ≈30% and the N-tosyl

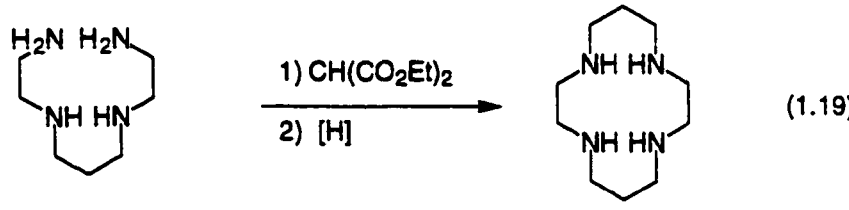


(1.18)

X = OTs, OMs, Cl, Br, I **23**

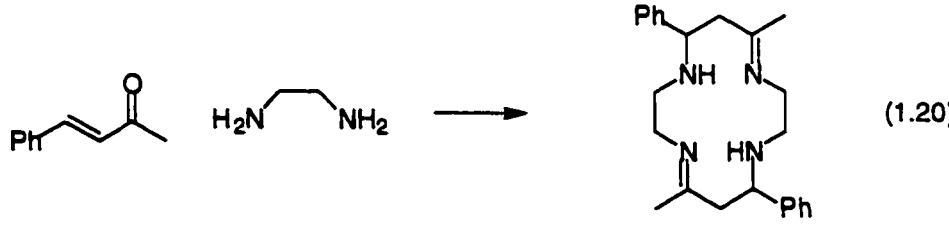
groups were hydrolyzed using hot sulfuric acid. One variation of this reaction used a tetraamine and a bis-electrophile,[49] while another variation used a diamine and a bis-electrophile.[50] Triflates have recently been used to protect the amine nitrogens.[51] After the macrocyclization, the nitrogens were deprotected under milder

conditions than the conditions needed to remove the tosyl groups. Tetraamines have also been treated with diethylmalonate.[52] The amide carbonyls were reduced with diborane to give the cyclams in moderate yield (equation 1.19).



(1.19)

A second approach to non-template formation was the condensation of amines with carbonyl compounds to form imines. These were then reduced to give the desired cyclam products. Treatment of benzylidene acetone with ethylenediamine produced imine cyclam **24** (equation 1.20).[53]



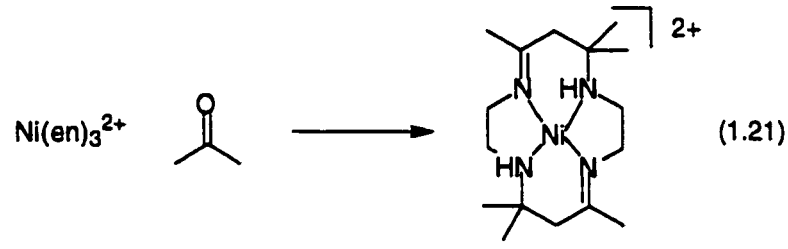
(1.20)

24

1.3.1b Template Synthesis of Cyclams

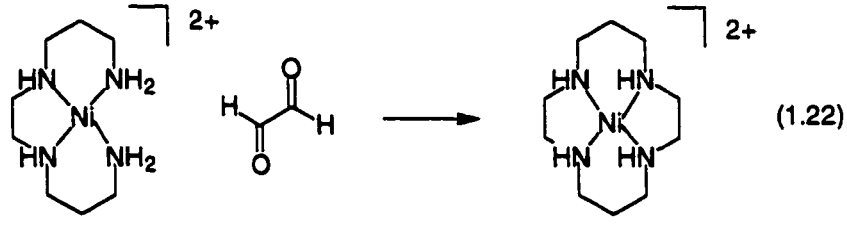
Although this imine formation/reduction has been used in the non-template area, it is as common, or more common in the template version. Curtis showed the first example of template

macrocyclization with nickel(II) tris(ethylenediamine) and acetone (equation 1.21).[54] This mixture formed the 5,7,7,12,14,14-



(1.21)

hexamethyliminecyclam nickel complex. The tetraamine nickel complex **25** was treated with glyoxal and the intermediate imine was reduced to give nickel complexed cyclam **26** (equation 1.22).[55] This route was elaborated using substituted tetraamines.[56]



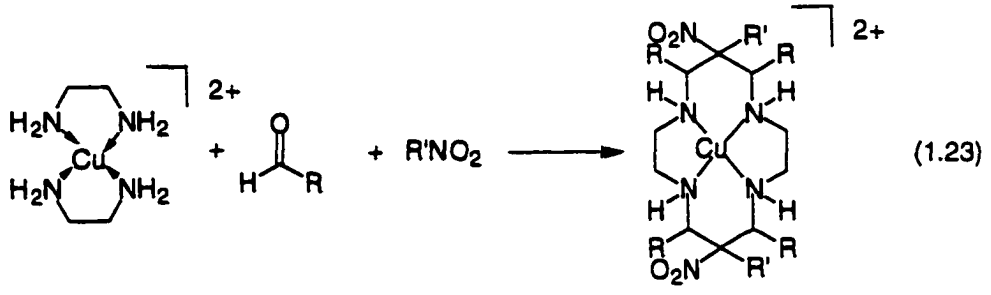
(1.22)

25 **26**

Copper complexes of ethylenediamine have been used in conjunction with an aldehyde and a carbon acid. (Nitromethane was the most common).[57] Thus, when copper complex **27** was treated with an aldehyde and a carbon acid, a copper cyclam, **28**, was produced (equation 1.23).

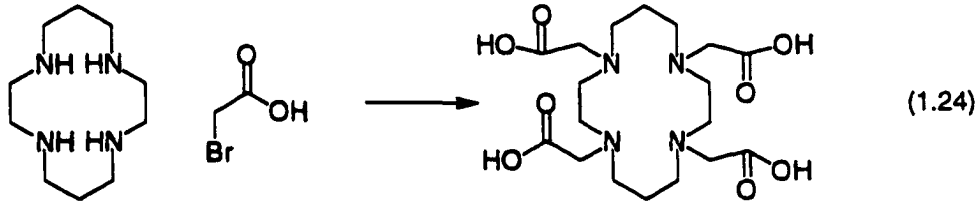
1.3.1c Pendant Cyclams

Cyclams with N-pendant functionalities are of particular interest. One way to synthesize substituted cyclams is to alkylate the



27 28 (1.23)

nitrogens with compounds that have an electrophile at one end and an oxygen at the other end. One of the most common methods for accomplishing this is to treat the cyclam with bromo- or chloroacetic acid (equation 1.24);[58] however, treatment with 3-bromopropionic

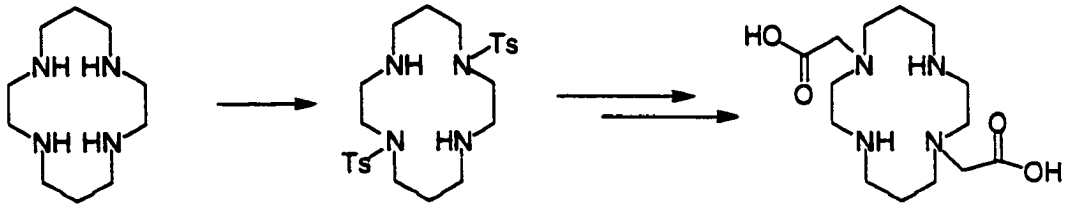


29 (1.24)

acid gave no product. Tetraacetic acid cyclam **29** has been studied with respect to the formation of calcium and magnesium chelates.[59] Ligand **29** has also been complexed to terbium. In this complex, all four amine nitrogens and all four carboxylates of the ligand were coordinated to the metal.[60] Zinc also was complexed to **29**. In this structure, only two trans carboxylates coordinated to the metal, occupying the two axial sites.[61]

Cyclam itself can be ditosylated selectively in a 1,8-fashion.[62] Treatment of this bis-protected cyclam with a variety of

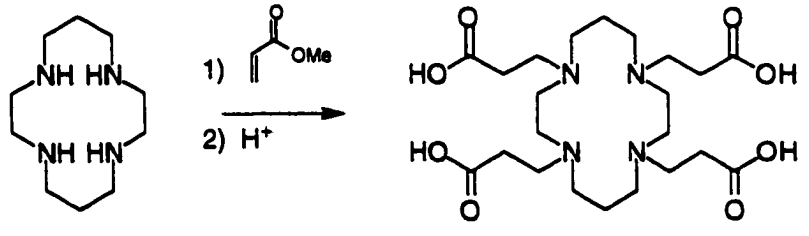
electrophiles and removal of the tosylate groups gave 1,8-disubstituted cyclams (equation 1.25). A crystal structure of the



(1.25)

30

copper complex of **30** showed, as expected, both carboxylates coordinated to the copper ion.[63] Although 3-bromopropionic acid did not alkylate cyclams, methyl acrylate did react with cyclam under Michael conditions to give the alkylated product. The ester groups were then hydrolyzed to give the tetrakis acid cyclam, **31** (equation 1.26).[64]

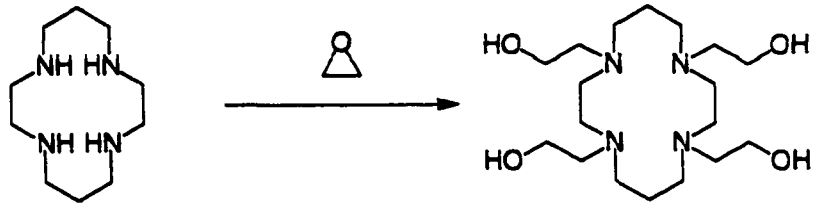


(1.26)

31

Cyclams reacted with ethylene oxide to form 2-hydroxyethyl derivatives, **32** (equation 1.27).[65] These cyclams had an increased rate of metal complexation. The pendant hydroxy arms provided a point of attachment for the incoming metal ion that was away from any remaining protons that were on the macrocycle. This reduced the destabilizing electrostatic repulsion between the positively

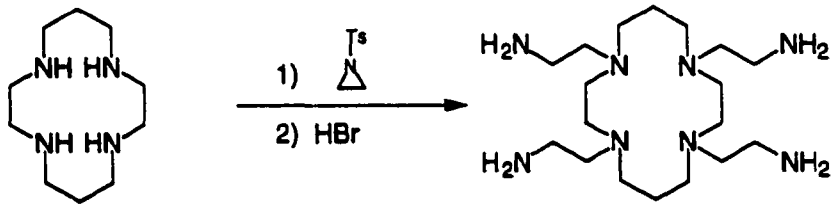
charged metal ion and any protonated nitrogens in the macrocycle. Both the 1,4- and the 1,11-(2-hydroxyethyl)cyclams have been synthesized and complexed to nickel(II). X-ray structures of these Ni-complexes have been obtained.[66]



(1.27)

32

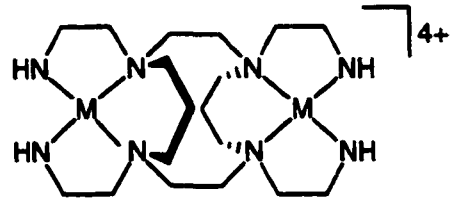
Nitrogen donors have also been appended to the cyclam ring. Treatment of cyclam with N-tosyl aziridine gave the tetrakis-(2-aminoethyl)cyclam derivative, **33** (equation 1.28).[67] Homo-bimetallic complexes of both copper and nickel have been isolated.



(1.28)

33

The X-ray crystal structures of these compounds showed a Cu-Cu distance of 5.479 Å and a Ni-Ni distance of 5.267 Å. Each metal ion



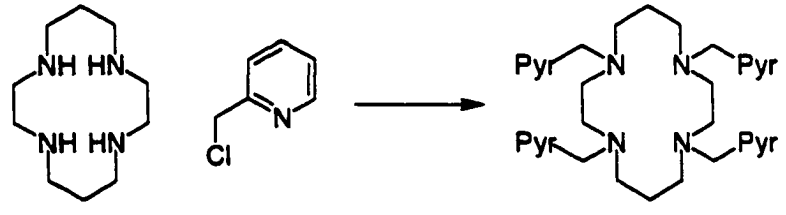
$M = Cu^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}$

Figure 1.2

was coordinated to two cyclam nitrogens and two ethylamino nitrogens. Each metal formed two five-membered rings and a six-membered ring (Figure 1.2).

Zinc also formed a homo-bimetallic structure with (2-aminoethyl)cyclam.[68] whereas cadmium and mercury formed mixtures of mono and dimetallic structures. A stable Cr(II) complex of 2-aminoethyl cyclam has also been synthesized.[69] When 3-aminopropyl groups were attached to cyclam, and the resulting ligand treated with nickel(II), a 1:1 nickel:ligand complex was formed in which only one propylamino group was coordinated to the nickel.[70]

Other nitrogen groups have been used as pendant donors. Cyclam has been alkylated using 2-chloromethylpyridine to give



(1.29)

34

34 (equation 1.29).[71] This was then complexed to copper and treated with bromide ion to give crystals of the formula $(Cu_2LBr_2)(ClO_4)_2$, where L = cyclam. The crystal structure showed, similar to the 2-aminoethylcyclam, that each copper was coordinated to two cyclam nitrogens and two pyridine nitrogens. This time, however, the metal was part of three five-membered rings and no

six-membered ring (Figure 1.3). Cyclams **35** and **36** have also been synthesized and complexed to copper (Figure 1.4).[72]

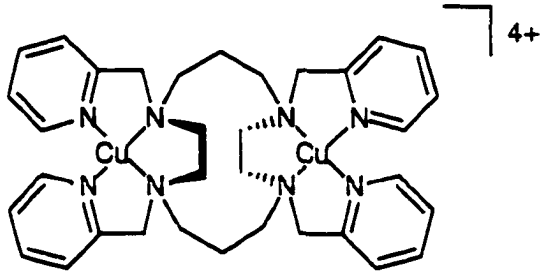
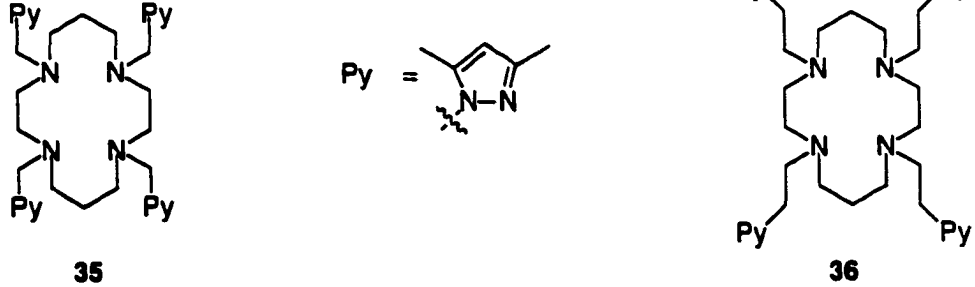


Figure 1.3

Cyclam with a pendant mono bipyridine moiety has been used to study the rate of metal complexation.[73] Mono (2-aminoethyl)cyclams have also been prepared and complexed to nickel.[74] Spectral studies on the complex indicated the pendant amine was coordinated at neutral pH, but when acid was present the amine dissociated to give a four coordinate nickel.



35 **36**

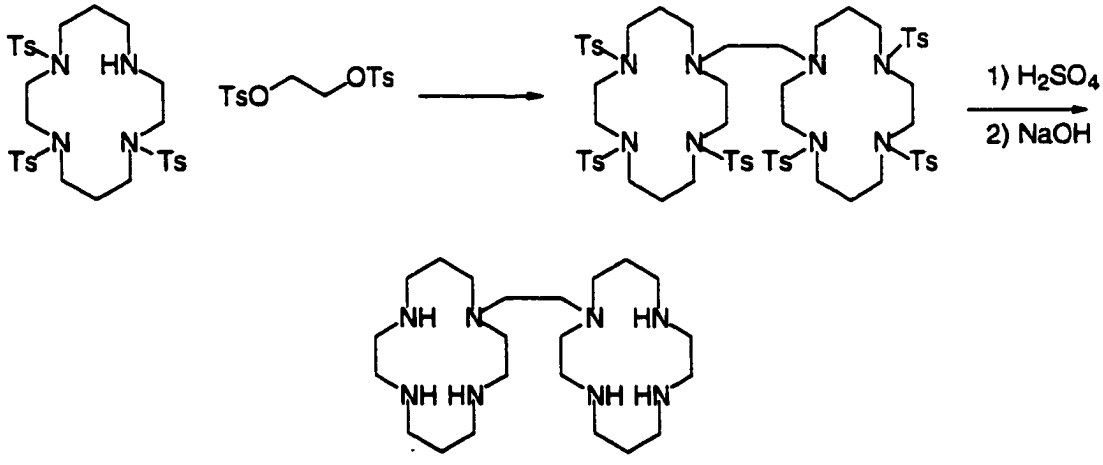
Figure 1.4

1.3.1d Bis-Cyclams

Bis-cyclams are compounds in which two cyclam rings have been attached by one or more linkers. These linkers usually connect the cyclams rings at the nitrogens. These linkers can be aliphatic or

aromatic and may contain other functional groups. Bis-cyclams show unique activity against HIV-1 and HIV-2 by inhibiting HIV fusion/uncoating.[75] A number of bis-cyclam compounds have been synthesized and tested against HIV.[76] From these tests, a list of structural requirements for good activity has been compiled and include: two chelating macrocyclic rings, 9.5-11.5 Å distance between metal binding centers, and an optimum 14-membered macrocycle.

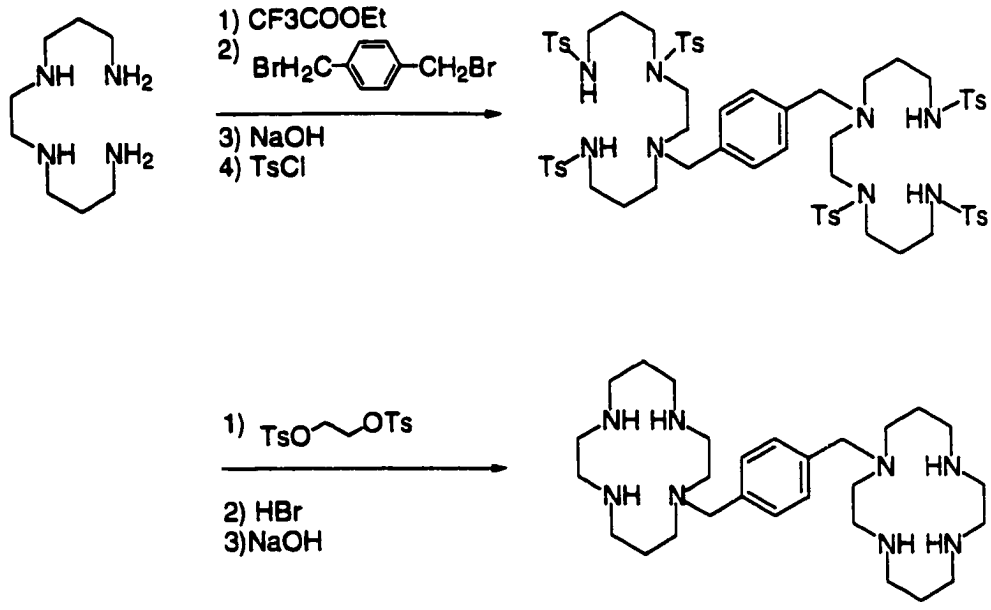
Tri-protected cyclams were treated with α,ω-alkyl tosylates to give bis-cyclam, **37**, in moderate yield (equation 1.30).[77] This reaction was also successful with bis-benzyl bromides. A variation



(1.30)

37

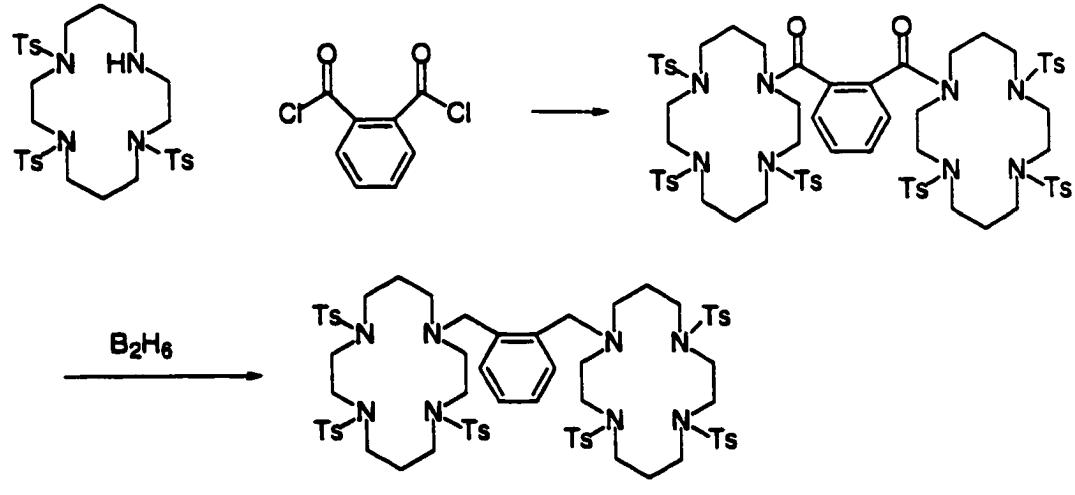
of this in which a tetraamine was triprotected and then treated with bis-benzyl bromide was recently published.[78] After changing the protecting groups, the cyclam rings were closed with 1,2-bistosyl-ethane and the protecting groups were removed to give **38** (Scheme 1.6).



38

Scheme 1.6

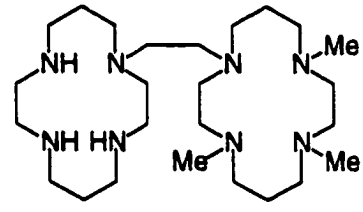
Another route used both aromatic[79] and aliphatic[80] bis-acid chlorides. Treatment of the triprotected cyclam with bis-acid chlorides, followed by reduction of the resulting amide carbonyls gave the desired bis-cyclams, **39** (equation 1.31).



(1.31)

39

Bis-cyclams have also been complexed to metals. Titration of **40**, (Figure 1.5) with copper(II) demonstrated a distinct break in the UV-Vis absorption after one equivalent had been added, indicating a stepwise complexation.[81] The copper cyclam absorbed at 530 nm and the value stopped increasing before the copper methyl-cyclam started absorbing at 640 nm. Considering this fact, the mono-copper bis-cyclam was treated with zinc to form a mixed metal complex.



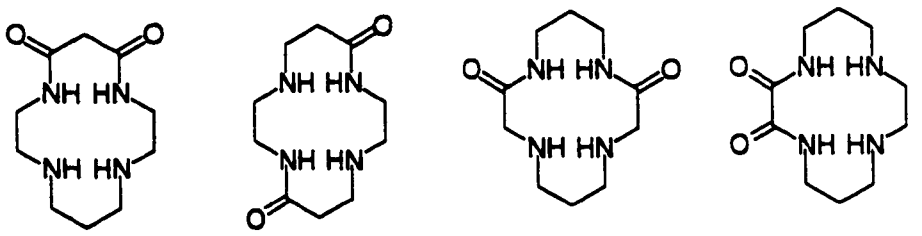
40

Figure 1.5

1.3.2 Dioxocyclams

1.3.2a Synthesis of Dioxocyclams

A subclass of cyclams are the dioxocyclams, in which two of the amines have been replaced with two amides. They are structurally between polyamines and oligiopeptides. The two carbonyl groups have been synthesized in four different orientations: a 1,3; 1,7;, 1,2; 1,8; (Figure 1.6) the most common of these being the 1,3. Although cyclams coordinate a variety of metals, their selectivity is poor. The amide nitrogens of the dioxocyclams help to selectively coordinate copper,[82] nickel,[83] cobalt,[84] platinum[85] and palladium.[85] Due to the amide functionality, these metals can be decomplexed at low pH, unlike their cyclam counterparts. The carbonyl can be

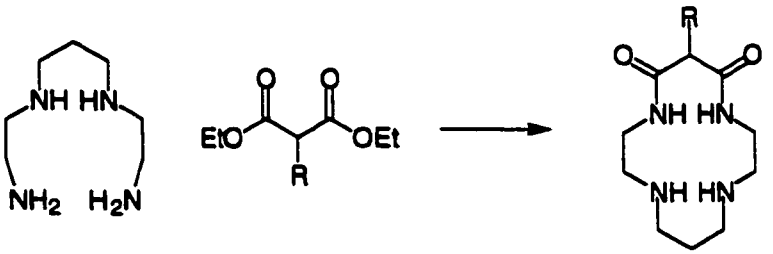


1, 3 1, 8 1, 7 1, 2

Figure 1.6

protonated, which then tautomerizes and decomplexes the metal. Nickel, palladium, and platinum prefer to coordinate in a square planar geometry while copper prefers to be five coordinate and cobalt favors an octahedral geometry with two solvent molecules occupying the vacant sites.

The first dioxocyclam to be synthesized was the 5,7-dione (a 1,3 orientation) of Tabushi.[52] Treatment of N,N-bis(2-aminoethyl)-1,3-propane diamine with diethyl malonate in ethanol at reflux gave the desired dioxocyclam, **41**, in 30% yield (equation 1.32).

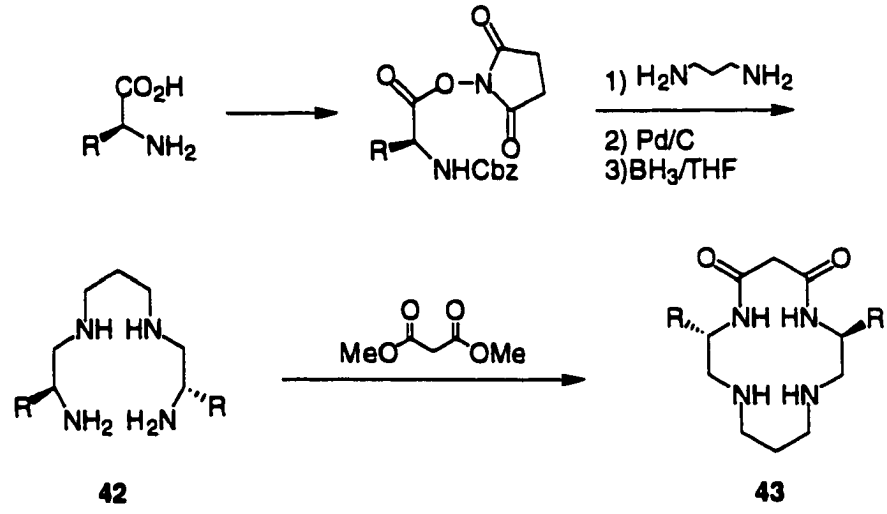


(1.32)

41

Because the protons on the carbon between the carbonyls can be removed and alkylated, substituted dioxocyclams have also been synthesized.

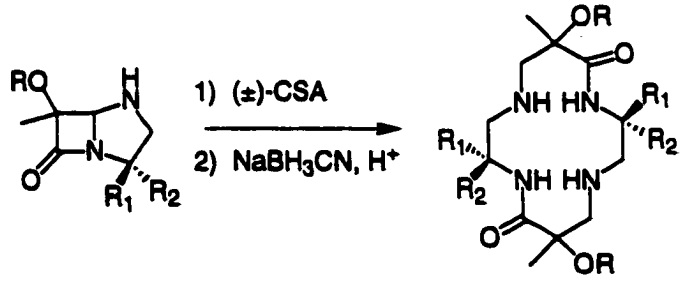
Burrows, *et al.* synthesized a variety of chiral C_2 symmetric 5,7-dioxocyclams.[86] Starting from amino acids, chiral tetraamines were synthesized by the route in Scheme 1.7. In the synthesis of **42**, each step led to a crystallization, thus omitting the need for chromatography and resulting in yields from 37-62%. However, the



Scheme 1.7

cyclization gave low yields (8-12%) of **43**, and the use of even more reactive acylating reagents was unsuccessful at increasing the yield.

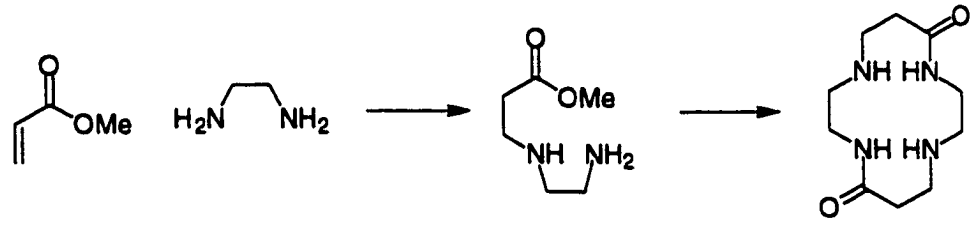
A number of 5,12-dioxocyclams have been synthesized by the Hegedus group.[87] Ring expansion and dimerization of azapenams led to, after reduction of the resulting imine bonds, highly substituted 5,12-dioxocyclams (equation 1.33). The use of an optically active



(1.33)

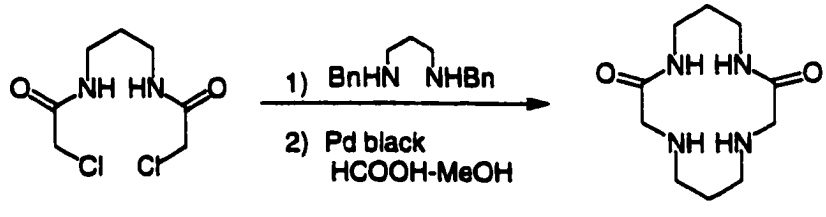
azapenam under these conditions gave the 5,12-dioxocyclam in good yield as one diastereomer.[88]

Another synthesis of 5,12-dioxocyclams used methyl acrylate and ethylenediamine.[89] The resulting N-(2-aminoethyl)-β–alanine methyl ester **44** was allowed to dimerize over three days to form the dioxocyclam **45** (equation 1.34).



44 **45** (1.34)

More recently, other dioxocyclams have been synthesized. Treatment of dimethyl oxalate with N,N'-bis(3-aminopropyl) ethylenediamine under very dilute conditions gave the 2,3-dioxocyclam in 60% yield.[90] A 3,9-dioxocyclam was synthesized from bis(α-chloroamide) **46**, and N,N-protected propanediamine (equation 1.35).[91] The isolated yield of the dioxocyclam **47** was only 30%.

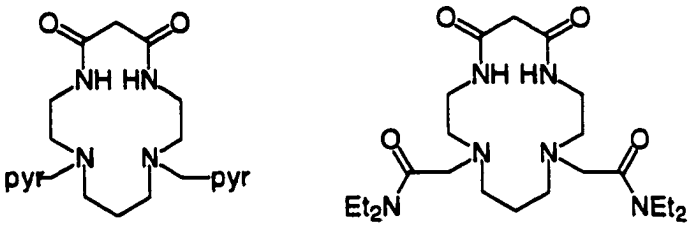


46 **47** (1.35)

1.3.2b Pendant Dioxocyclams

Although many examples of alkylated cyclams are in the literature, the synthesis of substituted dioxocyclams is only now

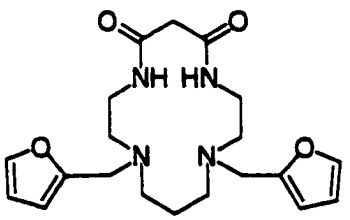
becoming more prevalent. Nitrogen-alkylation is by far the most common method of substituting these dioxocyclams. Two of the earliest examples of an alkylated dioxocyclam were alkylation using bromomethylpyridine,[92] and [α-chloromethyl diethylamide] (Figure 1.7).[93] These bis-alkylated dioxocyclams **48** and **49** were used to



48 **49**

Figure 1.7

study cation binding and transport of alkali and alkaline earth metals. It was determined these dioxocyclams have little to no affinity for these hard cations. More recently, methylfuran rings have been attached to these 5,7-dioxocyclams **50** (Figure 1.8).[94]

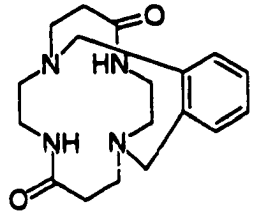


50

Figure 1.8

Dioxocyclams with the 5,12 carbonyl orientation have been N-alkylated with ortho-bis(bromomethyl)benzene and a crystal structure has been solved (Figure 1.9). This molecule should easily

complex metals. Also, these dioxocyclams have been N-alkylated with pentafluoropyridine (Figure 1.9).[95]



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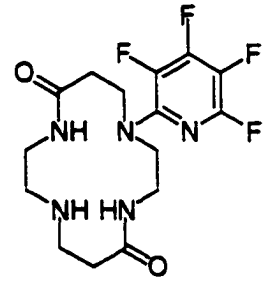
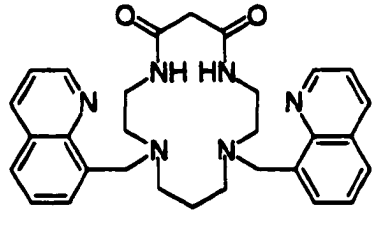


52

Figure 1.9

Although the free dioxocyclam ligands are interesting, it is the metal complexes that have been studied the most. Copper(II), which forms the most stable complex with dioxocyclams, has been studied numerous times. In a seminal study, Kimura *et al*[82] showed that copper(II) is readily complexed to the 5,7-dioxocyclam with concomitant dissociation of the two amide protons to give a neutral complex.

N-Alkylation of 5,7-dioxocyclams was accomplished with 8-bromomethylquinoline (Figure 1.10).[96] The resulting alkylated



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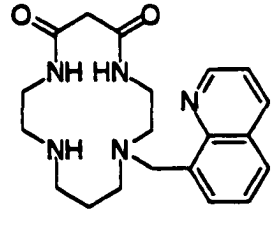
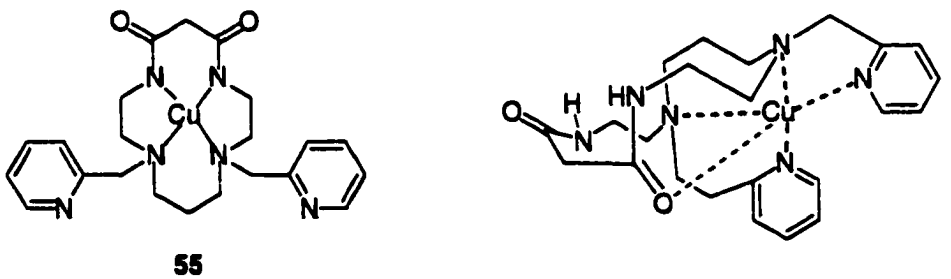


54

Figure 1.10

dioxocyclam was then complexed to copper and a crystal structure was solved. The Cu-N (both amide and amine) bonds were longer than normal Cu-N amide and amine bonds, suggesting that the substitution on the nitrogen reduced the coordinating ability of the ligand. The two quinoline ligands in **53** were located on the apical positions of the copper. These Cu-N bonds were 2.7-2.8 Å which were too long to be considered normal Cu-N bonds. When one quinoline group was appended to the dioxocyclam, **54**,[97] the copper was in a distorted square-pyramidal configuration. The apical Cu-N bond length was 2.3 Å, which is longer than a normal Cu-N bond but shorter than in **53**. Cyclic voltammographic studies on Cu-complex of **53**, suggested it does not stabilize Cu(III) as well as the unalkylated dioxocyclam ligands (CuL(alkyated) = +0.78V vs SCE, CuLo(free ligand) = +0.64V vs SCE).

Methylpyridine was also attached to the dioxocyclam ligand which was then complexed to copper (Figure 1.11).[98] The IR spectrum of **55** displayed two carbonyl stretching frequencies (1631 cm-1, 1695 cm-1). This suggested that one of the amide oxygens



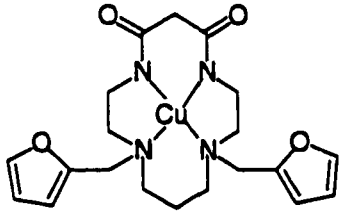
55

Figure 1.11

was coordinated and the other amide was not coordinated. A crystal structure of the bis-alkylated copper complex showed a distorted trigonal-bipyrimidal orientation around the copper with one amide

oxygen coordinated and the two amide nitrogens not coordinating. Cyclic voltammogram studies showed a decrease in Cu(III) stabilization compared to the unsubstituted ligand. This result parallels the quinoline dioxocyclam study.[97]

Along with pendant nitrogen donors, oxygen donors have also been used to study dioxocyclam copper complexes. When bromomethylfuran was used to alkylate the 5,7-dioxocyclam, both mono- and di-alkylation products were isolated.[94] These alkylated dioxocyclams were then complexed to copper with copper acetate to give **56** and **57** (Figure 1.12). Attachment of the methylfuran



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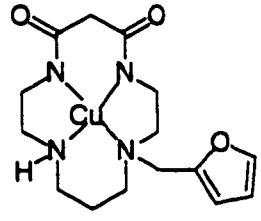
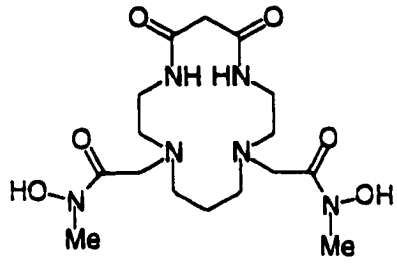


57

Figure 1.12

moiety significantly red shifted the UV-Vis absorption from 505 nm for the copper complex of the free ligand to 525 nm and 546 for the mono and dialkylated dioxocyclams, respectively. This red shift was attributed to a weakening of the in-plane bonding due to an increase of the substitution on the amines. Unlike the 8-methylquinoline copper complex shown above,[97] for which the aromatic nitrogens were coordinated to the copper, the oxygens of the furans were not coordinated to the copper.[94] This could be due to the weaker coordinating ability of the oxygen of the furan.

An interesting study was recently published by Santos *et al*,[99] in which, the 5,7-dioxocyclam was appended with hydroxamic acids



58

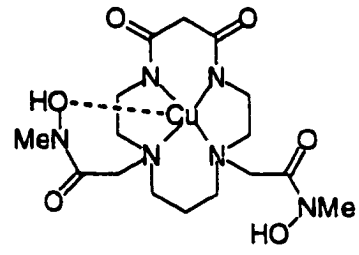
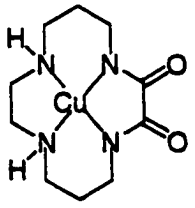


Figure 1.13

and then the copper complex was synthesized. The copper ion had a choice of donor atoms to fill the fifth coordination site; an amide carbonyl, an amide nitrogen, and a hydroxamic oxygen. Although a crystal structure of this copper complex was not elucidated, ESR and potentiometric studies, along with some molecular modeling were carried out to describe the coordination of the copper. At neutral pH, the copper was coordinated to the four nitrogen atoms of the ring and one hydroxamic oxygen.

The 2,3-dioxocyclam also formed stable complexes with copper.[90] When the free ligand was mixed with KOH and $CuCl_2$, a monocopper complex **59** was formed. When this mono-copper complex was treated with an excess of $Cu(ClO_4)_2$, a trimetallic species **60** was isolated (Figure 1.14). The three copper atoms were all in the same plane as the carbonyls. This suggested there was electron delocalization throughout the system via the amide linkages and the copper atoms.



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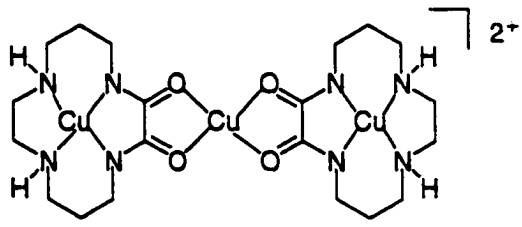
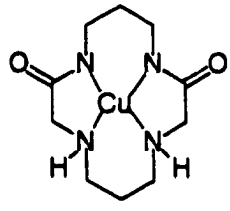


60

Figure 1.14

The 3,9-dioxocyclam copper complex **61** was studied as a potential radiopharmaceutical and PET imaging candidate (Figure 1.15).[91] The 3,9-dioxocyclam formed a copper complex at a lower pH than did the copper complex of the 5,12-dioxocyclam. This, along with the fact that the 14-membered dioxocyclam accommodated



61

Figure 1.15

copper(II) ions nicely, made the 3,9-dioxocyclam appear to be the best candidate for the complexation of ^{62}Cu, ^{64}Cu, ^{67}Cu for potential radiotherapeutic applications.

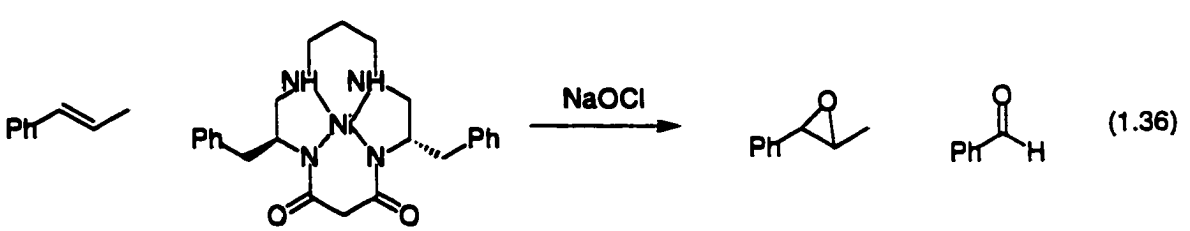
Although copper complexes are more stable than nickel complexes, the copper(II) is paramagnetic which limits characterization by NMR spectroscopy. Because nickel(II) is not paramagnetic, ^{1}H-NMR and ^{13}C-NMR spectroscopy can be used to study these complexes. The dissociation of the nickel ions from the

dioxocyclam and the free cyclam has been studied.[100] The postulated mechanism for acid decomplexation of the metal is believed to be rapid protonation on the carbonyl oxygen. This increased the nitrogen-carbon double bond character which weakened the nickel-nitrogen bond. Slow loss of the metal ion followed by tautomerization gave the free dioxocyclam.

A crystal structure of a 5,7-dioxocyclam nickel complex with two pendant 2-methylfurans was solved.[101] In the structure, the dioxocyclam took on a cis-geometry with both of the methylfuran rings on the same side of the dioxocyclam macrocycle. However, the furan oxygens were not coordinated to the nickel. This result was similar to the copper complex of the same ligand.

Optically active nickel(II) complexes of 5,7-dioxocyclams have been studied for the oxidations of alkenes. The yields and selectivity, however, were poor (equation 1.36).[86] Other square-planar complexes of nickel(II) have shown the ability to transfer oxygen to alkenes, usually with the epoxide as the product.[102] The use of trans-β-methylstyrene, sodium hypochlorite and **62** resulted in formation of the epoxide and benzaldehyde, with no asymmetric induction.

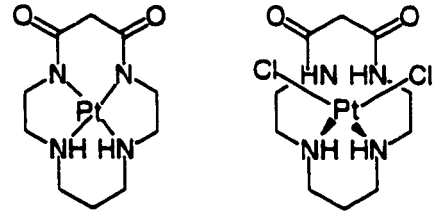
Platinum(II) was also complexed to a 5,7-dioxocyclam.[103] For these platinum complexes, two different crystal structures were



(1.36)

62

solved. The major product had the platinum coordinated to all four nitrogen atoms, **63**. When platinum was complexed to the unsubstituted dioxocyclams and crystallized, a minor product was also obtained. In the minor structure, the metal is in an "out" position, coordinating to only the two amine nitrogens plus two chlorines. This platinum "out" species **64**, gradually converted into "in" the platinum species, **63**, upon dissolution (Figure 1.16).



"in" **63** "out" **64**

Figure 1.16

1.4 Rationale

One area of research that is now beginning to be developed is the synthesis of bis-dioxocyclams. The Hegedus group recently published an efficient synthesis of ether-linked bis-dioxocyclams[104] from ether linked bis-chromium carbene complexes. These carbene complexes are easily synthesized from the tetramethylammonium "ate" complex, **1**, pivaloyl chloride and the appropriate diol. The bis-chromium carbene complexes can be made with a four, five, six, or twelve atom bridge. These are then transformed into the bis-dioxocyclam bridged with the same number of atoms. The dioxocyclams with the shorter chain lengths can be separated into

their diastereomers, a meso and a d,l pair.[104] All of the ether-linked bis-dioxocyclams complex to transition metals such as copper(II) and nickel(II). They have also been used to study the hydrolysis of phosphodiesters.[105]

Although bis-dioxocyclams have not shown anti-HIV activity, bis-*cyclams* are known to be potent HIV uncoating inhibitors. Amide carbonyls can be completely reduced to the corresponding amines under a variety of conditions. Unfortunately, when the ether-linked bis-dioxocyclams were subjected to the conditions for reducing the amide carbonyls, the tertiary ether linkages were cleaved, destroying the tricyclic ring system. It was postulated that if alkyl-linked bis-dioxocyclams could be synthesized, they should be more robust and survive the conditions needed to reduce the amide carbonyls. If this could be accomplished, a new class of potentially anti-HIV active compounds could be synthesized. In order for alkyl-linked bis-dioxocyclams to be synthesized, alkyl-linked bis-chromium carbene complexes must first be prepared (Figure 1.17).

1.5 Results and Discussion:

1.5.1 Synthesis of Alkyl-linked Bis-Chromium Carbene Complexes

Unfortunately, there were only a few examples of carbon-linked bis-carbene complexes in the literature. Tungsten aminocarbene complexes were alkylated via deprotonation of the α-

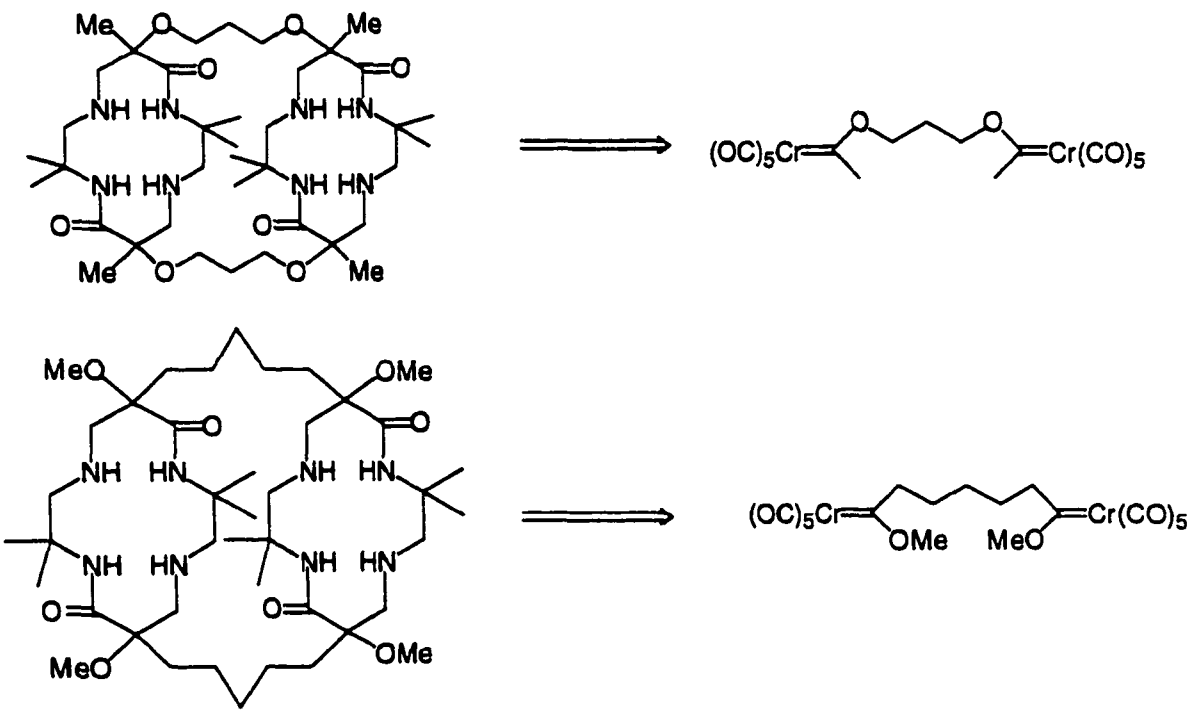


Figure 1.17

carbon with butyllithium and treatment with diiodo alkanes to give the bis-carbene complexes in moderate to good yields.[106] Bis-tungsten alkoxycarbene complexes with an isolated carbon-carbon double bond have been prepared via a metathesis reaction.[107] More recently, both tungsten and chromium bis-carbene complexes have been prepared using an α,β-unsaturated carbene complex as a Michael acceptor, and an α-anion of the carbene complex as the Michael donor.[108] Chromium carbene complexes also participate in Aldol-type reactions with non-enolizable aldehydes to give unsaturated bis-carbene complexes.[109] When aromatic bis-aldehydes were used, highly conjugated bis-carbene complexes were produced. Wulff recently extended this methodology to enolizable aldehydes

using $SnCl_4$ as a Lewis acid, although the yields were only moderate.[110]

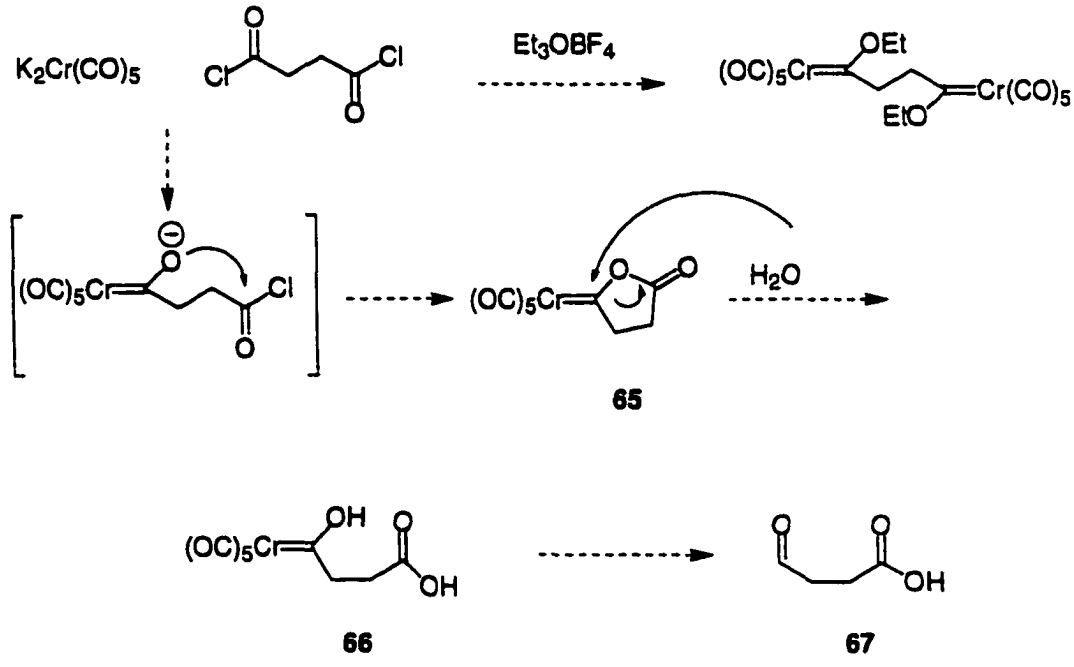
1.5.1a From Acid Chlorides

Acid chlorides can be transformed into chromium carbene complexes with $K_2Cr(CO)_5$ and Et_3OBF_4. Since there are many available bis-acid chlorides, it was believed this would be the most logical place to start.

The first substrate tried was succinyl chloride. When the dianion was treated with succinyl chloride, no desired product was isolated. The reaction mixture turned yellow after treatment with Et_3OBF_4, indicating a chromium species of some sort had been formed, but it quickly decomposed.

A possible decomposition pathway for this reaction is given in Scheme 1.8. If only one acid chloride was attacked by the chromium dianion, the resulting oxygen anion could attack the other acid chloride moiety to form **65**. Mixed-anhydride chromium species of this type are very reactive at the carbene carbon and any nucleophile could displace the carboxylate. Attack of this species with water could form hydroxycarbene complex **66**. Hydroxycarbene complexes are known to decompose into the corresponding aldehydes.

When the carbon chain was lengthened by two carbons by using adipoyl chloride, the desired 1,6-bis-carbene complex **68** was

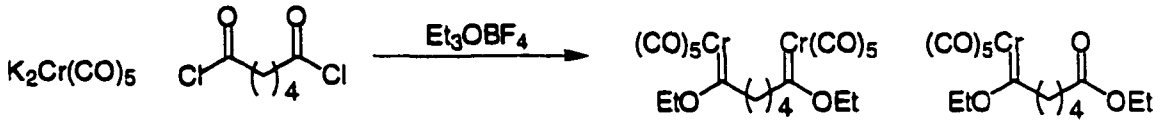


Scheme 1.8

isolated, albeit in low yield. When the reaction was kept at -78 °C, **68** was isolated in erratic yield, but no better than 28%, along with varying amounts of the mono-ester **69**. Warming the reaction mixture immediately from -78 °C to 0 °C resulted in the isolated yield being reduced to 6%. Increasing the temperature from -78 °C to room temperature resulted in no desired product. Conditions could not be developed to give consistent yields above 28% (Table 1) and so another route to bis-carbene complexes was attempted.

1.5.1b From Bis-lithio Compounds

When $Cr(CO)_6$ was treated with an alkyllithium, followed by a hard alkylating reagent, such as Me_2SO_4, chromium carbene complexes were produced. Polylithio anions are difficult to prepare



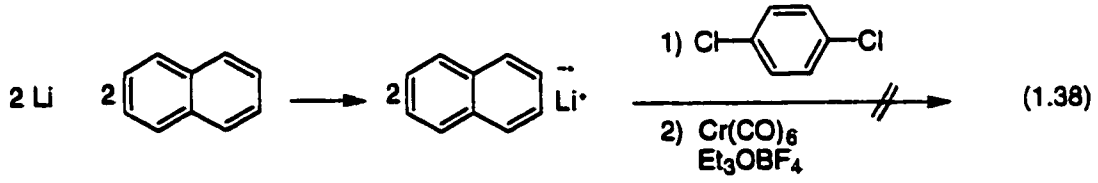
28%

68 69

Time	Temperature	Yield **68**
1 hour	-78 °C	0-28%
1 hour	-78 °C -->0 °C	6%
1 hour: 1 hour	-78 °C -->0 °C	17%

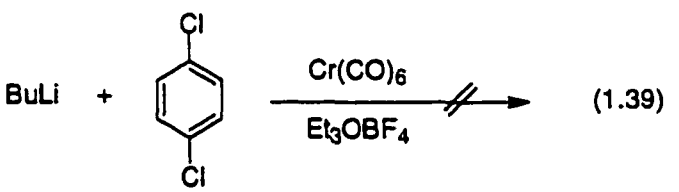
Table 1

due to their inherent instability even at low temperatures. Naphthalene has been shown to catalyze the lithium-halogen exchange with aryl chlorides.[111] For example, lithium metal reacts with chlorobenzene only at temperature above -55°C. This anion then reacts with pivalaldehyde to give the alcohol in 76% yield. Addition of 3% naphthalene gives the same alcohol in 98% yield after 45 minutes at -78°C. Lithium-halogen exchange of dichlorobenzene was catalyzed by naphthalene to give a stepwise addition of two electrophiles in good yield. If an aryl bis-anion could be synthesized, either as a dianion or stepwise, it should react with $Cr(CO)_6$ to form bis-carbene complexes.



(1.38)

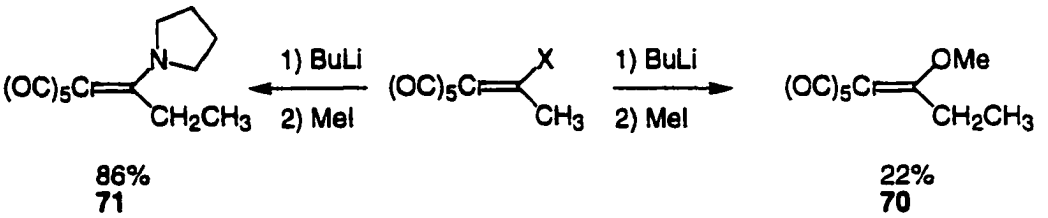
Treatment of lithium naphthanelide with p-dichlorobenzene and then with $Cr(CO)_6$ followed by Et_3OBF_4 did not result in the formation of a bis-carbene complex and only unidentified products were isolated (equation 1.38). A lithium-halogen exchange was attempted with p-dichlorobenzene and *n*-butyllithium, but no product was isolated (equation 1.39). Due to these initial setbacks, this route was abandoned for a more promising pathway to bis-chromium carbene complexes.



(1.39)

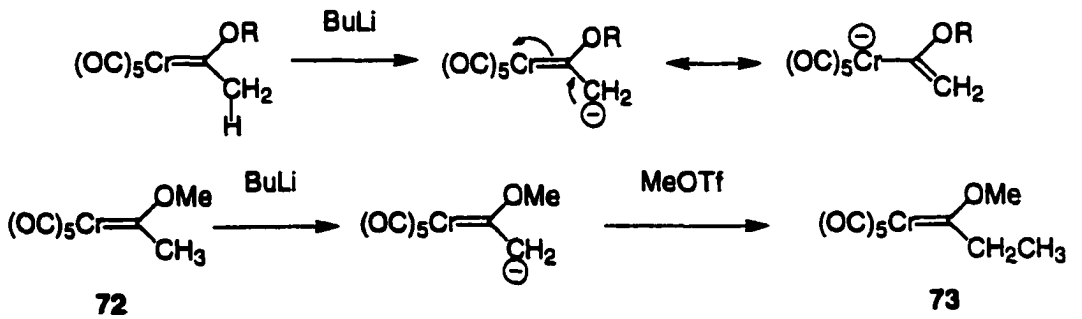
1.5.1c From α-alkylation

Deprotonation of the α-carbon of chromium carbene complexes, followed by alkylation is another method of generating new chromium carbene complexes. Wulff has shown aminocarbene complexes were alkylated at the α-position by treatment with a strong base and an electrophile.[112] Alkoxycarbene complexes were not as reactive and only the most reactive electrophiles were able to alkylate these anions.[113] This reactivity difference paralleled the ability of the heteroatom to donate electron density from its lone pair into the carbon-metal bond. For example, methoxy(methyl) chromium carbene complex was alkylated by methyl iodide in only 22%[112] yield whereas pyrrolidinyl(methyl)chromium carbene complex was alkylated with methyl iodide in 86% yield (equation 1.40).[111]



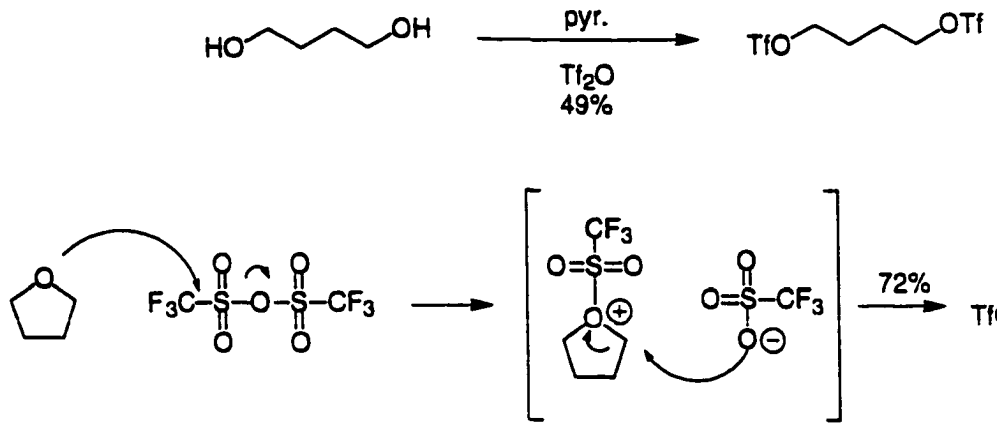
(1.40)

Treatment of the α-anion of a chromium carbene complex with a bis-electrophile should give bis-chromium carbene complexes. Ethoxy- or methoxy(methyl)chromium carbene complex was deprotonated with *n*-butyllithium to give the resulting anion. This anion was deep red in color due to the delocalization of the electrons into the pentacarbonyl fragment. This anion was treated with a variety of bis-electrophiles and the resulting products were isolated. When the α-anion of ethoxy(methyl)chromium carbene complex was treated with 1,6-dibromo- and diiodohexane, no reaction occurred and only starting material was recovered. When benzyl bromide or α,α'-bis-bromo-m-xylene was used, very little, if any product was observed. When **72** and methyl triflate were used, however, an 88% of the ethyl(methoxy)carbene complex was isolated (equation 1.41).



(1.41)

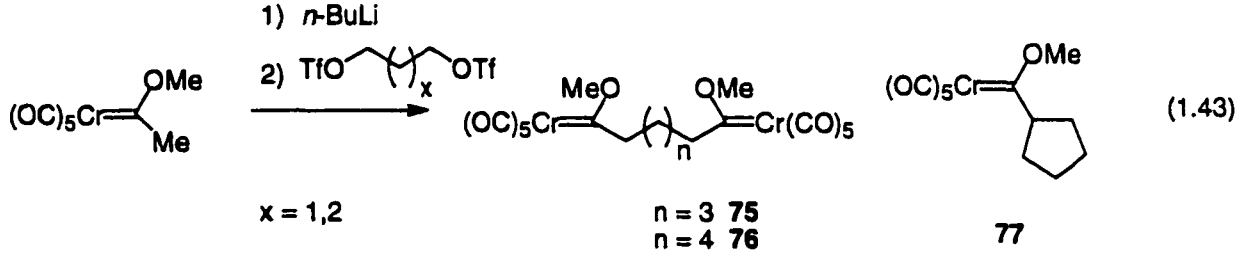
With the success of alkylating methoxy(methyl) chromium carbene complex with methyl triflate, a (1,n)-alkyl bis-triflate was



needed. Treatment of 1,4-butanediol with trifluoromethanesulfonic anhydride and pyridine gave the desired 1,4-bis(trifluoromethanesulfonyl)butane in 49% yield as a crystalline solid. However, THF reacts with trifluoromethanesulfonic anhydride to give 1,4-bis-(trifluoromethanesulfonyl)butane in greater than 70% yield (equation 1.42).[114] There are a number of advantages for using THF as the carbon atom source. First, it is easier to dry THF than it is to dry 1,4-pentanediol. Secondly, there is no pyridine needed and thirdly, only one equivalent of trifluoromethanesulfonic anhydride was required instead of the two equivalents needed for the 1,4-butanediol.

When the α-anion of (methoxy)(methyl)chromium carbene complex was treated with an excess of 1,4-bis(trifluoromethanesulfonyl)butane, the yields of the bis-carbene complex were low and a large amount of cyclized carbene complex **77** was formed. Complex **77** was the product of α-dialkylation, and could not be completely freed of starting material (equation 1.43). Inverse addition, for which the anion was added to a solution of the triflate, only

increased the amount of **77** isolated. Taking these results into consideration, the triflate had to be added to a large excess of the α-anion. This reduced the amount of cyclized carbene complex significantly. It was also found as the concentration of the triflate decreased, the amount of **77** decreased and the amount of **76** increased. Decreasing the concentration of the triflate decreased the effective rate of addition. Using this method, consistent yields of 60% were obtained (Table 2). This method was also scalable up to 1 gram of triflate without a reduction in the yield.



(1.43)

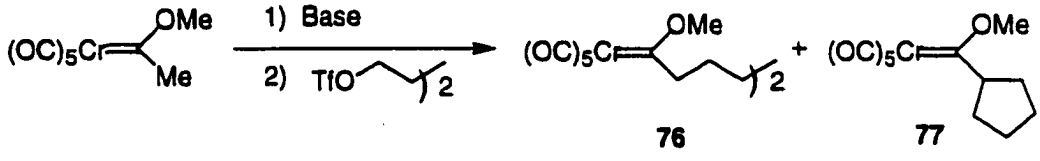
M of triflate	yields **76**
0.56 M	7 %
0.07 M	30 %
0.015 M	70 %

Table 2

When 1,3-bis(trifluoromethanesulfonyl)propane was used, the yield dropped to 30% and no cyclized carbene complex was observed. The use of 1,2-bis(trifluoromethanesulfonyl)ethane gave no desired product. The reduction in yield for the 1,3- and 1,2-bis-triflates may be due to the instability or the purity of the triflates. Although these compounds were crystalline solids at 0°C, they quickly melted at

room temperature, which made them difficult to purify and could facilitate their decomposition.

Lithium cations are known to form tight ion pairs with oxygen anions, decreasing their nucleophilicity. Perhaps the lithium was forming a tight ion pair with either the chromium or carbon. To test this, KHMDS was used as a base instead of butyllithium (Table 3). This only decreased the amount of desired product isolated. In another attempt to increase the reactivity of the α–anion, lithium sequestering agents were added to the reaction mixture. The use of HMPA and TMEDA did not result in any of the desired product but



76 77

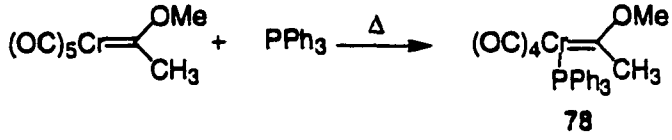
Base	Additives	76	77
KHMDS	----	19 %	(a)
nBuLi	HMPA	0 %	(a)
nBuLi	TMEDA	0 %	(a)
nBuLi	12-crown-4	17 %	72 %

(a) not determined

Table 3

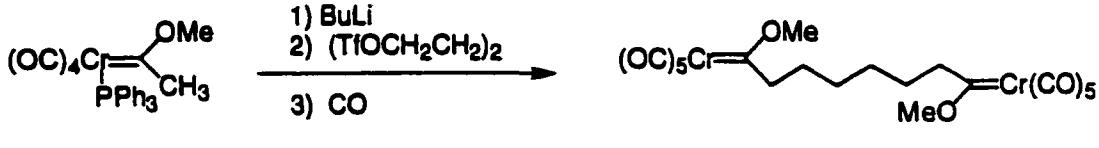
only a mixture of starting material and **77**. When 12-crown-4 was added, the amount of desired product dropped to 17% while the amount of cyclized carbene complex, **77**, increased to 72%.

Carbon monoxide ligands are strongly π-accepting and stabilize a negative charge on the chromium by delocalizing electron density away from the metal. Increasing the electron density on the



78 (1.44)

chromium by substituting a triphenylphosphine for a CO would make the α-protons less acidic and the resulting anion more nucleophilic. Treatment of methoxy(methyl)chromium carbene complex with Ph_3P in 3:1 benzene:hexane gave the tetracarbonyl(triphenylphosphine) carbene complex, **78** (equation 1.44).[113] When **78** was subjected to the conditions developed for alkylating (methoxy)methylchromium carbene complex (**74**, dilute conditions), the reaction gave an inseparable mixture of the desired 1,6-bis-triphenylphosphine substituted bis-carbene complex and **78**. The PPh_3 was displaced by CO under moderate pressure to give **76** and PPh_3. This mixture was then purified by column chromatography (equation 1.45). Unfortunately, the yields for the three steps were not significantly better than the yields for deprotonation of methoxy(methyl)-chromium carbene with *n*-BuLi and alkylation of that anion with bis-triflates.

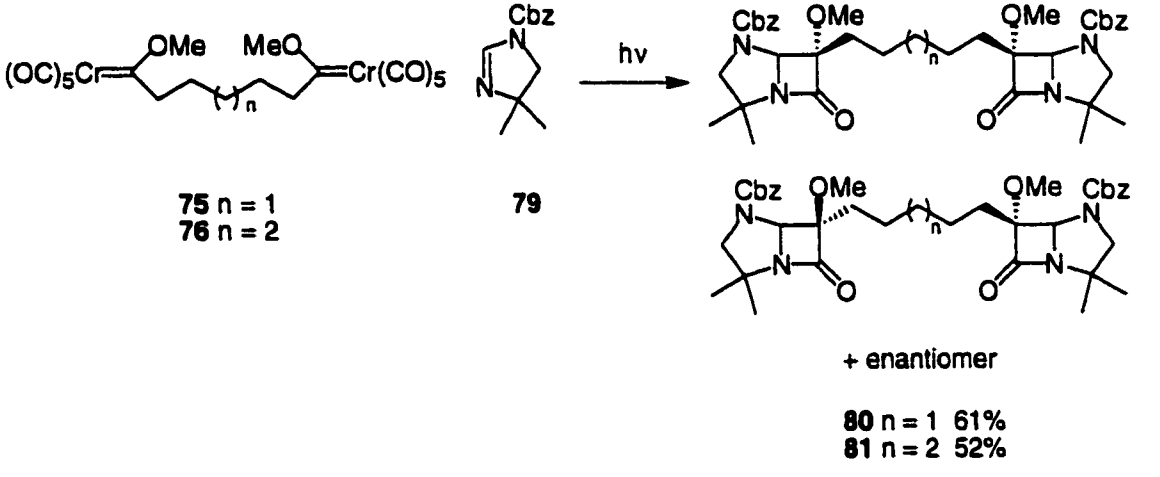


76 (1.45)

1.5.2 Photochemistry of Bis-Chromium Carbene Complexes

The photochemistry of chromium carbene complexes has been well-studied by the Hegedus group.[35] When chromium carbene complexes are irradiated in the presence of N-protected imidazolines, azapenams are produced. When the reaction is run under CO pressure, $Cr(CO)_6$ can be recovered and reused.

Irradiation of **75** and **76** with gem-dimethyl imidazoline, **79**, gave the protected azapenams, **80**,**81** in good yield (equation 1.46). This reaction was either run at room temperature or at 50°C (above 50°C, the carbene complexes decomposed). The elevated temperature only decreased the amount of time needed to complete the reaction. This photoreaction was also carried out with chiral



75 n = 1
76 n = 2

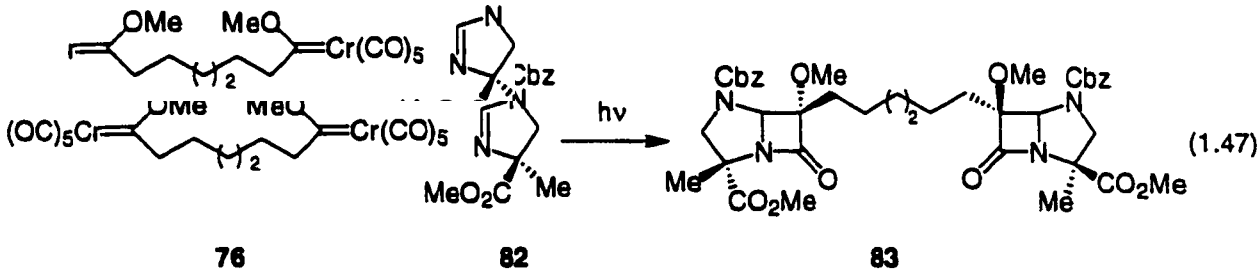
79

+ enantiomer

80 n = 1 61%
81 n = 2 52%

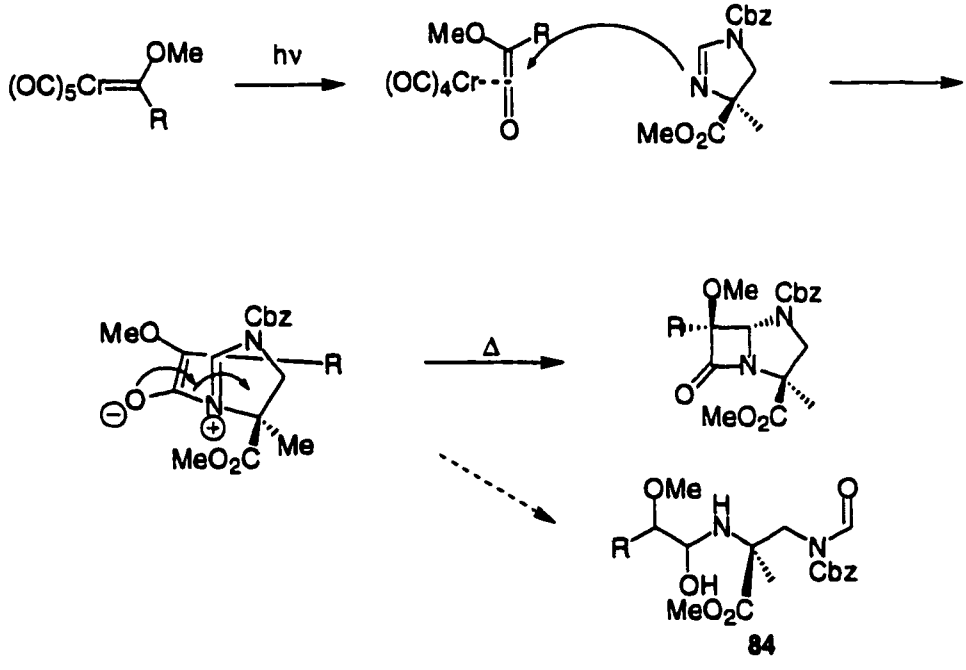
(1.46)

imidazoline, **82**, to give one diastereomer of protected azapenam **83** in moderate yield (equation 1.47). The use of the chiral imidazoline required the reaction to be run at elevated temperatures to ensure good yields. If the reaction were run at room temperature, an acyclic by-product, **84**, coming from non-ring closure of the zwitterionic



76 82 83

species, could be detected. The reaction is believed to proceed by a stepwise mechanism with attack of the imine on the ketene intermediate followed by conrotary ring closure (Scheme 1.9).



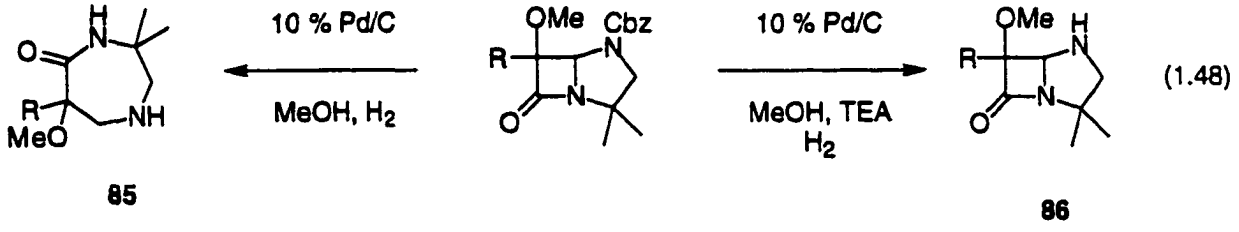
84

Scheme 1.9

1.5.3 Dimerization of Free-Azapenams

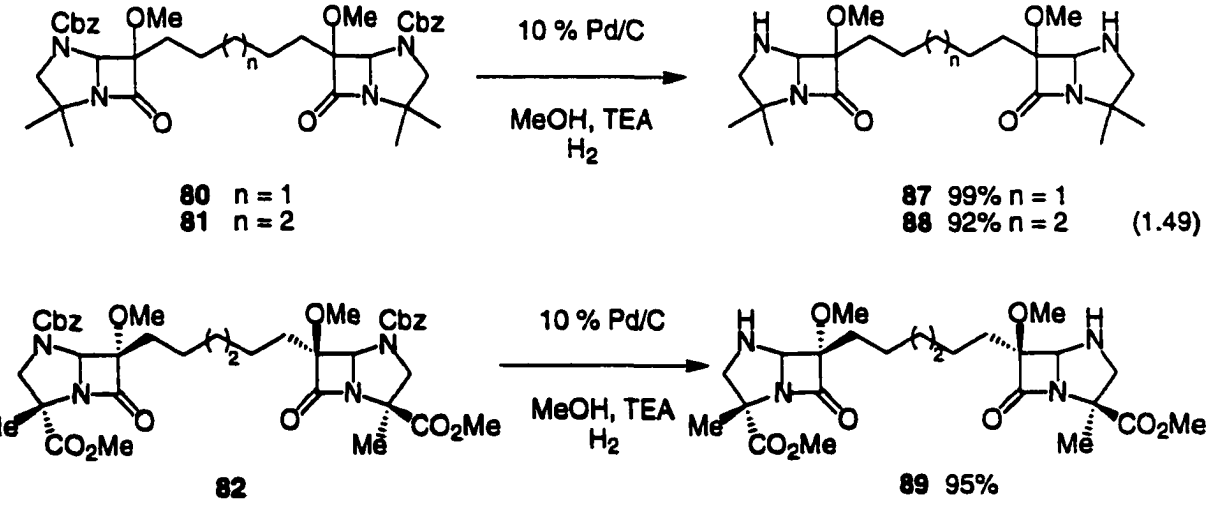
Using the standard conditions for the hydrogenolysis of the Cbz protecting group, hexahydrodiazapinones were produced instead of free azapenams.[114] These were believed to be formed by acid-catalyzed ring opening to a seven-membered imine which was then reduced to give compounds like **85**. It was found that hydrogenol-

ysis in the presence of triethylamine gave free azapenams, **86** (equation 1.48).



85 **86**

Using these basic conditions, hydrogenolysis of azapenams **80**, **81**, **82** produced the free azapenams **87**, **88**, **89** in excellent yield (equation 1.49). Treatment of free azapenams **87** and **88** with (±)-CSA for five days resulted in the formation of tetraazamacrocycles **91** and **92**, in 35% and 41% yield respectively (equation 1.50). Compound **89** under the same conditions gave bis-imine cyclam **93**



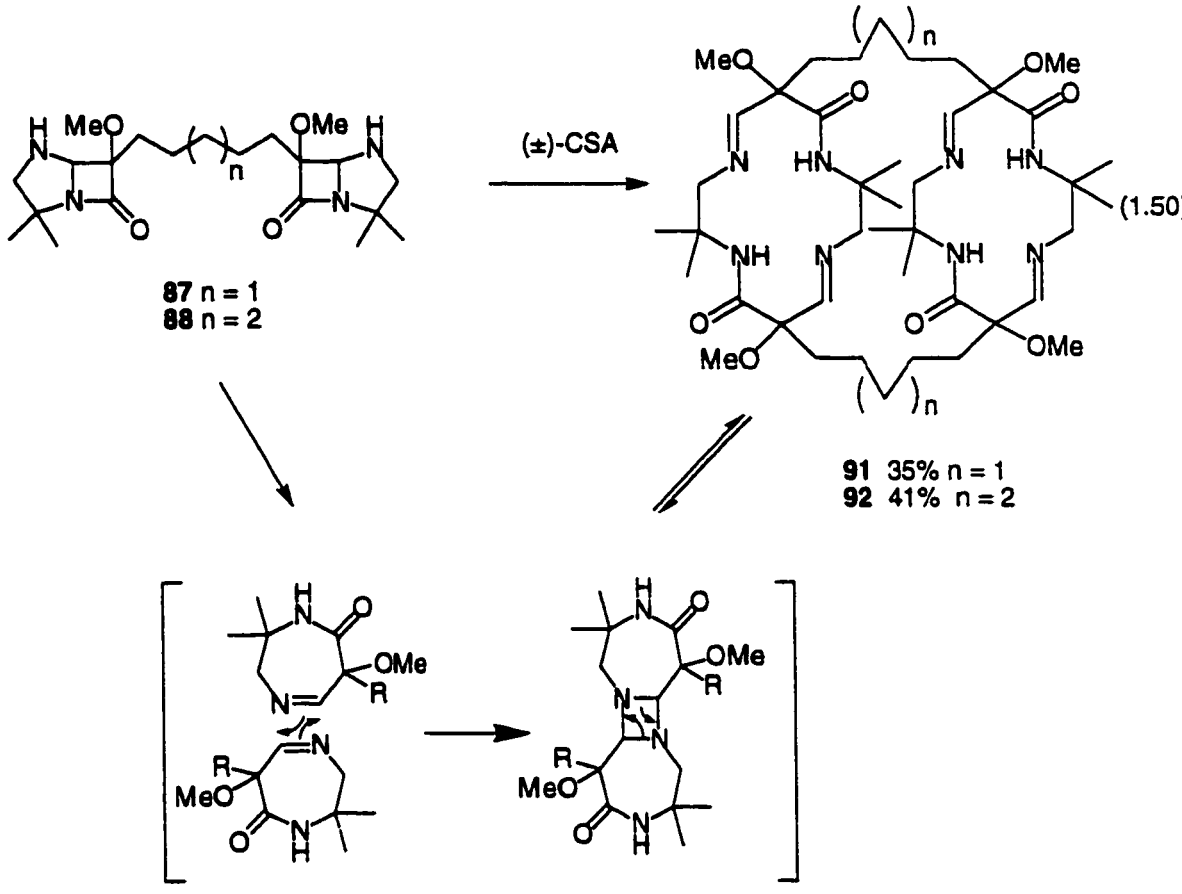
80 n = 1
81 n = 2

87 99% n = 1
88 92% n = 2

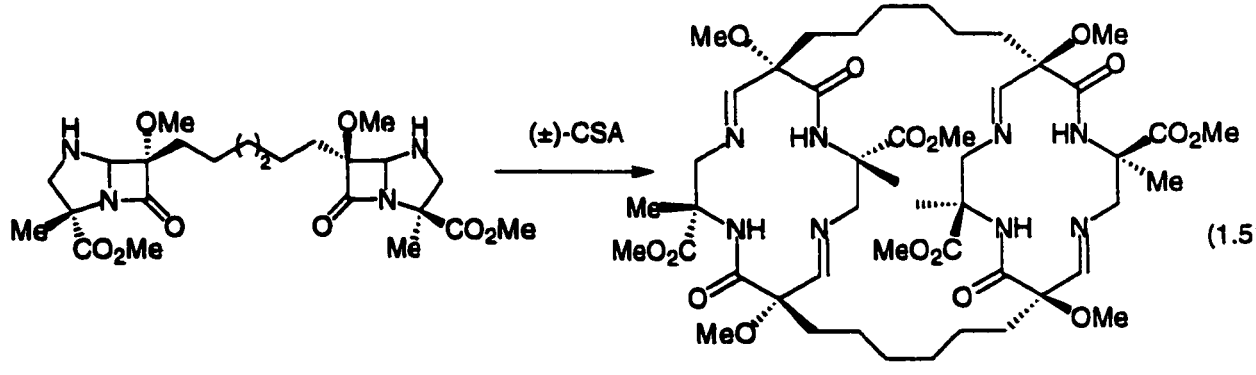
82

89 95%

in 48% yield (equation 1.51). These compounds were believed to be formed via acid catalyzed ring opening of the azapenam to the seven membered imine. This imine then underwent a head-to-tail [2+2]



dimerization followed by a retro [2+2] ring expansion to give the 14-membered tetraazamacrocycles.



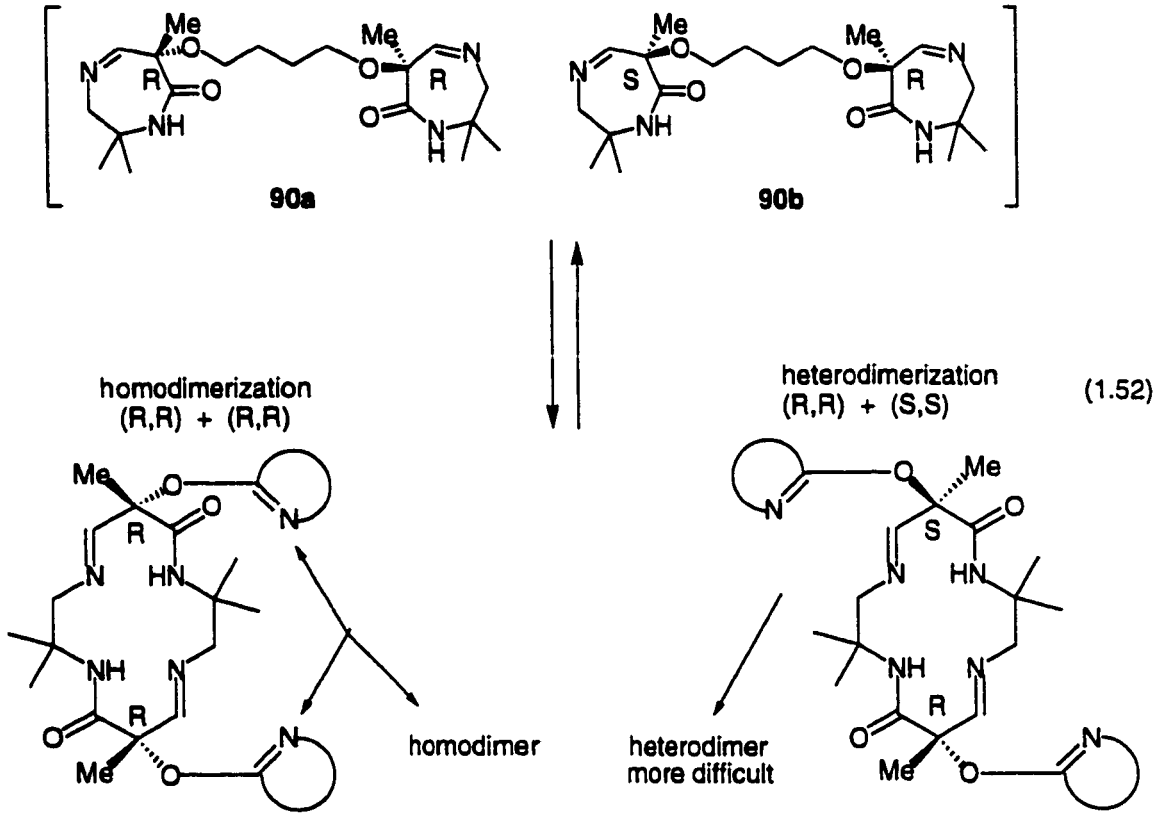
89

93
48%

Alkoxy-linked bis-azapenams showed a strong tendency to dimerize with molecules of like stereocenters. Treatment of a racemic mixture of alkoxy-linked bis-azapenams with (±)-CSA resulted in three diastereomers: the (R,R,R,R), (S,S,S,S) (d,l) pair and the (R,R,S,S) meso compound. When an (R) or (S) **90a** dimerized with another (R) or (S) **90a**, the resulting imine cyclam had the two remaining seven-membered imines on the same face of the cyclam ring (equation 1.52). This facilitated dimerization of these two moieties producing a homodimer (where all four stereocenters have the same configuration). This pathway can also happen when an (R,S) **90b** dimerized with another (R,S) **90b**.

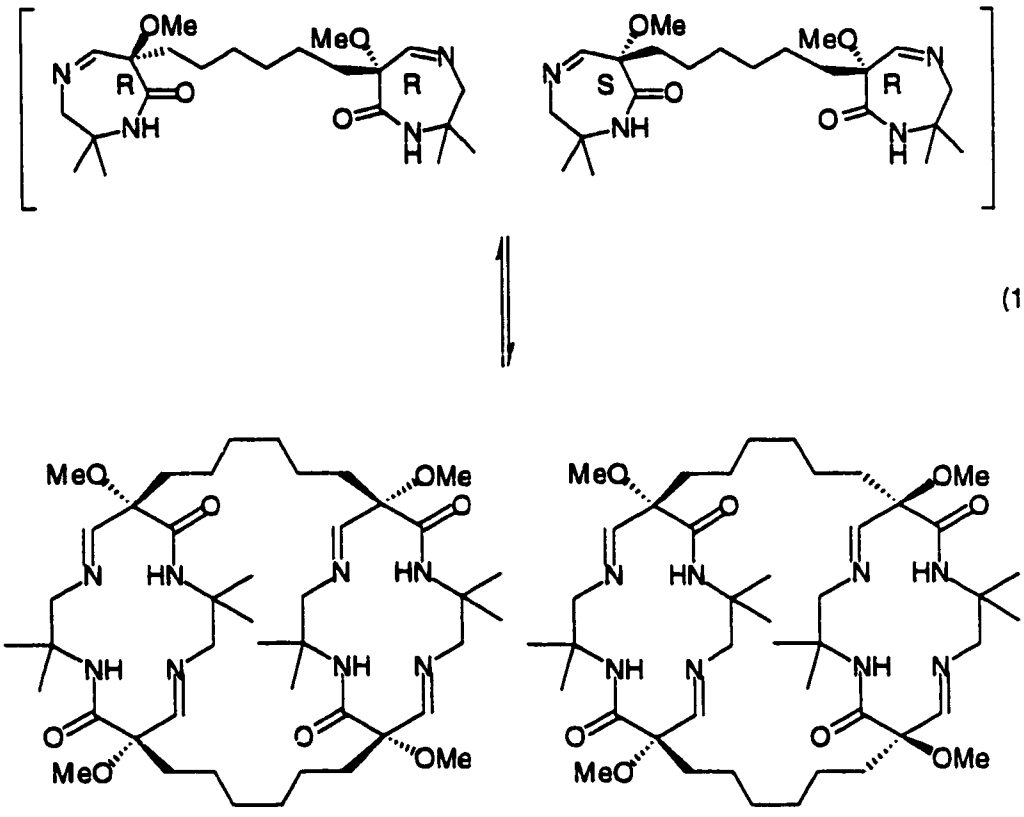
When an (R) **90a** dimerized with an (S) **90b**, the resulting imine cyclam has the two seven-membered imines on opposite sides of the cyclam ring (equation 1.52). This heterodimer cannot easily dimerize the remaining imines. Since the process is reversible, the heterodimer reverts back to the seven-membered imine and dimerizes with another molecule of the same stereochemistry to undergo a homodimeriztion.

This analogy can be applied to the alkyl-linked bis-dioxocyclams. The ^{1}H- and ^{13}C-NMR spectra of **91** clearly showed that it was a mixture of diastereomers, but these could not be separated by conventional techniques. Compound **92**, however, only exhibited one set of peaks in both the ^{1}H and ^{13}C-NMR spectra. Although it had one set of peaks, it had to be a mixture of diastereomers (equation 1.53). These diastereomers also could not be separated. This behavior was likewise seen with the dioxocyclams linked with long chains in the alkoxy-linked series.[104]



Since **89** existed as a single diastereomer, only one diastereomer was expected and observed.

Reduction of the imine bonds would freeze the equilibrium and give stable dioxocyclams. Treatment of imine-cyclams **91,92** with $Na(CN)BH_3$ under acidic conditions, resulted in decomposition of the compound (equation 1.54). The same conditions applied to **93** also resulted in decomposition of the compound (equation 1.55). Other imine cyclams have been reduced with catalytic Pd/C and H_2, however, these conditions only returned unchanged starting material when applied to **91**, **92**, and **93**. Due to the inability to reduce these imines and that the diastereomers could not be separated, further studies on these compounds were halted.

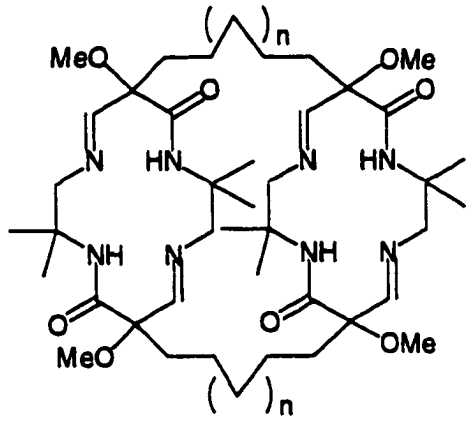


(1.53)

1.6 Conclusions

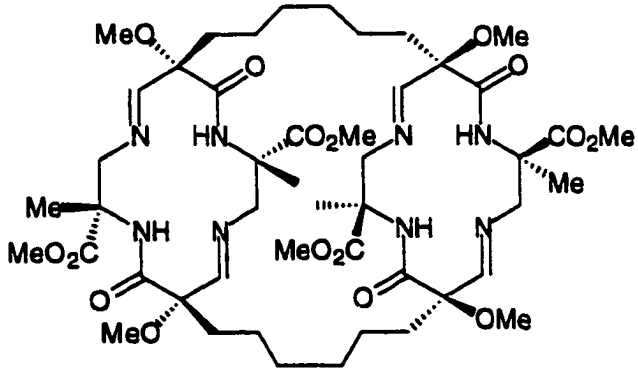
A route to alkyl-linked bis-chromium carbene complexes has been developed via α–alkylation of (methoxy)(methyl)chromium carbene complexes using bis-triflates as the electrophile. These bis-carbene complexes were synthesized in good yield as long as the carbon chain length was longer than four units. The 1,5- and 1,6-bis-carbene complexes were readily synthesized using up to 1 gram of bis-triflate. These chromium carbene complexes smoothly underwent the photoreaction with chiral and achiral imidazolines to produce N-protected azapenams. Removal of the protecting group and dimerization proceeded without problem to yield the bis-imine

bis-dioxocyclams. Unfortunately, the imines were unable to be reduced and the alkyl-linked bis-dioxocyclams were not accessible.



91 n = 1
92 n = 2

$NaCNBH_3$, H^+, $Pd/C\ H_2$ → decomp. or starting material (1.54)



93

$NaCNBH_3$, H^+, $Pd/C\ H_2$ → decomp. or starting material (1.55)

1.7 Experimental

Experimental Section

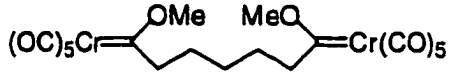
General Procedures: All NMR spectra (300 MHz for ^{1}H-NMR and 75 MHz, for ^{13}C-NMR) were recorded in $CDCl_3$ and chemical shifts are given in δ relative to TMS (δ 0.00 for ^{1}H) and $CDCl_3$ (δ 77.0 for ^{13}C) unless otherwise stated. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR. Mass specta were recorded on a Fisons Instraments VG autospec. THF was distilled from sodium-benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2; MeOH was stored over 3 Å sieves prior to use. Column chromatography was performed with ICN 32-63 nm, 60 Å silica gel. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. The following compounds were prepared according to literature methods: pentacarbonyl(methoxy)(methyl)carbene chromium[115], 1,4-bis(trifluoromethanesulfonoyl)butane[116].

1,3-bis(trifluoromethanesulfonoyl)propane

Into a dry addition funnel attached to a 100 mL round bottomed flask was placed 1.0 g (13.8 mmol) of 1,3-propanediol, 2.3 g (29.1 mmol) of pyridine and 13 mL of CH_2Cl_2. Into the flask was placed 8.2 g of trifluoromethanesulfonoyl anhydride and 25 mL CH_2Cl_2. The flask was cooled to 0 °C under Ar. The diol solution was added dropwise to the anhydride. The solution was then warmed to room

temperature for 1 hour. The organic solution was washed with water (2x20 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to yield 3.2 g (9.3 mmol 71%) of a clear oil. This highly reactive material was used without further purification. ^1H-NMR: δ 4.6 (t, *J*=5.5 Hz, 4H), 2.4 (p, *J*=5.5 Hz, 2H).

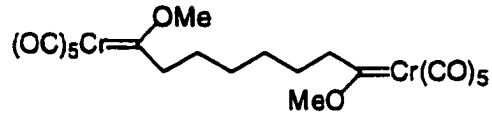
Bis-carbene complex 75



Into a dry 1L 2-necked round bottomed flask with an attached addition funnel was placed 1.6 g (6.5 mmol) of methoxy(methyl)carbene complex and 130 mL of dry ether. To the addition funnel was added 1.0 g (2.9 mmol) of the 1,3-bis(trifluoromethanesulfonoyl)propane and 250 mL of dry ether. The flask was cooled to -78°C under argon and 4.2 mL (6.7 mmol) of *n*-BuLi was added via syringe. The solution was stirred for 20 minutes, followed by the addition of trifluoromethanesulfanate over 2 hours. The reaction was then warmed to 0°C for 2 hours. The reaction was washed with 300 mL 5% $NaHCO_3$ (aq), 300 mL water, and 300 mL brine. The organic layer was dried over Na_2SO_4. After filtration, the solvent was removed under reduced pressure in the dark and the residue was purified quickly using flash chormatography (silica gel) eluting with hexanes to 2% ethyl acetate/hexanes to yield 483 mg (0.894 mmol, 30%) of a yellow oil. ^1H-NMR: δ 4.7 (brs, 6H), 3.2 (t, 4H, *J*= 7.5 Hz), 1.5-1.3 (m, 6H). ^{13}C-NMR: δ 363.0, 222.9, 216.0, 67.0, 62.0, 28.6, 25.5. IR (thin film): ν

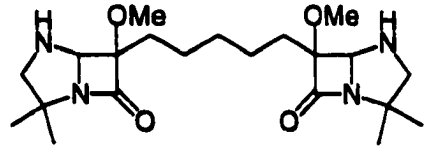
2953, 1946 cm^{-1}. HRMS (FAB) m/z calculated for $C_{19}H_{16}Cr_2O_{12}$ (M+) 539.9452 found 539.9458.

Bis-carbene complex 76



Bis-carbene complex **76** was synthesized by a method similar to that of **75** starting with 1.6 g (6.2 mmol) of methoxy(methyl)carbene complex in 124 mL of dry ether, 1.0 g (2.8 mmol) of 1, 4-bis(trifluoromethanesulfonoyl)butane in 250 mL of dry ether and 3.9 mL (6.2 mmol) of *n*-BuLi to yield 1.0 g (1.8 mmol, 63%) of product as a yellow solid. ^{1}H-NMR: δ 4.8 (s, 6H), 3.3 (t, 4H, *J*= 7.5 Hz), 1.25-1.6 (m, 8H). ^{13}C-NMR: δ 363, 223, 216, 67.6, 62.8, 28.8, 26.0. IR (thin film): ν 2062, 1932 cm^{-1}. Elemental Analysis: calculated for $C_{20}H_{18}Cr_2O_{12}$. theoretical: C 43.33 H 3.27: Found: C 43.35 H 2.91.

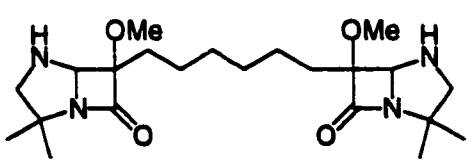
Bis-Azapenam 87



Into a dry 125 mL Ace pressure tube was placed 0.30 g (0.56 mmol) of **75**, 0.25 g (1.06 mmol) of imidazoline **79**, and 22 mL of CH_2Cl_2. This mixture was freeze-pump-thaw degassed three times. It was then flushed with 80 psi CO three times and pressurized with 80 psi

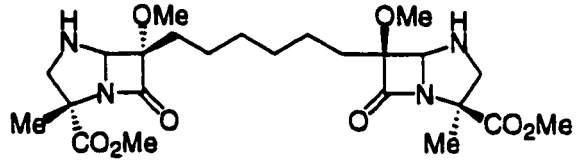
CO This was then irradiated (4 x 500 W halogen lamps) at 50°C until the yellow color had faded (about 6 hours). The solvent was removed and the residue was dissolved into methanol and placed into the freezer. The $Cr(CO)_6$ precipitated and was removed by filtration and the solvent was removed under reduced pressure. This residue was dissolved in 1:1 hexane:ethyl acetate and exposed to air and sunlight (2 days or until clear). The solution was filtered and the solvent was removed. Purification was accomplished by flash choromatography (silica gel) using 1:1 hexane:ethyl acetate to yield 0.24 g (0.35 mmol, 62%) product. The bis-azapenam, 0.34 g (0.50 mmol) was dissolved in 25 mL of dry MeOH along with 200 mg of Pd/C (5%) and 30 drops of triethylamine. The pressure tube was charged with 80 psi H_2 and stirred at room temperature for 2 hours. The palladium was removed by filtration and the solvent was removed to give 0.20 g (0.49 mmol, 99%) of a white solid. ^{1}H-NMR: δ 6.5 (s, 2H), 3.41, (s, 6H), 3.1 (d, *J*=11.4 Hz, 2H), 2.62, (d, *J*=11.4Hz, 2H), 2.2; (brs, 2H), 1.7-1.1, (m, 24H). ^{13}C-NMR: δ 175, 91.8, 77.2, 62.1, 60.7, 53.3, (30.4, 30.3), (28.2, 28.1), 25.0, (22.3, 22.2), 21.7. IR (thin film): v 1747 cm^{-1}. HRMS (FAB) m/z calculated for $C_{21}H_{37}N_4O_4$ (M+1) 409.2815 found 409.2804.

Bis-Azapenam 88:



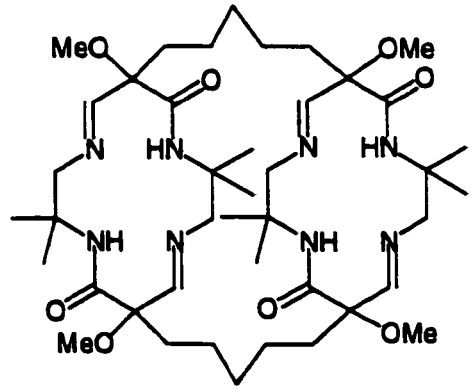
Into a dry pressure tube was placed 0.75 g (1.3 mmol) of bis-carbene **76**, 0.59 g (2.6 mmol) of imidazoline **79**, and 130 mL of dry CH_2Cl_2. This was degassed using the freeze-pump-thaw method 3 times. It was then flushed with CO (80 psi) 3 times, pressured with 80 psi CO and irradiated (450-W Conrad-Honovia 7825 medium pressure mercury lamps with a Pyrex well) until the yellow color had faded (about 24 hours). The solvent was removed and the residue was dissolved into methanol and placed into the freezer. The precipitated $Cr(CO)_6$ was removed by filtration and the solvent was removed under reduced pressure. This residue was dissolved in 1:1 hexane:ethyl acetate and exposed to air and sunlight (2 days or until clear). The solution was filtered and the solvent was removed. Purification was accomplished by flash chromatography (silica gel) using 1:1 hexane:ethyl acetate to yield 0.38 g (41%) of the N-protected bis-azapenam. The bis-azapenam was dissolved in 25 mL of dry methanol, along with 190 mg of Pd/C (5%) and 25 drops of triethylamine. The tube was filled with 80 psi of H_2 and stirred 1 hour at room temperature. The palladium was removed by filtration and the solvent was removed to give 0.23 mg (0.54 mmol, 92%) of a white solid. ^{1}H-NMR: δ 4.7 (s, 2H), 3.4 (s, 6H), 3.06, (d, J=11 Hz, 4H), 2.66, (d, J= 11 Hz, 4H), 2.2 (s, 2H), 1.6-1.1 (m, 24 H). ^{13}C-NMR: δ 175, 91.9, 77.2, 57.7, 56.2, 48.9, 25.4, 23.9, 20.5, 18.0, 17.4. IR (thin film): ν 1747, 1731 cm^{-1}. HRMS (FAB) m/z calculated for $C_{22}H_{39}N_4O_4$ (M+1): 423.2971, found 423.2962.

Bis-Azapenam 89



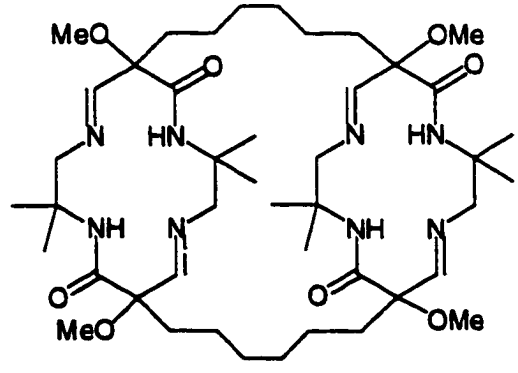
Azapenam **89** was synthesized using the exact method as for **88** starting with 0.55 g (0.99 mmol) of **76**, 0.52 g (1.88 mmol) of **82**, and 33 mL of CH_2Cl_2 to yield 0.33 g (0.42 mmol, 42%) of product. The protecting group was subjected to hydrogenolysis in the same way as for **76** starting with 0.33 g (0.42 mmol) of bis-azapenam, 160 mg of Pd/C (5%), 20 drops of triethylamine and 20 mL of MeOH to yield 0.20 g (0.40 mmol, 95%) of a white solid. ^{1}H-NMR: δ 4.86, (s, 2H), 3.77, (s, 6H), 3.69, (d, J=12 Hz, 2H), 3.50, (s, 6H), 2.74, (d, J=12 Hz, 2H), 1.78 (s, 6H), 1.7-1.3, (m, 14H). ^{13}C-NMR: δ 174.6, 171.9, 92.2, 79.2, 65.9, 60.7, 53.4, 52.6, 29.7, 28.2, 22.3, 17.2. IR (thin film): ν 1754, 1736 cm^{-1}. HRMS (FAB) m/z calculated for $C_{24}H_{39}N_4O_8$ (M+1) 511.2768 found 511.2752.

Bis-Dioxotetraazacyclotetradecadiene 91:



The bis-azapenam, **87**, 0.20 g (0.50 mmol) was dissolved in 60 mL of dry CH_2Cl_2. To this was added 70 mg of racemic camphorsulfonic acid and the solution was stirred at room temperature for 5 days. The organic layer was washed one time with 50 mL 5% $NaHCO_3$ (aq). This aqueous layer was extracted 2X 20mL CH_2Cl_2. The organic layers were combined and dried over Na_2SO_4, filtered and the solvent was removed. The residue was purified by flash chromatography (basic alumina) eluting with 98:2 CH_2Cl_2: CH_3OH to yield 81 mg (0.10 mmol, 35%) as a white solid. ^{1}H-NMR (CD_2Cl_2) δ (9.75, 9.0) (s, 4H), 7.65-7.55 (m, 4H), 4.65 (m, 4H), 3.4-3.2 (m 16H), 2.2-1.0 (m 44H). ^{13}C-NMR (CD_2Cl_2): δ 169.6, 167.9, 82.5, 71.3, 37.6, 30.8, 25.4, (23.9, 23.7). IR (thin film): ν 1676, 1557 cm^{-1}. HRMS (FAB) m/z calculated for $C_{42}H_{73}N_8O_8$ (M+1) 817.5551, found 817.5537.

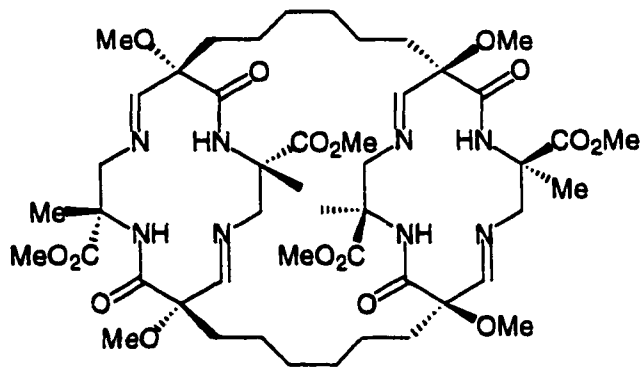
Bis-Dioxotetraazacyclotetradecadiene 92



Bis-Dioxotetraazacyclotetradecadiene 92 was synthesized according to the procedure for **91** starting with (0.23 g, 0.54 mmol) of **88**, 30

mg of camphorsulfonic acid, and 50 mL of CH_2Cl_2 to yield 83 mg (0.10 mmol, 41%) of product. ^{1}H-NMR: δ (9.87, 9.86), (s, 4H), (7.71, 7.70), (s, 4H), 3.58, (d, *J*=13 Hz, 4H), 3.3-3.2, (m, 16H), 1.8-1.1 (m, 48H). ^{13}C-NMR (CD_2Cl_2): δ 170, 168, 83.4, 70.9, 54.1, 39.1, 30.2, 25,7, 23.70, 23.66. IR (thin film): v 1681, 1555, cm^{-1}. HRMS (FAB) m/z calculated for $C_{44}H_{77}N_8O_8$ (M+1) 845.5864 found 845.5850.

Bis-Dioxotetraazacyclotetradecadiene 93



Bis-Dioxotetraazacyclotetradecadiene **93** was synthesized according to the procedure for **92** starting with 0.17 g (0.32 mmol) of azapenam **89**, 20 mg of camphorsulfonic acid, and 35 mL of CH_2Cl_2 to yield 80 mg (0.08 mmol, 48%) of product. ^{1}H-NMR: δ 9.6 (s, 4H), 7.7 (s, 4H), 4.2-3.6 (m 20H), 3.4-3.2 (m, 12H), 2.0-1.1 (m, 36H). ^{13}C-NMR: δ 172.1, 169.3, 168.7, 83.0, 60.3, 52.7, 51.5, 36.4, 34.0, 28.6, 24.8, 21.2. IR (thin film) v 1741, 1680, 1516 cm-1. HRMS (FAB) m/z calculated for $C_{48}H_{77}N_8O_{16}$ (M+1) 1021.5458, found 1021.5452.

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Chapter Two

Synthesis of Polyether-Linked Mono and Bis-Dioxocyclams

2.1 Introduction and Background

2.1.1 Introduction

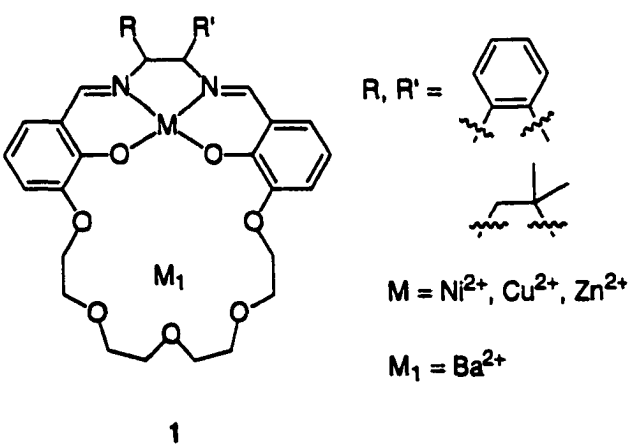
Supramolecular chemistry has been an active area of research for well over a decade.[1] It can be thought of as the organization of one molecule interacting with another molecule or ion. Supramolecular chemistry deals more with intermolecular forces, such as hydrogen bonding and van der Waals forces, than it does with molecular bonds. One of the simplest types of a supramolecule is the metal-complexed crown ether. The metal complexes of crown ethers have been well-studied, along with the metal complexes of cryptands and spherands.

More recently, molecules have been synthesized which can accommodate two or more metal ions within the same cavity. These molecules with two or more metal ions at specified distances from each other have been used to model copper proteins[2] and hemocyanin.[3] These polynuclear complexes have also been used to study the redox chemistry of two metal centers at specified

distances.[4] They have also been used to study the electron-transfer process[5] and metal-catalyzed reactions.[6] The following background provides an overview of the synthesis and properties of some di- and tri-nuclear heterometallic complexes, focusing specifically on those complexes which contain both a "hard" and a "soft" metal ion.

2.1.2 Heterodimetallic Complexes

A variety of salen-type ligands have been used to prepare hetero-dinuclear metal complexes (Figure 2.1). Structures such as **1** have a salen moiety for the complexation of the soft transition metals and usually a crown ether moiety for the hard cations.[7] Nickel, copper, and zinc have all been complexed to these ligands along with barium as the hard cation.



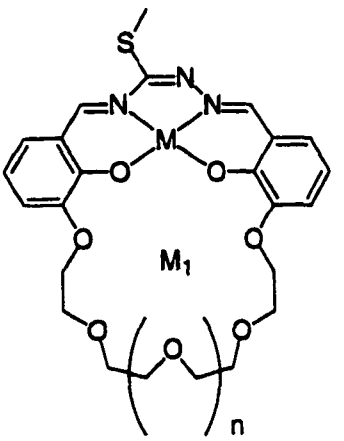
1

Figure 2.1

Complexation of barium to the copper complex caused an anodic shift of the reduction potential as compared with the barium-free compound. The barium ion reduced the electron density at the phenolic oxygens which, in turn, decreased the electron density of

the aromatic rings. This action caused the transition metal ion to become more positive; and thus reduce at a less negative potential.

Another salen-type ligand, **2a,b**, was recently described (Figure 2.2).[8] This ligand was complexed to nickel, copper and zinc



$M_1 = Na^+, Li^+, K^+, Rb^+, Cs^+$

M = Ni, Cu, Zn

n = 1 **2a**
n = 2 **2b**

Figure 2.2

along with sodium, lithium, potassium, rubidium and cesium. The most studied complexes, however, were the NiBa•**2a** and the CuBa•**2a** complexes. The NiBa complex was crystallized from methanol/THF and pentane. It was elucidated from the crystal structure of NiBa•**2a**, that the complex had formed a dimer. The two barium ions in the crown ether moiety were bridged to each other through two triflate anions. The nickel ions were positioned opposite each other as in Figure 2.3.[9] The ZnBa•**2a** analog has also been crystallized.[10] The crystal structure was very similar to that of the NiBa with the addition of I^- to the apical coordination position of the zinc.

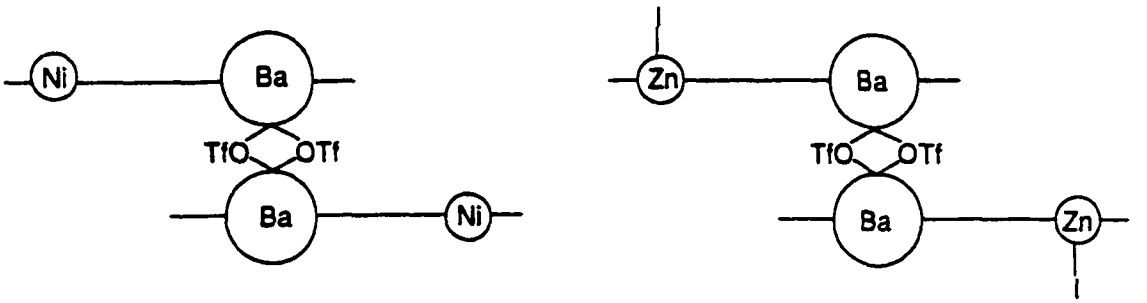
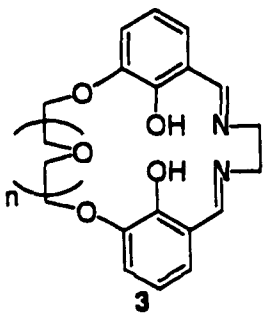


Figure 2.3

A crystal structure of the NiBa•**2b** was solved by using I_3^- and I^- as the counterions instead of triflates.[2] This formed a monomeric structure with three additional methanol molecules in the crystal lattice. The barium was bonded to ten oxygens with the crown ether buckled so that all the oxygen atoms could coordinate to the barium.

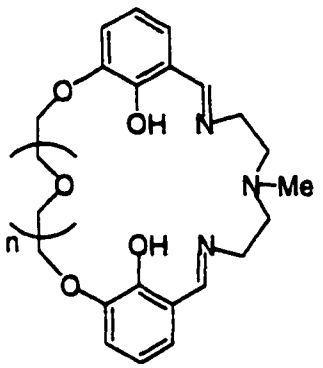
Other hetero-dinuclear ligands, **3a-g**, have been discussed and are shown in Figure 2.4. The soft metal ions used in these studies were Ni(II) and Cu(II). Barium, along with all of the lanthanides (La - Lu) and yttrium, were used as the hard metal ions. The focus of this study was to determine the site of complexation and which metal ion coordinated more strongly to which site.

The barium complexed solely to the crown ether and the phenolic oxygens. Nickel, on the other hand, preferentially coordinated to the softer imine nitrogens. In mono-nuclear lanthanide complexes, the metal ion preferentially complexed to the crown ether moiety. Hetero-dinuclear complexes of Ln (Ln = any lanthanide) and nickel were easily synthesized either from the nickel complex and a lanthanide salt or the lanthanide complex and a nickel salt. When the barium complex of **3d** was treated with a $LnCl_3$,

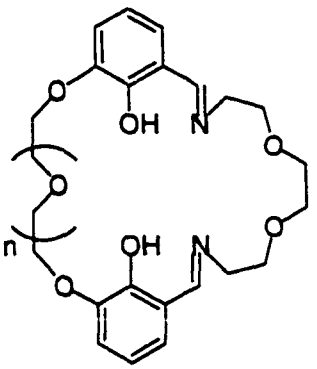


3

3a n = 1
3c n = 2



3b n = 1
3d n = 2
3f n = 3



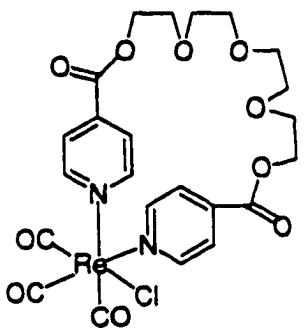
3e n = 2
3g n = 3

Figure 2.4

the barium, which was coordinated to the crown ether moiety, forced the lanthanide to coordinate to the Schiff base which resulted in the formation of a hetero-dinuclear complex. This result was in contrast with the results of the reaction using UO_2^{2+}. When UO_2^{2+} was treated with the barium complex **3d** , the UO_2^{2+} coordinated to the Schiff base moiety. The complexation of UO_2^{2+} weakened the barium coordination to the crown ether moiety which caused it to be released. The end result was formation of a mono-nuclear uranium complex. The reason for this discrepancy of the f-block metal ions was due to the exact coordination site of the metal. The lanthanide did not chelate completely inside the Schiff base but rather was coordinated on top of it. The UO_2^{2+} coordinated in the plane of the salen ring which caused the destablization of the coordination around barium.

An unusual rhenium complex, **4**, was recently published.[11] Although this compound only complexed Li^+ weakly (Figure 2.5), the

Li ion was bound tightly enough to decrease the luminescence of the rhenium complex. It was postulated that the rhenium compound was the source of all emissions and that the Li^+ only was binding to the excited rhenium compound. The lithium complex of **4** was believed to electrostatically stabilize the radical anion on the pyridine ligand, lowering the energy gap between the excited state and the ground state. This decreased the emission intensity and the excited-state lifetime.

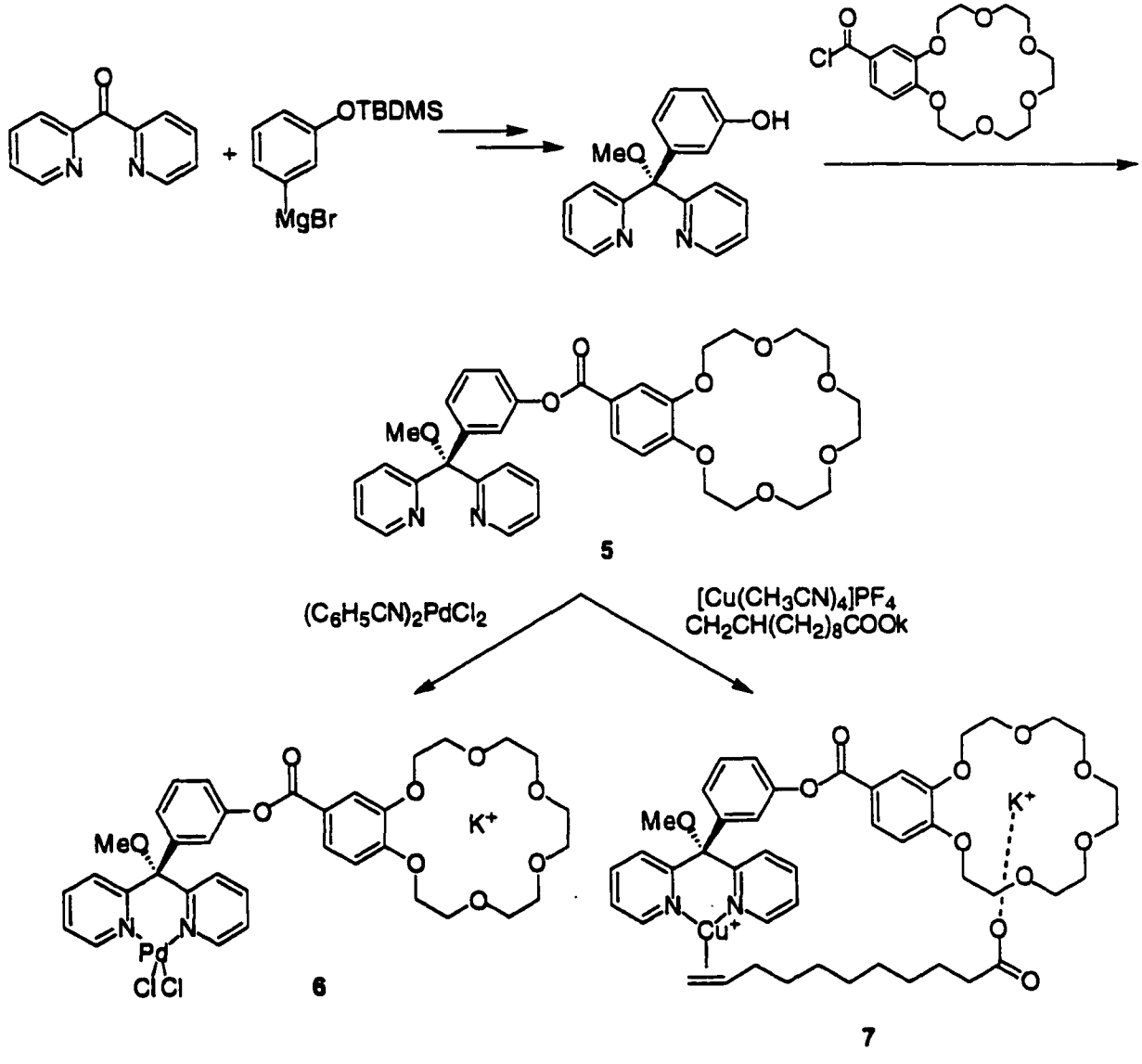


4

Figure 2.5

A novel bimetallic complex was used to study olefin binding.[12] Di(2-pyridyl)ketone was transformed into ligand **5** via Scheme 2.1. Treatment of **5** with bis(benzonitrile)palladium(II) chloride followed by $KMnO_4$ gave K-Pd complex, **6**. For the olefin binding studies, a Cu(I) complex was used instead of Pd(II). Copper(I) was chosen because it coordinates olefins in a trigonal manner. Treatment of **5** with $[Cu(CH_3CN)_4]PF_4$ then with potassium 10-undecenoate yielded complex **7**. Shifts in the ^{1}H-NMR spectra suggested that complex **7**

had formed although the ^{1}H-NMR peaks were broadened due to Cu(II) contaminates. Also, when **5** was treated with $[Cu(CH_3CN)_4]PF_4$

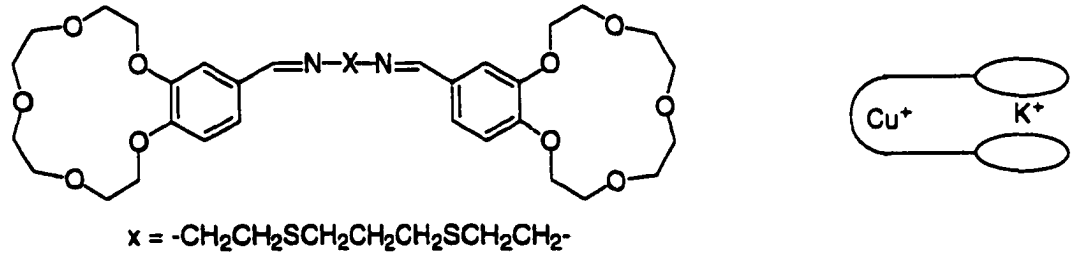


Scheme 2.1

and then potassium 6-heptenoate, no complex was formed. This molecule was too short to bridge the distance between the Cu(I) and the K^+.

2.1.3 Heterotrimetallic Complexes

When a soft coordination site was linked to two crown ethers moieties, one of two coordination events occurred.[13] First, if the hard metal ion was small and could coordinate completely within the cavity of the crown ether, two hard metals coordinated forming a dimetallic complex. This, then, was treated with $CuPF_4$ to form the trimetallic complex with the copper coordinating to the imine nitrogens and the thioethers. Secondly, if the metal ion was large and did not fit completely into the crown ether, a sandwich complex formed (Figure 2.6).



x = $-CH_2CH_2SCH_2CH_2CH_2SCH_2CH_2-$

Figure 2.6

Other trimetallic complexes have been studied. One variation of the above bis-crown ether example was a polyether moiety linking two sites for soft cations.[14] In this example, tetra(ethylene glycol) linked two porphyrin moieties. The prophyrins were then complexed to Zn(II). Treatment of this di-zinc complex with Na^+ or K^+ caused a gradual shift of some signals in the ^1H-NMR spectum. These shifts did not reach a limiting value which indicated a weak complexation of the alkali metal (Figure 2.7).

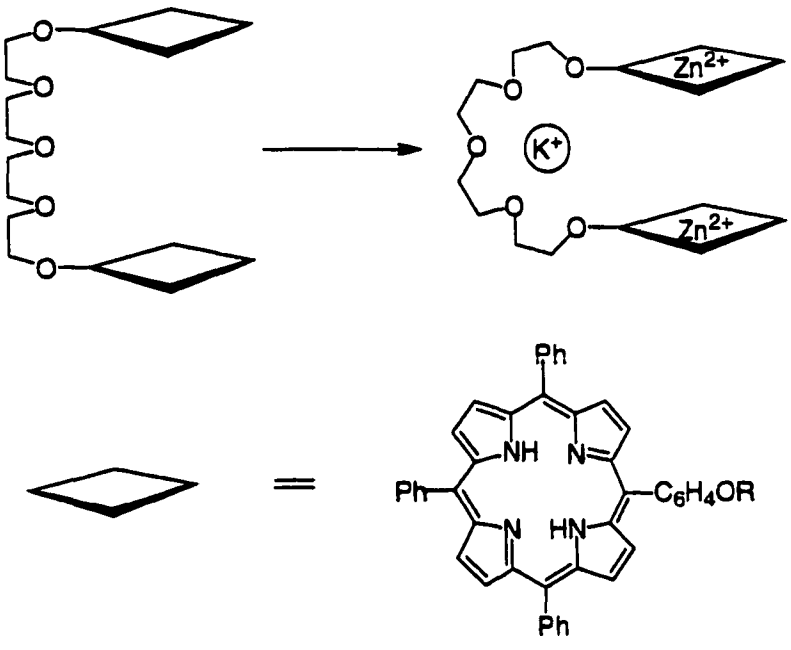


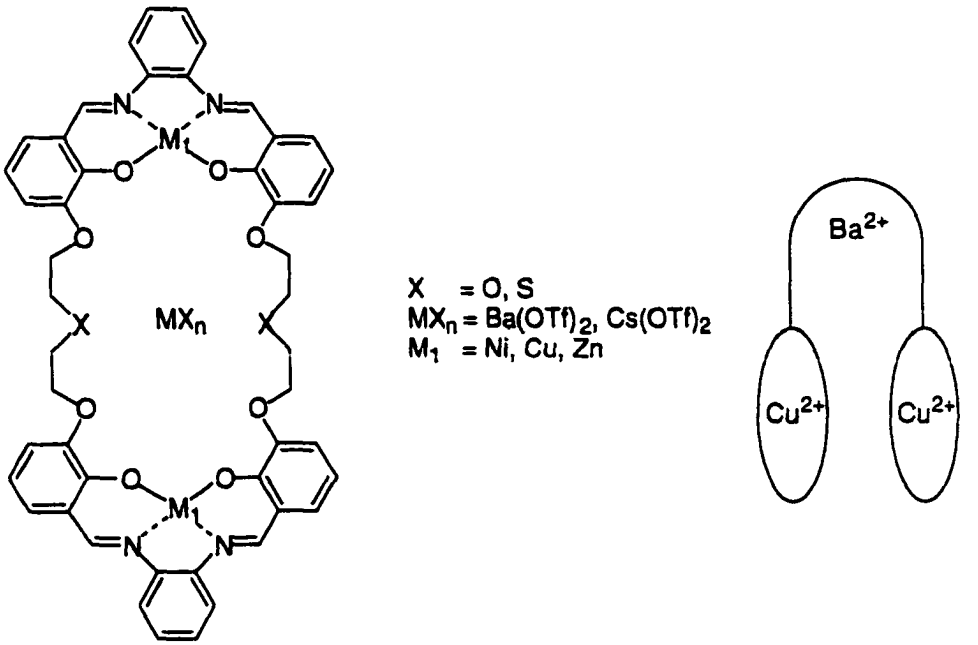
Figure 2.7

The trimetallic complexes of Reinhoudt were more interesting.[4] These complexes had the general structure of **8** with M_1 = nickel, copper, and zinc and MX_n = $Ba(OTf)_2$, and CsOTf. The X-ray crystal structures of the $BaNi_2$ and the $BaCu_2$ complexes have been solved. The polyethylene oxide moiety wrapped around the barium ion to bring the salen ligands parallel and within close proximity to each other. The Cu-Cu distance was 3.50 Å and the Ni-Ni distance was 3.42 Å (Figure 2.8).

2.1.4 Gadolinium Complexes

2.1.4a Introduction

Macrocyclic complexes of the lanthanides (which are considered hard metal ions) have been studied for a number of years.[15] These macrocyclic complexes have been used in



8

Figure 2.8

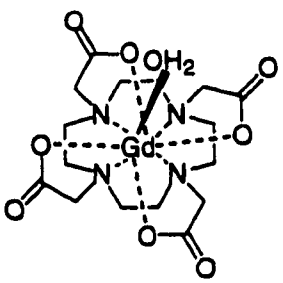
radiopharmaceuticals,[16] hydrolysis of phosphodiesters,[17] and as NMR shift reagents.[18] One of the most important developments of lanthanide chemistry, however, was the use of gadolinium (Gd) complexes as contrast agents for MRI.[19]

2.1.4b Magnetic Resonance Imaging

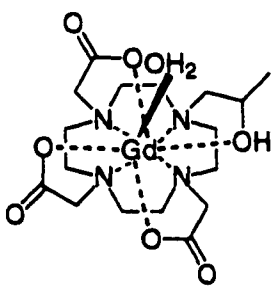
Magnetic resonance imaging, or MRI, has become a powerful tool in the diagnosis of disease. Unfortunately, the images produced from the MRI can have poor contrast between the various types of tissues. Contrast agents were developed to improve the difference in the MRI images. One of the most common contrast agents is DO3A-Gd complex. Gadolinium is the metal ion of choice because of its high magnetic moment and long relaxation time.[20] There two main parameters with determine signal intensity of MRIs. They are T_1,

which is a spin-lattice relaxation component and T_2 which is a spin-spin relaxivity component. Most gadolinium complexes affect T_1. One of the most important contributors to T_1 is τ_m, which is the exchange rate of the water bound to the metal ion with bulk water.

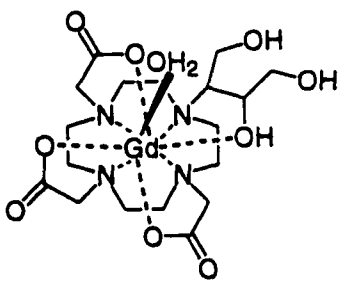
For any MRI contrast agent to be clinically viable it must possess the following properties: the complexes must be highly water soluble; it must have high relaxivity (at least one water



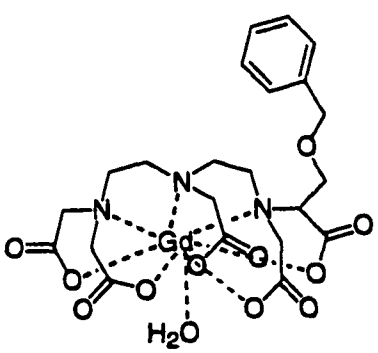
Dotarem



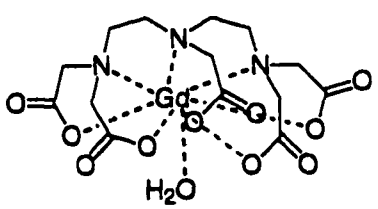
ProHance



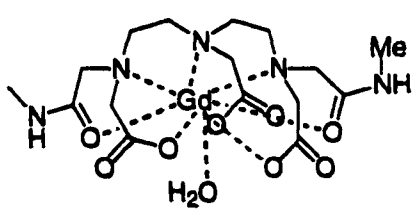
Gadovist



MultiHance



Magnevist



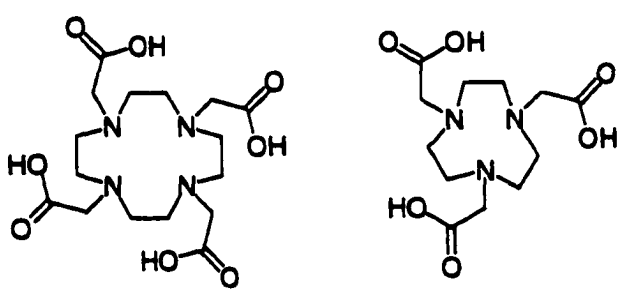
Ominscan

Figure 2.9

molecule coordinated directly to the metal ion); it must be inert to the loss of Gd(III) (both the metal ion and the free ligand are toxic), the complex must be non-toxic and have low osmolality. There have been six gadolinium-containing complexes approved for use in humans for MRI contrast agents (Figure 2.9).[15b] Three of these complexes, Dotarem, ProHance, and Gadovist, are macrocyclic tetraaza molecules while the others, Magnivist, Omniscan, and MultiHance, are open chain polyamines. The following discussion will focus solely on macrocyclic complexes of gadolinium.

2.1.4c Gadolinium Complexes

DOTA (1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid) was first synthesized in 1980.[21] The thermodynamic parameters of the gadolinium complex of DOTA were found to depend on the internal cavity size, rigidity and the nature of the donating atoms.[22] A comparison of the thermodynamic stabilities of the gadolinium complexes of NOTA (1,4,7-triazacyclononane-N,N',N'',N'''-tetraacetic acid) and DOTA was carried out (Figure 2.10). As expected, Gd-DOTA was much more stable than Gd-NOTA, most

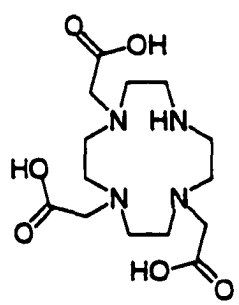


DOTA NOTA

Figure 2.10

likely due to the larger ring size.

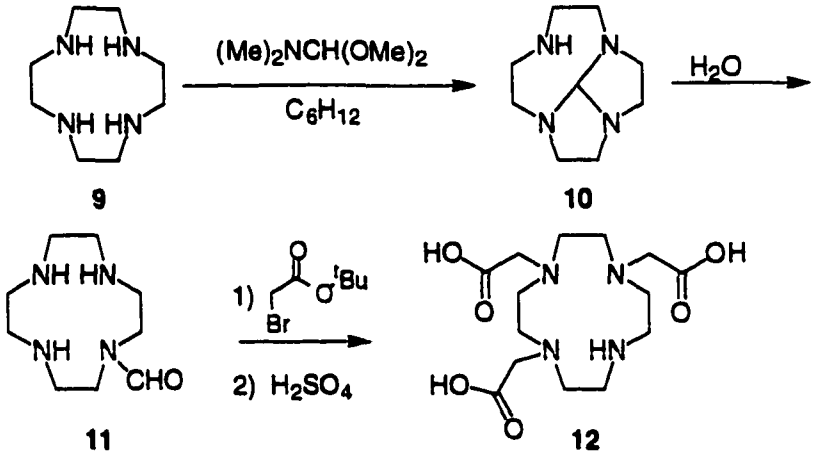
A problem encountered with many contrast agents was they carried an overall charge. Injecting a concentrated solution of one of these compounds into the blood could disrupt the osmotic pressure of the cells. A neutral complex would eliminate this problem. To this end, a new ligand, DO3A, (1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane) was synthesized (Figure 2.11).[23] This ligand formed neutral complexes with gadolinium and could be functionalized further at the remaining secondary amine.



DO3A

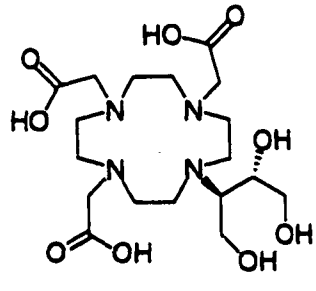
Figure 2.11

The synthesis of DO3A proceeded as follows (Scheme 2.2). Treatment of 1,4,7,10-tetraazacyclodecane with N,N-dimethylformamide dimethylacetal gave 1,4,7,10-tetraazatricyclo[5.5.1.0]-tridecane. Hydrolysis of this compound gave the formyl tetraazacyclodecane. Treatment of formamide **11** with t-butyl bromoacetate, followed by H_2SO_4 gave DO3A.



Scheme 2.2

Modifications aimed at increasing the hydrophilicity of gadolinium-DO3A were attempted by attaching a trihydroxybutyl group to the secondary nitrogen (Figure 2.12).[24] When the gadolinium-complex of this ligand (DO3A-butrol) was compared to DO3A in terms of stability, DO3A-butrol was less thermodynamically stable than the



±-DO3A-butrol

Figure 2.12

parent ligand because of intramolecular hydrogen bonding. This hydrogen bonding would decrease the electron density of the coordinated hydroxylic oxygen atom. Kinetically, however, DO3A-butrol was more stable than DO3A by an order of magnitude. The

steric bulk of the trihydroxybutyl side chain caused the increase in kinetic stability of DO3A-butrol.

In an attempt to synthesize a pH-dependent ligand, methylpyridine was attached to DO3A (Figure 2.13).[25] It was postulated that the pyridine nitrogen would coordinate to the metal ion. Then, when the complex was in acidic solutions, the protonated pyridine would decomplex from the metal and a water molecule would coordinate in its place. A MRI contrast agent of this type would be very beneficial for the detection of tumors which have extracellular regions which are slightly more acidic than the surrounding tissue.[26] It was found, however, that the pyridine was resistant to protonation and the hydration number of the metal ion did not change from pH 8-3.

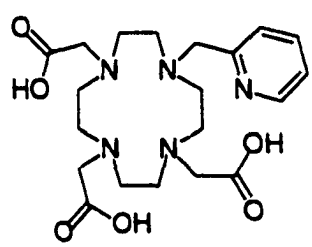
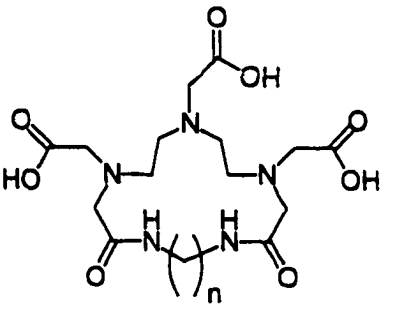


Figure 2.13

Other compounds which contain more nitrogens in the macrocycle have been synthesized. Cyclic polyamine diamides, such as **13**, have been synthesized and complexed to gadolinium.[27] The gadolinium complex of **13a** formed a dimeric sandwich compound in which each gadolinium was coordinated to three carboxylate anions and two amine nitrogens of one ligand and the two amide oxygens an one amine nitrogen of another. The gadolinium complex of **13b** formed a 1:1 Gd:L compound. An X-ray structure of the mono-

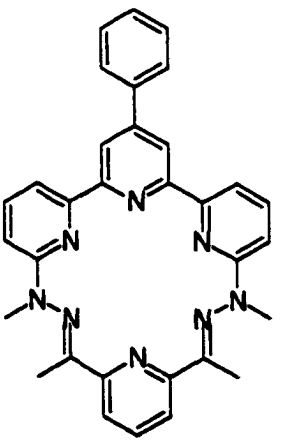
gadolinium complex was solved and it was determined that the extra methylene unit allowed more flexibility in the molecule to coordinate completely to one gadolinium. The complex **13b** was also found to be more water soluble than compound **13a**.



13a n = 2
13b n = 3

Figure 2.14

Ligand **14** has also been synthesized and complexed to gadolinium.[28] This complex was stable between pH 4.5-7 with no significant decomposition after six days, but had a half-life 2.5 days



14

Figure 2.15

in 15% $NH_{3(aq)}$ or in an aqueous solution at pH 4. The relaxivity decreased significantly when the pH was raised above 6.0. This behavior is similar to complexes with more than one water molecule coordinated to the metal ion; however, no other evidence for this was obtained.

2.1.4d Dinuclear Gadolinium Complexes

Dinuclear gadolinium contrast agents have the potential to be even more effective than their mono-nuclear counterparts because the dinuclear complexes should have an increased relaxivity. A 34-membered macrocycle with six carboxymethyl pendants was synthesized and complexed to gadolinium (Figure 2.26).[29] A crystal structure of this complex was obtained and showed two gadolinium

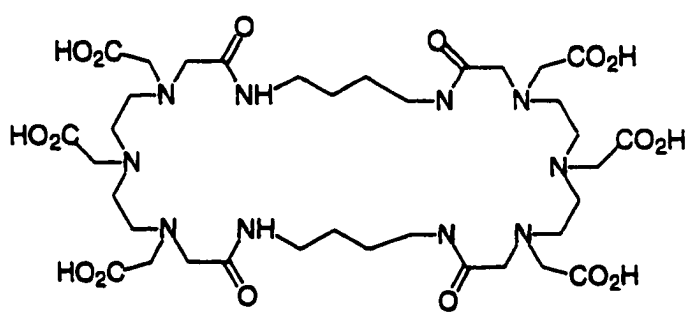


Figure 2.16

metal ions coordinated to the ligand. The dinuclear complex did show an increase in relaxivity over the mono-gadolinium of the same ligand.

2.2 Rationale

Bis-dioxocyclams which are linked through the ethers, have been synthesized with a variety of chain lengths. These have then been complexed to transition metals including copper and nickel. Substituting the 1,n-diols that were used to make these linked bis-dioxocyclams with poly(ethylene glycols) would create a third cavity capable of complexing hard cations. Barium and other alkali and alkaline earth metals, along with the lanthanides, have all been complexed to poly(ethylene glycol) moieties. Gadolinium, which is a lanthanide, is the metal of choice for MRI contrast agents. Bis-dioxocyclams linked through a polyether bridge which are complexed to gadolinium would open up a unique class of potentially useful MRI contrast agents.

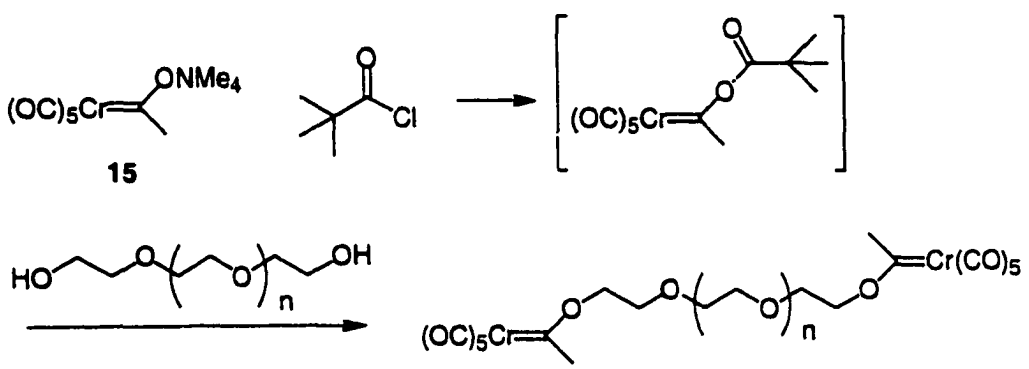
2.3 Results and Discussion

2.3.1 Synthesis of Dioxocyclams

Bis-carbene complexes, which are linked through the oxygens, can be synthesized in good yield from the tetramethylammonium "ate" complex, **15** and the appropriate diol. The use of poly(ethylene glycols) as a diol source should give the poly-ether linked bis-carbene complexes. These poly-ether linked bis-carbene complexes should undergo the photochemistry with imidazolines, followed by dimerization and reduction to give poly-ether linked bis-dioxocyclams. These compounds would then have three sites for

metal complexation: two cyclam rings for soft metals such as nickel and the poly-ether bridge for a hard cation such as gadolinium.

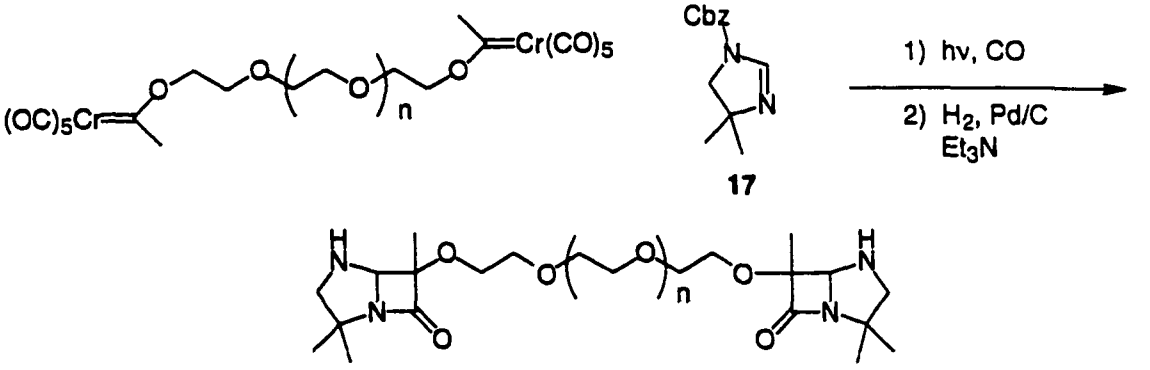
Treatment of **15** with pivaloyl chloride followed by the slow addition of either tri(ethylene glycol) or tetra(ethylene glycol) at -40 °C, gave the bis-carbene complexes **16a,b** in good yield. (Scheme 2.3) The poly(ethylene glycols) must be exceedingly dry to ensure good yields. When the tri- and tetra(ethylene glycol) linked bis-carbene complexes were photolyzed in the presence of imidazoline **17**, polyether-linked protected bis-azapenams, **18a,b** were isolated



16a n = 1 68%
16b n = 2 89%

Scheme 2.3

in high yield. For this step, the carbene complex must be completely free of any excess pivaloyl chloride or pivalic acid. Otherwise the yields suffer considerably. Removal of the Cbz protecting group under basic conditions proceeded smoothly to give the free azapenams **18a,b** in high yield (equation 2.1).

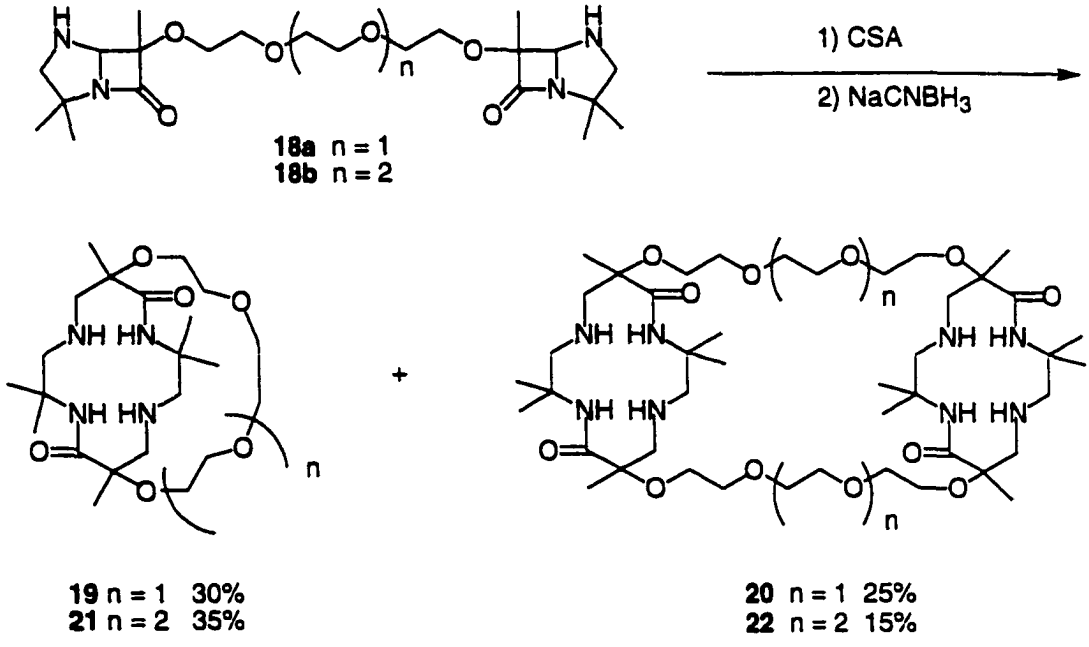


(2.1)

18a n = 1 74%
18b n = 2 76%

Acid-catalyzed ring opening/dimerization/reduction gave two compounds. In systems in which the azapenam were linked via a 1,n-diol, two bis-dioxocyclam diastereomers were isolated: the d,l pair of enantiomers and the meso compound. In this case, however, a "basket" compound was isolated instead of the d,l pair. The basket compound was a result of intramolecular dimerization/reduction. Compounds **19,20** were isolated for the tri(ethylene glycol) linked bis-azapenam and **21,22** for the tetra(ethylene glycol) linked bis-azapenam (Scheme 2.5).

The exact reason for this intramolecular dimerization is not known, since this phenomenon was not observed to any extent with the alkoxy-linked bis-dioxocyclams, even with linkages as long as twelve atoms. Since there was no chiral center to induce stereoselectivity a mixture of three compounds was obtained: the (R,R), (S,S) pair of enantiomers and the (R,S) meso compound. When the (R,R), (S,S) pair of enantiomers ring opened to the seven-membered imines, the centers of like configuration underwent a



Scheme 2.5

homodimerization (which was favored), and after reduction of the imine bonds, gave the basket cyclam (Figure 2.17).

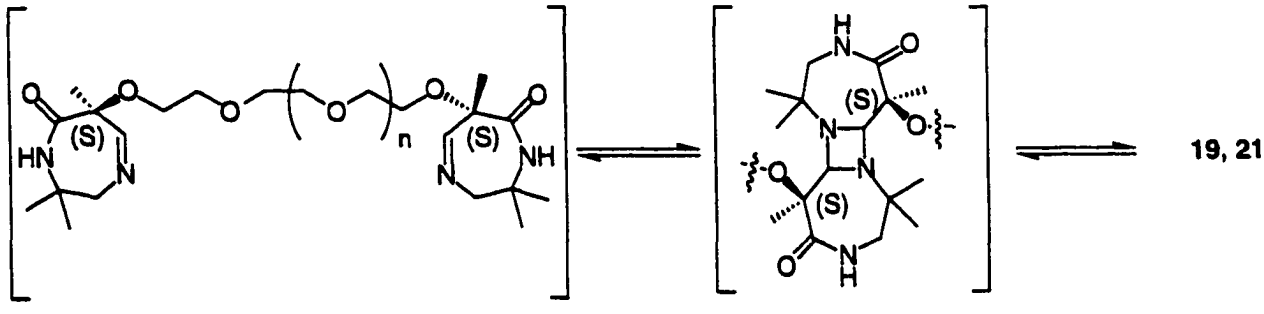


Figure 2.17

The meso compound, which had opposite stereochemistry at each azapenam, also preferred to homodimerize. It, however, could only dimerize with another meso compound. The meso compound cannot undergo an intramolecular dimerization because the bridge would start on opposite sides of the molecule (Figure 2.18).

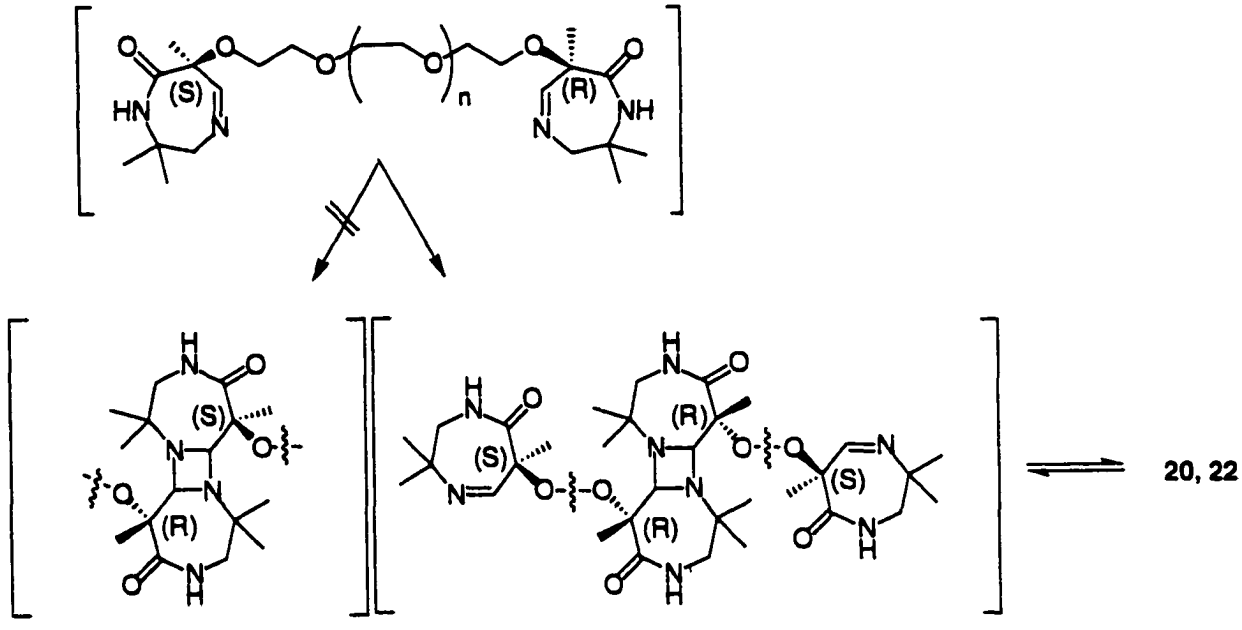


Figure 2.18

A single crystal was obtained for **21** by slow evaporation of a methanol:water mixture (Figure 2.19). The crystal structure was solved and clearly showed the 14-membered tetraazamacrocycle. The two amide carbonyl oxygens were anti to the polyether ring and were hydrogen bonded to a water molecule. The polyether bridge adopted the classic crown ether conformation, in which each $-OCH_2CH_2O-$ was in a gauche conformation while each $-CH_2-X-Y-CH_2-$ ($X=CH_2$, $Y=O$, or $X=O$, $Y=CH_2$) adopted an anti conformation. A second water molecule was trapped between the polyether bridge and the cyclam ring. It appeared the water molecule was hydrogen-bonded to the amines of the cyclam ring.

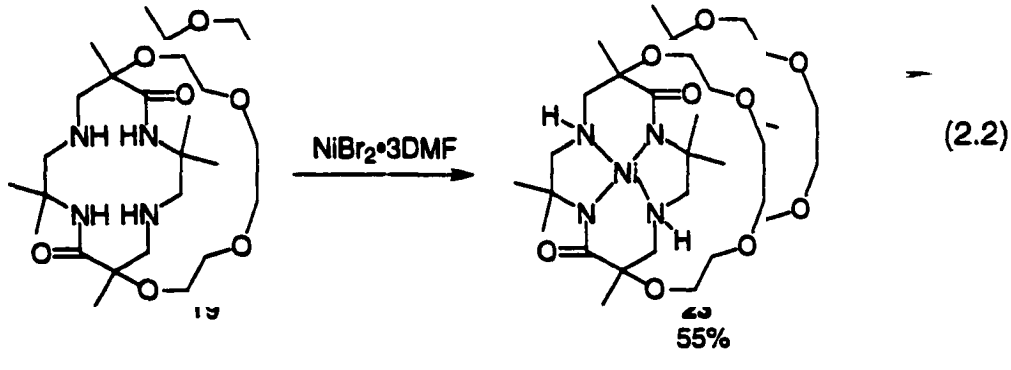
A crystal of **20** was also obtained by slow evaporation of a methanol:water mixture (Figure 2.20). Again, both cyclam rings were clearly visible with amide carbonyl oxygens anti to the bridging

ligand. The polyether bridge adopted the characteristic gauche conformation of crown ethers. Six water molecules were in the crystal lattice. Four of these water molecules were located outside the cyclam ring; two of these water molecules appeared to be hydrogen-bonded to the amide carbonyls. The other two water molecules were trapped inside the macrocyclic ring, similarly to **21**.

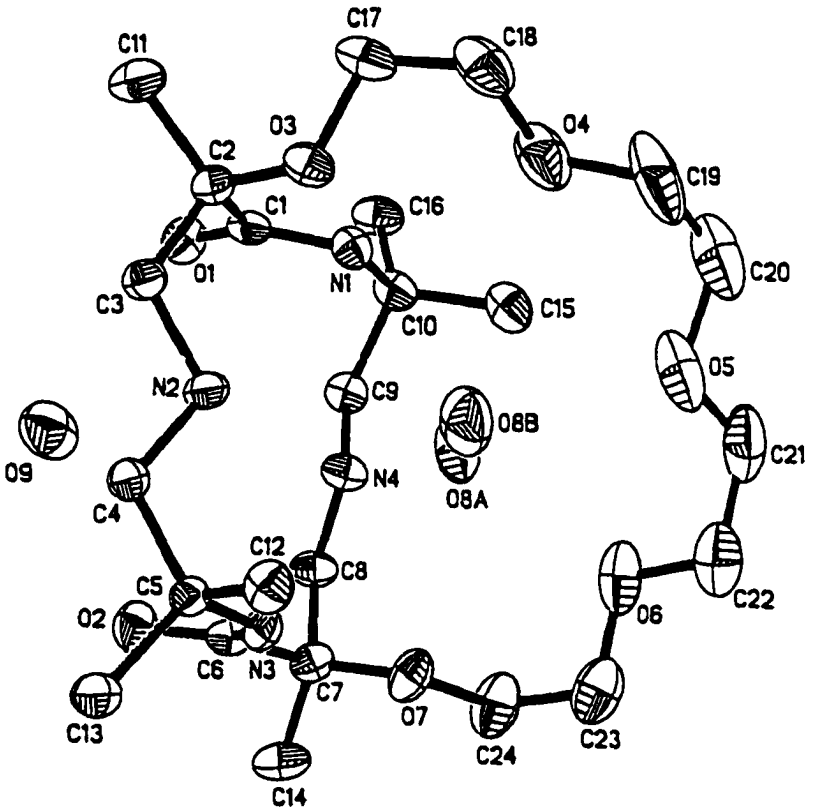
2.3.2 Nickel Complexes

Nickel(II) forms stable square planar complexes with dioxocyclams.[30] A variety of nickel(II) sources have been used with varying degrees of success. $NiBr_2 \cdot 3DMF$ is a source of Ni(II) that is soluble in most organic solvents. The yields of nickel complexation, however, are only moderate. Commercially available $Ni(BF_4)_2 \cdot xH_2O$, dried under vacuum before use, was also used. The third source of nickel(II) is from the reaction of $AgBF_4$ and $NiBr_2$. This is an *in situ* source of anhydrous $Ni(BF_4)_2$.

Triethylene glycol basket cyclam, **19**, was subjected to nickel complexation conditions. Treatment of triethylene glycol basket

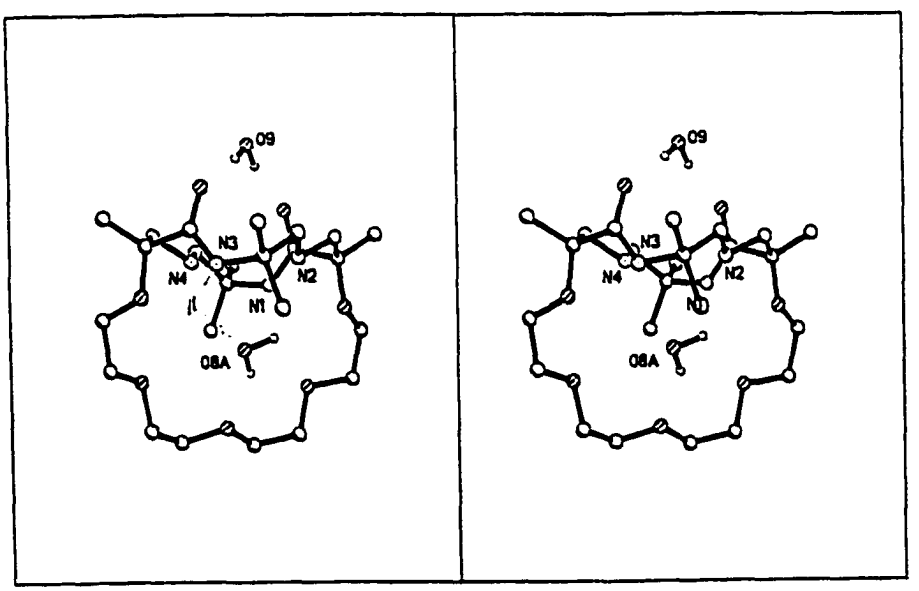


(2.2)



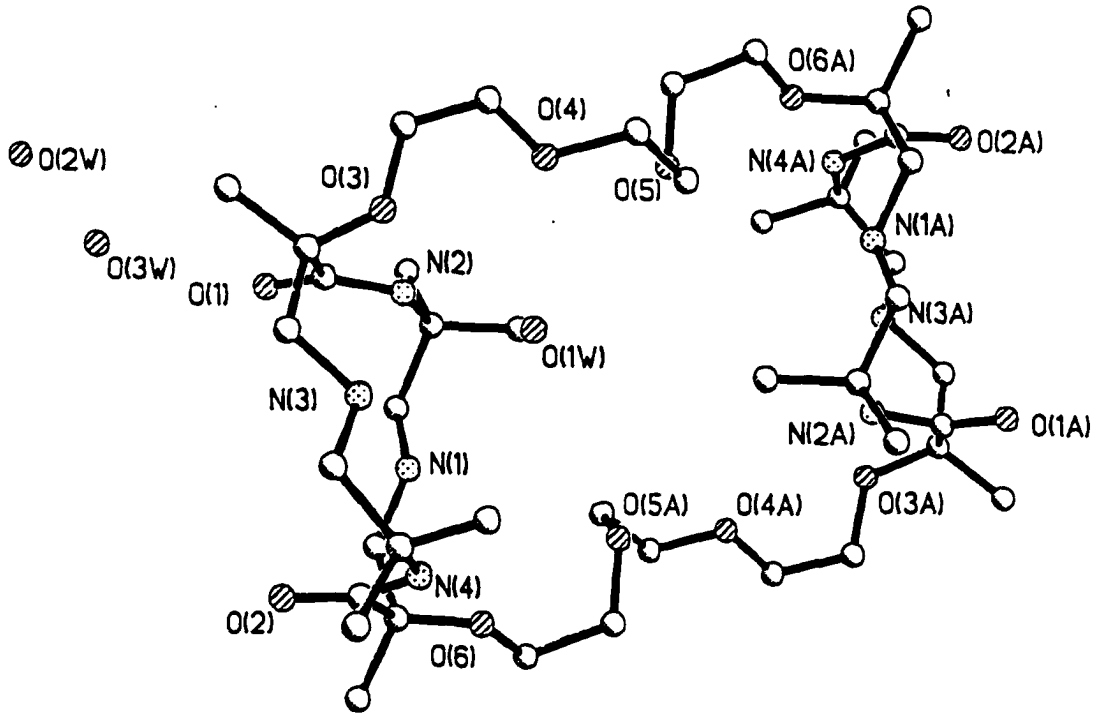
X-ray of **21**

Figure 2.19a



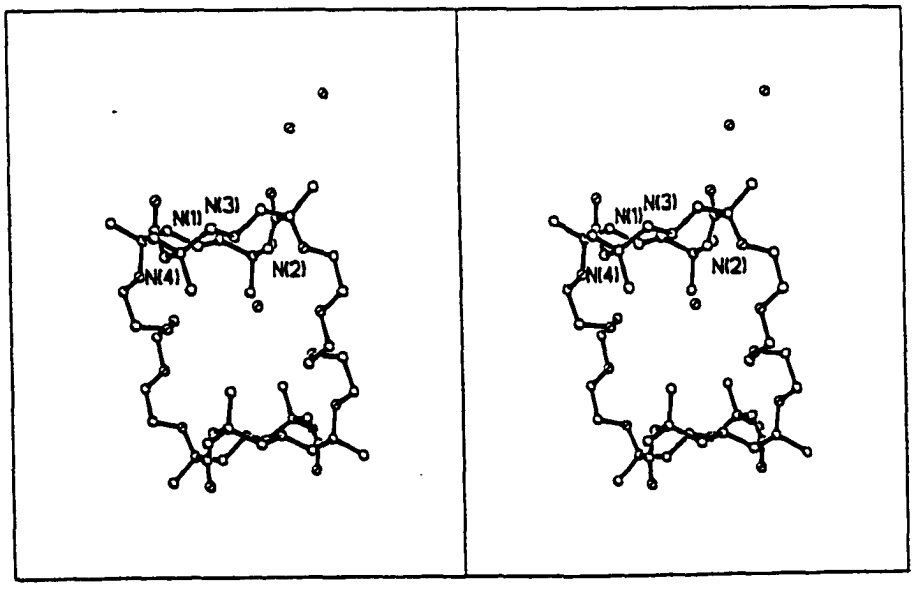
stereoview of **21**

Figure 2.19b



X-ray of **20**

Figure 2.20a

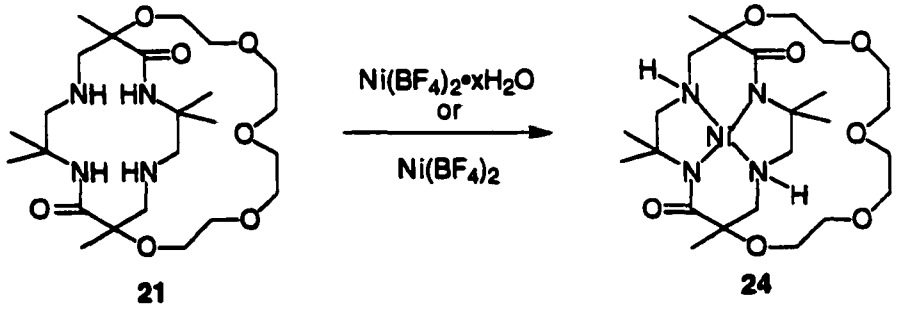


stereoview of **20**

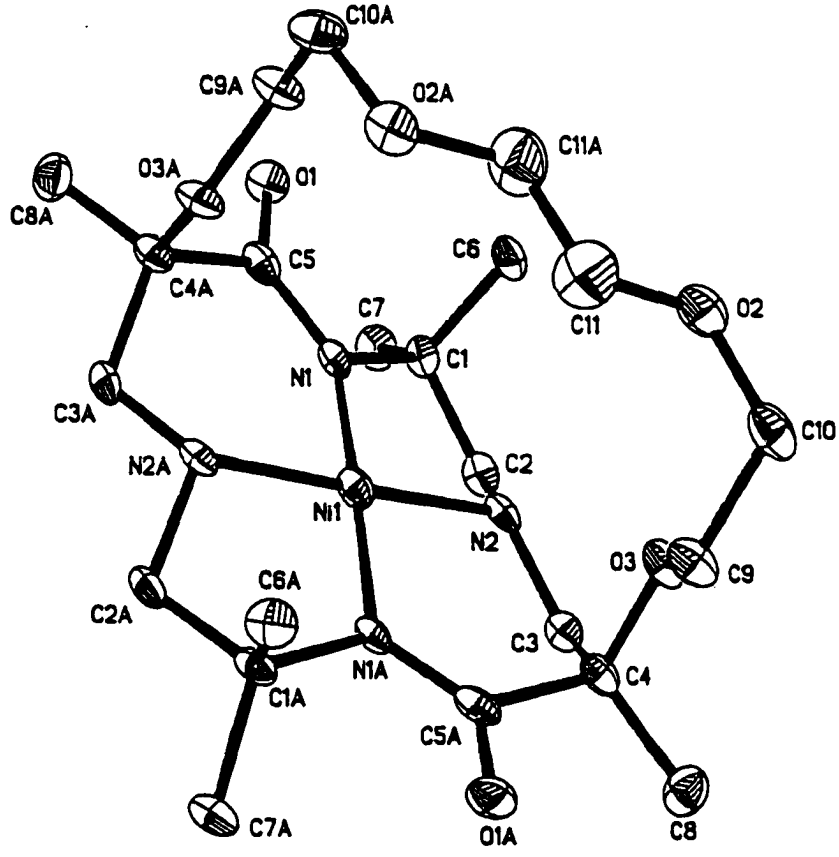
Figure 2.20b

cyclam with $NiBr_2 \cdot 3DMF$ resulted in a 55% yield of nickel complex **23** (equation 2.2). The pink solid was recrystallized from CH_2Cl_2:MeOH by slow evaporation to give X-ray quality crystals (Figure 2.20). The complexed nickel flattened the cyclam ring and the plane containing C_{10}-O_2-C_{11} was parallel to the N-Ni plane.

The tetraethylene glycol basket cyclam was also complexed to nickel. In this example, the reactivity of the commercial Ni(BF4)2 and the anhydrous $Ni(BF_4)_2$ generated *in situ* was compared. Treatment of **21** with $Ni(BF_4)_2 \cdot xH_2O$ that had been dried and stored in a vacuum desicator overnight gave the resulting nickel complex **24** in 77% yield (equation 2.3). When the anhydrous $Ni(BF_4)_2$ was generated *in situ*, and treated with **21**, a 100% yield of **24** was isolated. This pink solid was recrystallized from a slow diffusion of pentane into chloroform (Figure 2.22). As in the triethylene glycol linked basket cyclam, the nickel flattened the cyclam ring into a plane. The polyether bridge, which was longer than in the triethylene glycol basket cyclam, meandered in an S-shaped fashion, going directly over the nickel atom.

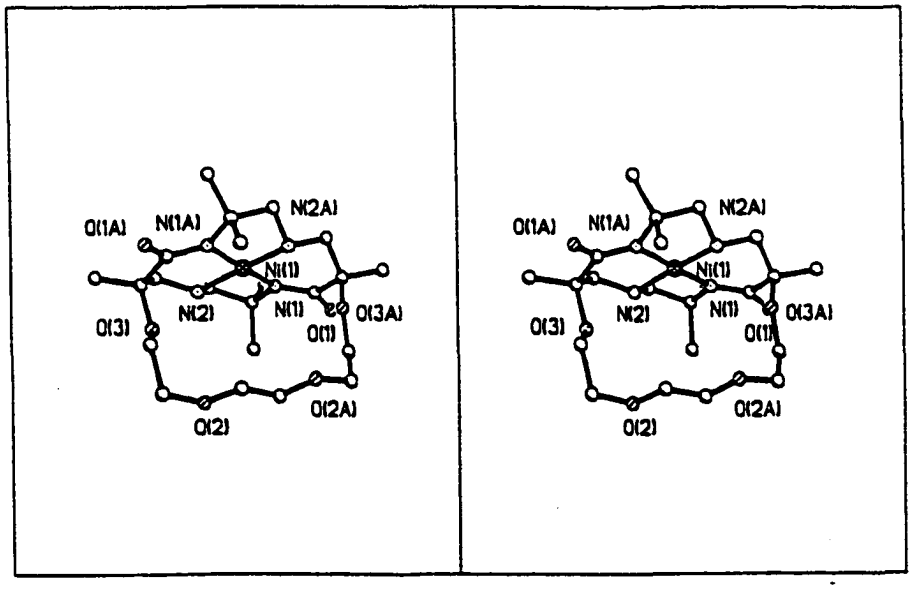


21 **24** (2.3)



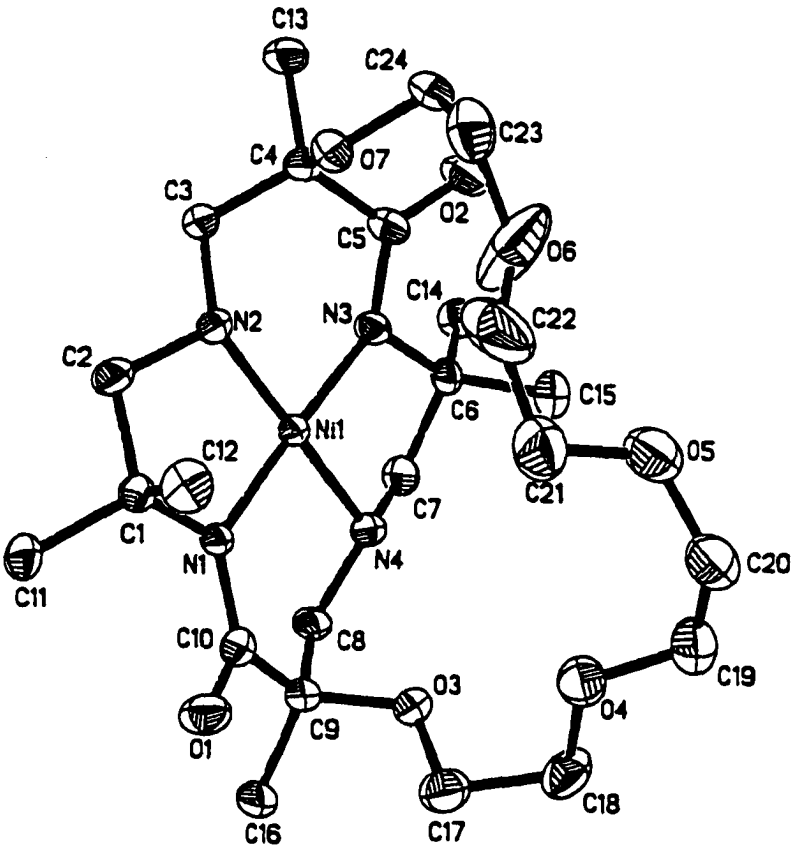
X-ray of **23**

Figure 2.21a



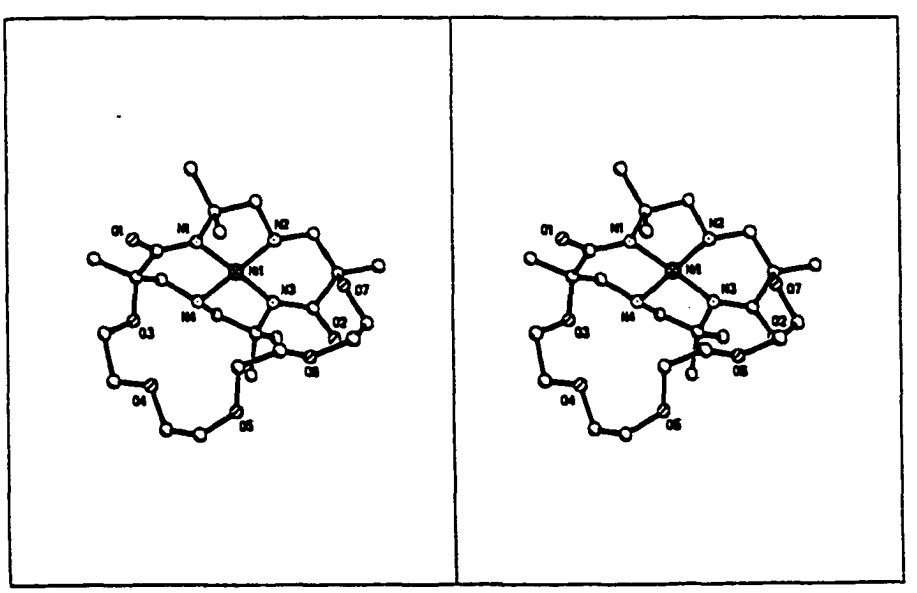
stereoview of **23**

Figure 2.21b



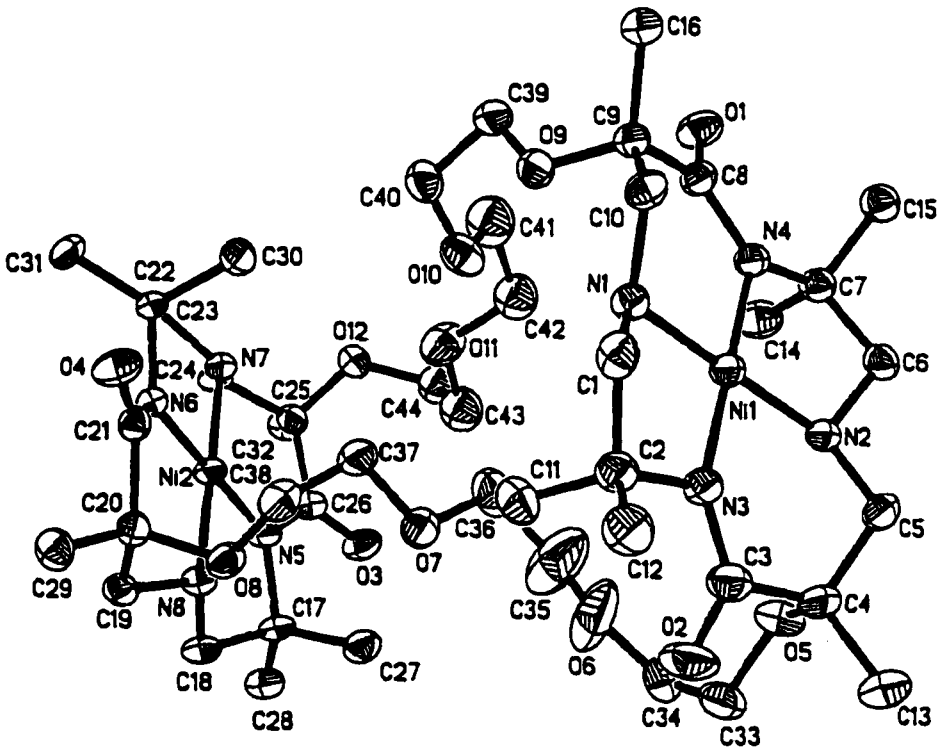
X-ray of **24**

Figure 2.22a



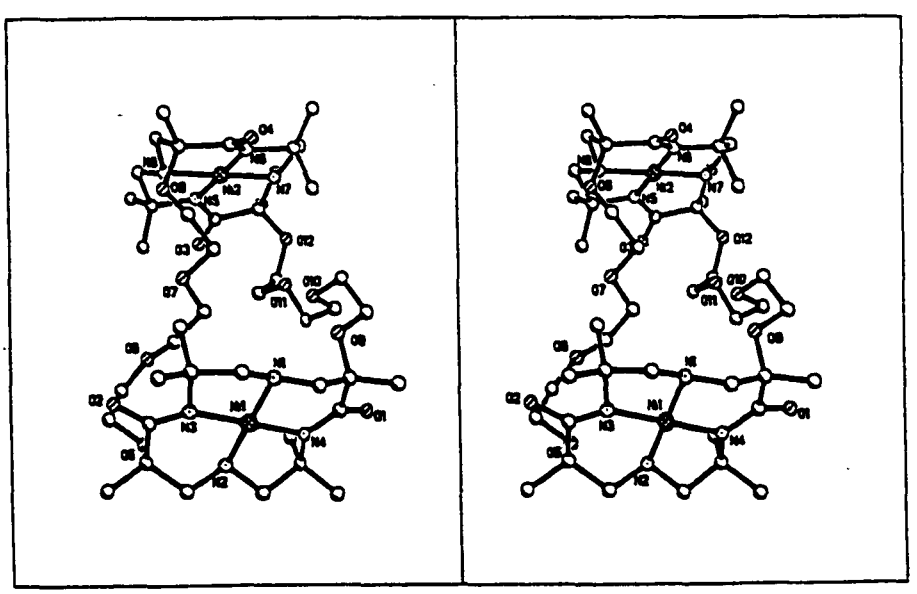
stereoview of **24**

Figure 2.22b



X-ray of **25**

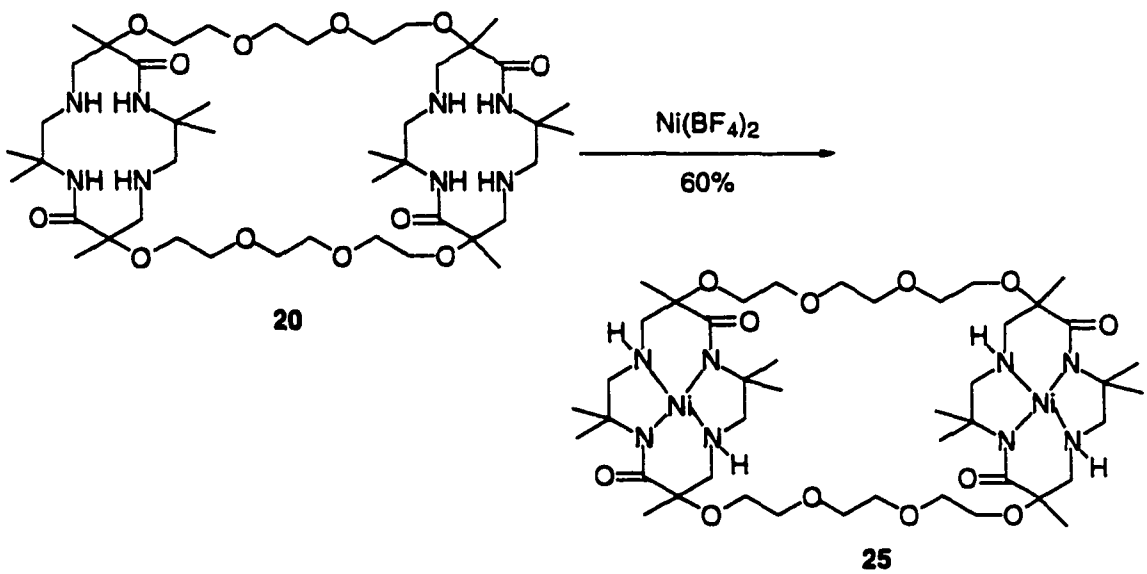
Figure 2.23a



stereoview of **25**

Figure 2.23b

Tri(ethylene glycol) linked bis-cyclam **20** was treated with $Ni(BF_4)_2$ generated *in situ* to give the bis-nickel complex **25** in 60% yield (equation 2.4). The complex was crystallized with slow diffusion of pentane into chloroform and the crystal structure was

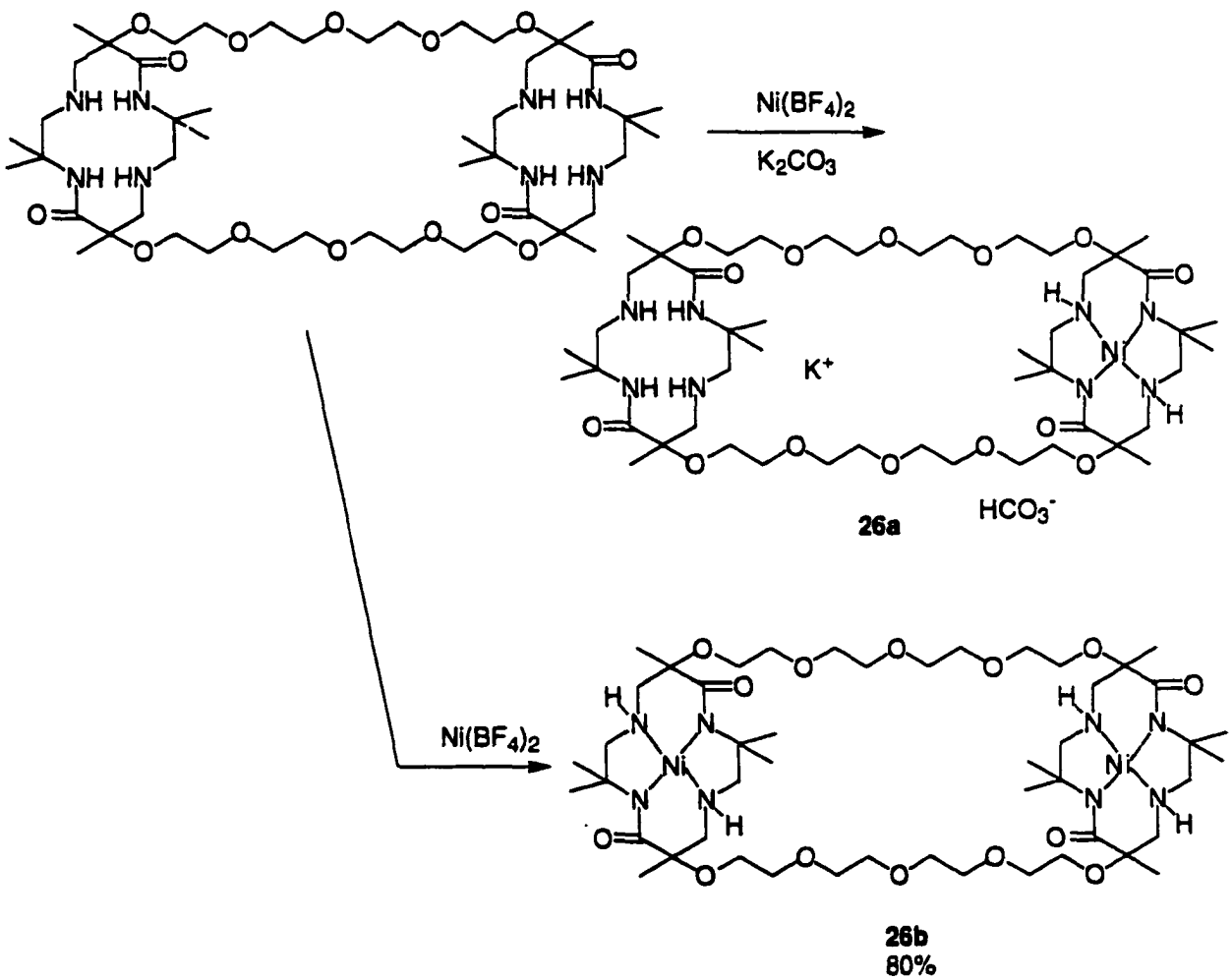


20 **25** (2.4)

solved (Figure 2.23). There were two interesting features in the crystal lattice of this compound. First, the two cyclams rings were not stacked one on top of each other; the bottom ring projected forward from the top cyclam ring. The Ni-Ni distance was 9.466 Å. The second and perhaps more interesting feature was the one cyclam ring was rotated about 90° with respect to the other cyclam ring. That is, the amine nitrogens of one ring, were over the amide nitrogens of the other ring. Both of these features were the result of crystal packing because both rings were identical by ^1H and ^{13}C-NMR spectroscopy.

The first attempt to complex nickel to the tetraethylene glycol bis-cyclam used $Ni(BF_4)_2 \cdot xH_2O$. When $Ni(BF_4)_2 \cdot xH_2O$ and **22** were

heated together in methanol with K_2CO_3, two pink compounds were isolated. The ^{1}H-NMR spectrum suggested one pink compound was the mono-Ni complex **26a** while the other was the bis-nickel complex **26b** (Scheme 2.6). In this reaction, K_2CO_3 was used as a



Scheme 2.6

proton scavenger. Potassium, a hard cation, possibly coordinated inside the polyether cavity, as occurred with a crown ether. Various attempts to complete the complexation failed to give a significant amount of the bis-nickel complex from the mono-nickel complex. It was believed the K^+ was coordinating in the polyether cavity and

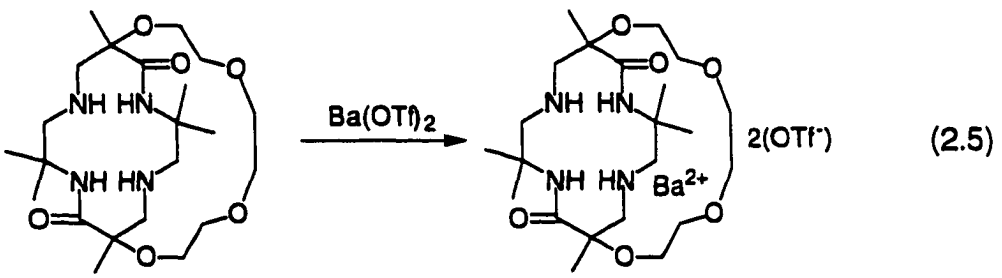
prevented the second nickel from coordinating to the cyclam ring. Switching the base from K_2CO_3 to triethylamine increased the yield of **26b** to 80% and there was no evidence for formation of the mono-nickel complex.

2.3.3 Barium Complexes

All of these ligands have the potential to complex a hard cation in their polyether cavity. Earlier it was inferred that a K^+ ion coordinated to the polyether bridge of **26a** preventing a second nickel from complexing to the second cyclam ring. Reinhoudt has shown that Ba^{2+} could be used as a template to cyclize macrocycles. These barium macrocycles were then complexed to transition metals and the redox activity was measured. Since the poly(ethylene glycol) linked bis-dioxocyclams also have two cavities for soft transition metals, the barium could also bring these two metals centers close enough to study their redox chemistry. Also, since both barium and gadolinium are hard cations the study of the barium complexes would be a preliminary study for the complexation of gadolinium.

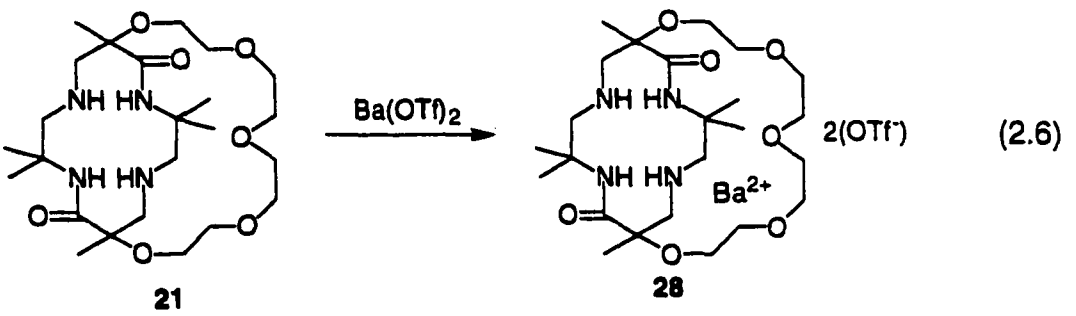
Triethylene glycol basket cyclam, **19**, was treated with a slight excess of $Ba(OTf)_2$ in methanol and heated to reflux. Cooling the solution to room temperature and removing the solvent produced a white solid (equation 2.5). Unfortunately, the ^1H and ^{13}C-NMR and IR spectra showed no significant changes from those of starting material. A FAB-MS (Fast Atom Bombardment Mass Spectroscopy) contained a strong peak at m/z 745, corresponding to **19**•$Ba(OTf)_2$-OTf. Loss of one triflate anion is common for complexes of this type. The base peak at m/z 459 was assigned to the free ligand. The base

peak was about twice as intense as the barium complex peak. This suggested the reaction either did not go to completion or the complex was not stable under the conditions for FAB-MS. Barium has seven naturally-occurring isotopes and the calculated isotope distribution pattern exactly matched the pattern observed in the MS.



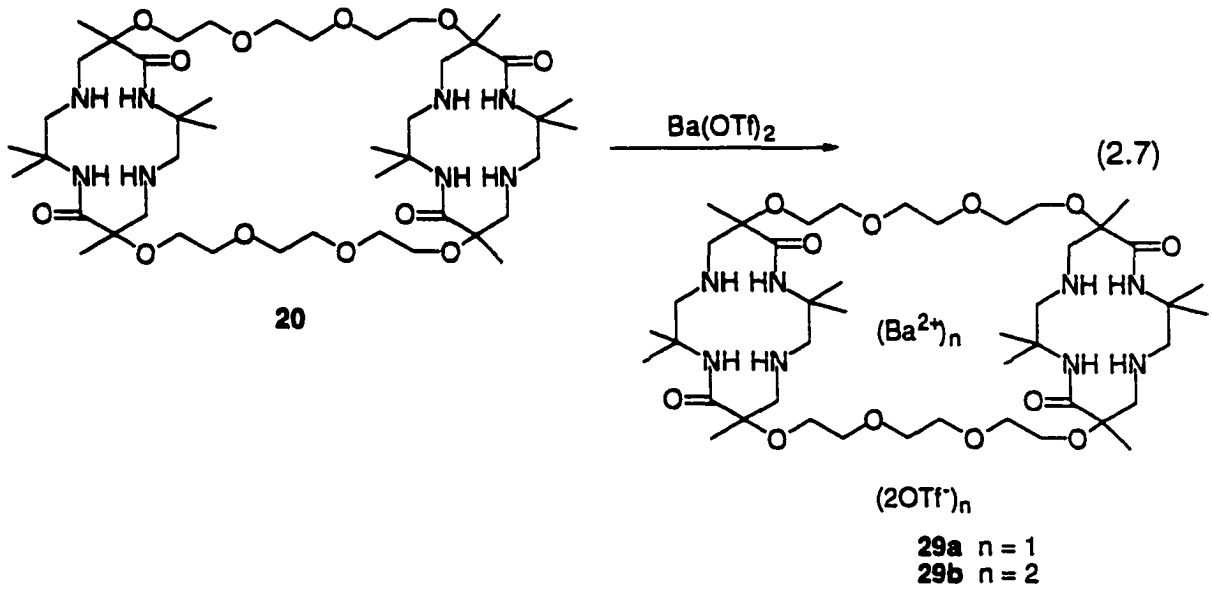
19 27 (2.5)

When **21** was treated with $Ba(OTf)_2$ under the same conditions as for **19**, a white solid was formed (equation 2.6). The ^1H and ^{13}C-NMR spectra of the product **28** showed small shifts as compared to **21** and the IR stretching frequency of the amide carbonyls in **28** shifted from 1668 cm^{-1} to 1654 cm^{-1}. This indicated that the amide carbonyls were coordinated to the barium. Notwithstanding these small differences in the spectra, the main evidence again came from the FAB-MS. This time the base peak at m/z 789 was assigned to **21**•$Ba(OTf)_2$-OTf. There was also a small peak for [**21**•$Ba(OTf)_2$-2(OTf^-)]+H at m/z 639. The free ligand peak at m/z 503 was substantially smaller than the complex peak. This suggested that the barium complex of this compound was more stable than the triethylene glycol barium complexes. This was most likely due to the increase in the size of the polyether cavity.

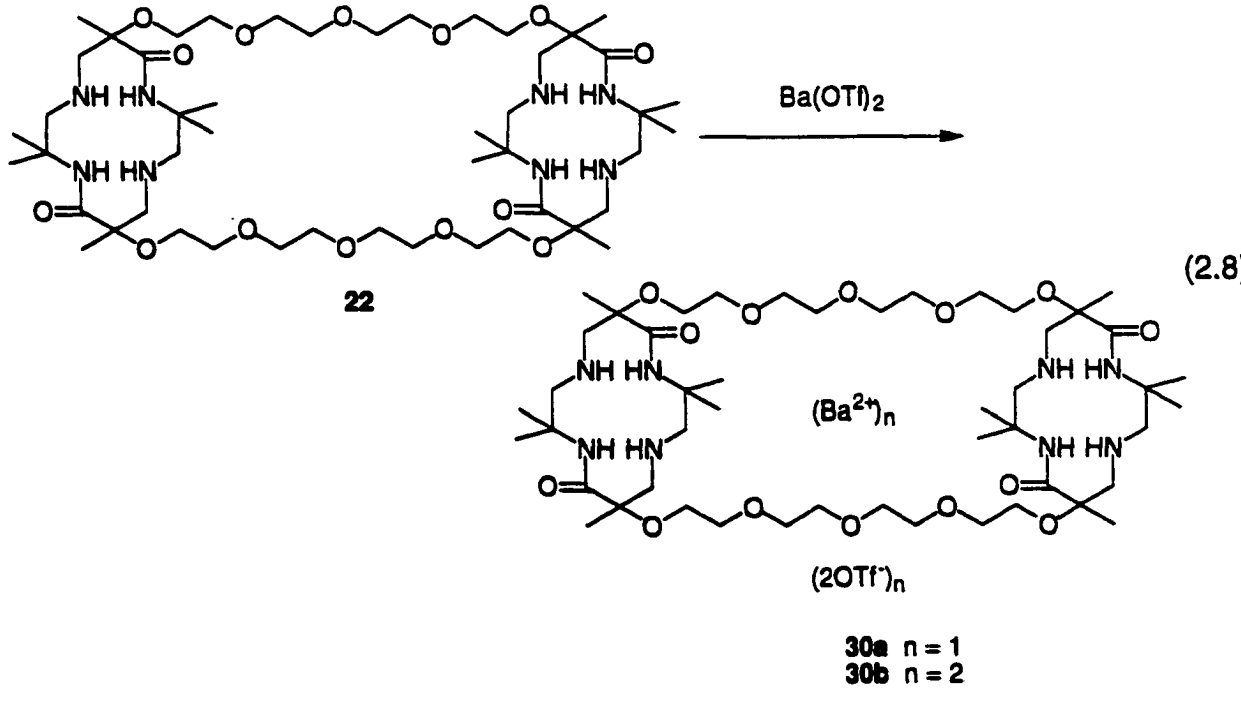


21 28 (2.6)

Triethylene glycol bis-cyclam **20** was also complexed with $Ba(OTf)_2$ (equation 2.7). The ^1H-NMR spectrum was significantly broadened and could not be completely analyzed. The ^{13}C-NMR spectra had only a few changes in the chemical shifts of the peaks. The IR stretching frequency for the amide carbonyl had shifted slightly from 1670 cm^{-1} to 1650 cm^{-1}. The three intense peaks in the FAB-MS each corresponded to a barium complex. The base peak at m/z 1203 corresponded to **20**•$Ba(OTf)_2$-OTf. The next peak appeared at m/z 1353. and was assigned to the **20**•$Ba(OTf)_2+H^+$. The highest mass peak at m/z 1639 corresponded to **20**•$2(Ba(OTf)_2)$-OTf. The 4:1:2 ratio of these peaks suggested that the mono-barium complex was the most stable. There was no peak which corresponded to the free ligand. This indicated that the reaction had gone to completion. The calculated isotope distribution patterns for **20**•$Ba(OTf)_2$-OTf and **20**•$Ba(OTf)_2+H^+$ matched the actual isotope pattern obtained from the MS. For **6**•$2(Ba(OTf)_2)$-OTf, which has two bariums, the predicted isotope pattern has ten peaks centered around m/z 1639. The complex also has ten peaks in the exact same ratios as was calculated.



Tetraethylene glycol bis-cyclam, **22**, was treated with $Ba(OTf)_2$ in hot methanol (equation 2.8). The resulting white solid had a ^1H-NMR spectrum that was significantly broadened, like the ^1H-NMR

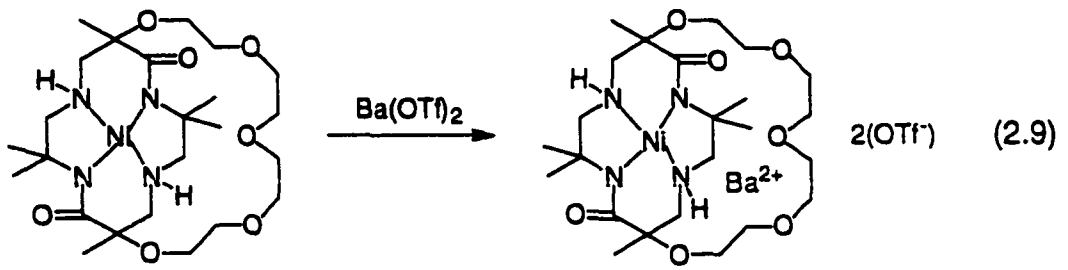


spectrum for the barium complex of **20**. The amide carbonyl stretching frequency in the IR shifted from 1670 cm^{-1} to 1634 cm^{-1}. This suggested strong carbonyl coordination to the barium. The three intense peaks in the FAB-MS each corresponded to a barium complex. The base peak at m/z 1291 and assigned to the **22**•$Ba(OTf)_2$-OTf. The peak at m/z 1727 was assigned to **22**•2($Ba(OTf)_2$)-OTf. The peak at m/z 789 might correspond to **22**•2($Ba(OTf)_2$)-2OTf. Again, the calculated isotope distribution for **22**•2($Ba(OTf)_2$)-OTf exactly matched the actual distribution from the MS.

2.3.4 Barium-Nickel Complexes

To test whether the polyether bridge could complex Ba^{2+} alone or if it needed the cyclam ring, especially the amide carbonyl oxygens for extra coordination sites, nickel complex **24** was treated with $Ba(OTf)_2$ in methanol at reflux. The solution was then cooled to room temperature and the solvent was removed, giving a pink solid (equation 2.9). The color was slightly changed to a lighter pink than the original nickel-complex. The ^1H and ^{13}C-NMR spectra had only slight changes as compared with starting material. As expected, the stretching frequency of the amide carbonyl did not change. The FAB-MS gave the strongest evidence for barium-complexation. Two of the most intense peaks appeared at m/z 845 and m/z 559. The m/z of 845 resulted from **24**•$Ba(OTf)_2$-OTf, and the m/z 559 was starting nickel-complex. These peaks were of equal intensity. The calculated isotope distribution for **24**•$Ba(OTf)_2$-OTf exactly matched

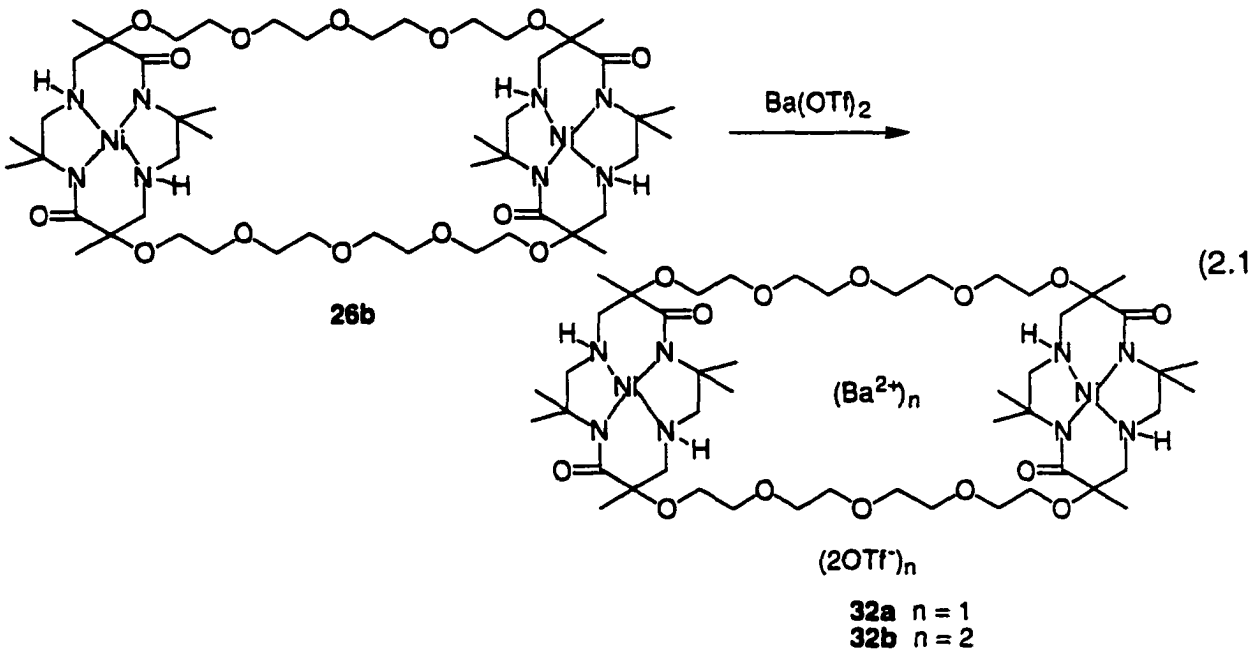
the actual isotope distribution resulting from one nickel atom, which has five isotopes, and one barium atom, which has seven isotopes.



24 31 (2.9)

When **26b** was treated with $Ba(OTf)_2$ under the same conditions, another compound only slightly less pink than the starting material was isolated (equation 2.10). The ^1H, ^{13}C-NMR and IR spectra did not significantly change from those of the starting material, but the FAB-MS did show interesting results. First, the lack of any starting Ni-complex peak indicated that the reaction had gone to completion and the complex was stable to the conditions of the MS. The first intense peak had a m/z of 1403, which corresponded to **26b**•$Ba(OTf)_2$-OTf, a complex that had two nickel ions and one barium ion. The next intense peak occurred at m/z 1838.6. This peak corresponded to **26b**•($2Ba(OTf)_2$)-OTf, a compound which had two nickel and two barium ions. The calculated isotope distribution for **26b**•($2Ba(OTf)_2$)-OTf, with nickel's five isotopes and barium's seven isotopes, matched the actual isotope distribution pattern obtained from the MS. Furthermore, a m/z peak at 845 and 1689 also lend evidence for complexation. These two peaks correspond to the [**26b**•$2(Ba(OTf)_2)$-2OTf $]^{2+}$ for the m/z 845 peak and **26b**•$2(Ba(OTf)_2)$-OTf-H^+ for the m/z 1689. Finally, a weak peak at

m/z 1990 corresponded to the **26b**• $(2Ba(OTf)_2)+H^+$. All attempts to recrystallize these compounds failed due to crystal twinning or powdering.



(2.1

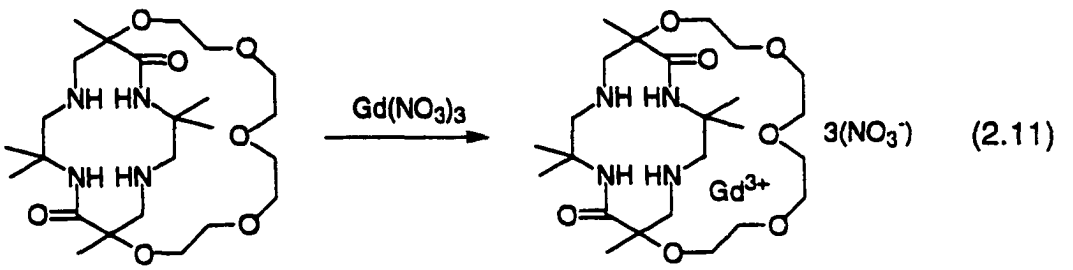
2.3.5 Gadolinium Complexes

The purpose of the barium complexation study was to prove that hard cations would coordinate with and without the presence of a soft transition metal ion. Due to the success of the barium complexation studies, a preliminary study on gadolinium complexation was undertaken. Gadolinium (Gd) is the choice metal for most MRI contrast agents because of its high magnetic moment and long relaxation time.[15b] Gadolinium, which has an ionic radius of 0.938 Å, is smaller than barium, therefore, it might possibly coordinate more strongly into the basket cyclams. Furthermore, because the polyether cavity is large, two gadoliniums might complex to the bis-cyclams. These bis-gadolinium metal complexes might be

more sensitive contrast agents. In any event, complexation to gadolinium will open up a new class of potential MRI contrast agents.

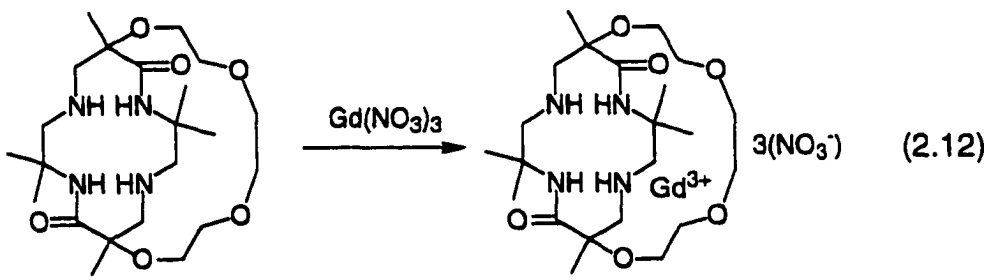
Tetraethylene glycol basket cyclam **21** was treated with $Gd(NO_3)_3$ in methanol at reflux, and after removal of the solvent, yielded a white solid (equation 2.11). Because Gd(III) is paramagnetic, ^1H and ^{13}C-NMR spectra could not be obtained. The FAB-MS of this compound had a base peak at m/z 503 which corresponded to the free ligand. It had a very weak peak for the complex at m/z 784 ((**21**•$Gd(NO_3)_3$)-NO_3). This result suggested the complex was unstable to the conditions for FAB-MS or that it was slow to complex the gadolinium. Therefore, the mixture was heated for 24 hours. Unfortunately, this gave no change in the FAB-MS spectrum. An IR spectrum of the mixture, however, revealed very positive results. The amide carbonyl stretching frequency had shifted from 1670 cm^{-1} to 1635 cm^{-1}. This, as with the barium complexes, suggested strong coordination of the amide carbonyl oxygens to the gadolinium. No free ligand amide carbonyl stretch was visible. Furthermore, when the free ligand was combined with the reaction mixture and an IR was taken, two distinctly different carbonyl peaks could be distinguished. With gadolinium's seven isotopes, the calculated isotope distribution pattern for **21**•$Gd(NO_3)_3$-NO_3, matched exactly with the distribution pattern obtained from the MS.

It was believed the cavity of **21** was too large for the gadolinium coordinate effectively. The radius of gadolinium is



21 33 (2.11)

0.938 Å which was smaller than the radius for barium by about 0.4 Å. Treatment of **19** with Gd(NO3)3 in methanol under the same conditions for **21** resulted in a white solid (equation 2.12). A FAB-

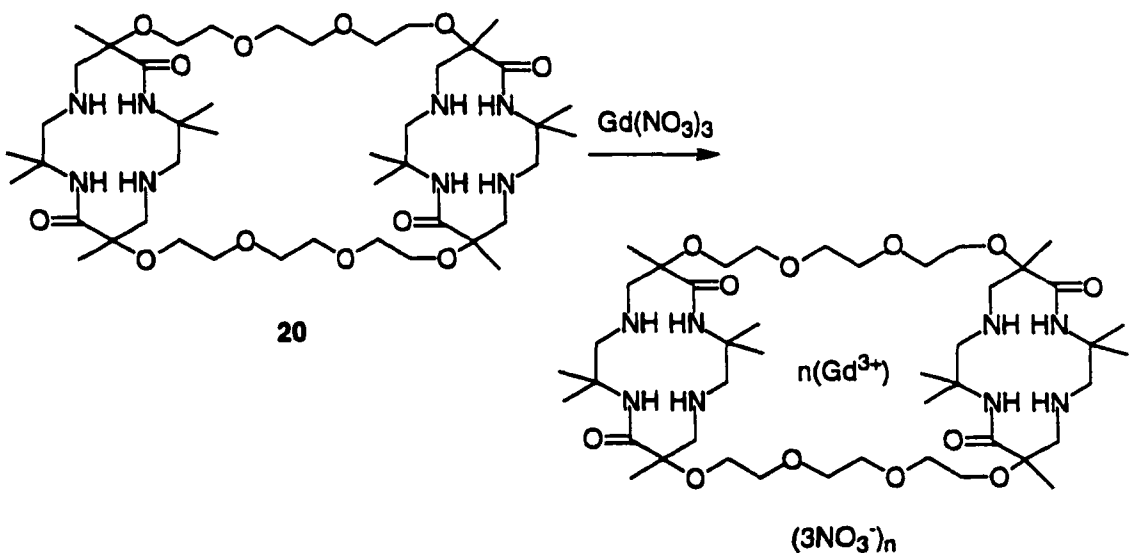


19 34 (2.12)

MS of the compound had a base peak at m/z 459 which was assigned to the free ligand. There was also a very weak peak at m/z 740 which corresponded to (**19**•Gd(NO3)3)-NO3. The IR spectrum, however, gave no evidence of the free ligand. The amide carbonyl had completely shifted from 1670 cm^{-1} to 1635 cm^{-1}.

With evidence that gadolinium had complexed to **19** and **21**, complexation with triethylene glycol bis-cyclam **20** was attempted. Treatment of **20** with one equivalent of Gd(NO3)3 in methanol at reflux, followed by cooling to room temperature and removal of the solvent resulted in a white solid (equation 2.13). The FAB-MS of this

compound had two intense peaks. The first was peak at m/z 917 was assigned to the free ligand. The second peak at m/z 1198 was assigned to **20**•Gd(NO3)3-NO3. The peak corresponding to the complex was more intense than that of the free ligand. The IR stretching frequency of the amide carbonyl had a peak at 1675 cm^{-1} corresponded to **20** and a shoulder at 1638 cm^{-1} which corresponded to **20**•Gd(NO3)3. This confirms the MS with both free ligand and complex present. Bis-cyclam **20** was then treated with two equivalents of Gd(NO3)3 under the same conditions as above and a FAB-MS was taken. First, there was a lack of a peak for the free



20

35a n = 1
35b n = 2

(2.13)

ligand indicating complete coordination. The base peak at m/z 1198 which corresponded to **20**•Gd(NO3)3-NO3. Now, however, there was a small peak at m/z 1541. This corresponded to **20**•2(Gd(NO3)3)-NO3, a compound in which two gadoliniums were present. As before, the calculated isotope distribution for **20**•2(Gd(NO3)3)-NO3 and

20•$Gd(NO_3)_3$-NO_3 exactly matched the actual distribution for both the mono-gadolinium complex and the bis-gadolinium complex. Attempts at crystallizing these gadolinium compounds were unsuccessful again due to crystal twinning and disorder.

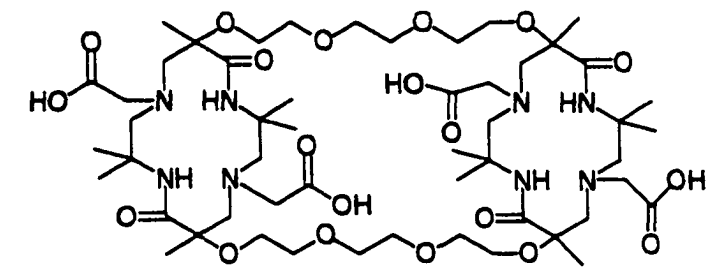
2.4 Conclusions

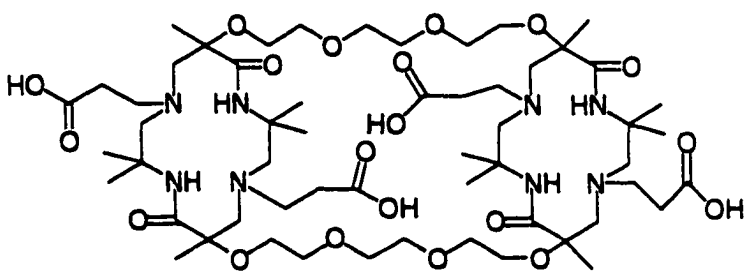
A new class of dioxocyclams has been developed. These dioxocyclams, which are either the mono "basket" dioxocyclams or the bis-dioxocyclams, have shown interesting properties. These ligands not only complex soft transition metals such as nickel, but also hard cations, such as barium. They also form hetero-dimetallic complexes of nickel and barium. These dioxocyclams also coordinate to gadolinium These gadolinium complexes open a new class of potentially useful MRI contrast agents. Although these ligands do not complex gadolinium tightly, they can be modified in order to increase their complexation abilities.

2.5 Future Directions

Future direction of this project will focus on increasing the stability of the gadolinium complexes. A potential method for accomplishing this is to treat the dioxocyclams with bromoacetic acid. This will add two more coordination sites to the ligand which should increase the stability of the gadolinium complex. Also, cyclam derivatives undergo Michael reactions with α,β-unsaturated acids. These acid moieties would yield ligands whose carboxylate groups

are one carbon further away from the cyclam ring, increasing flexibility. Once a stable gadolinium complex is found, its relaxation properties will be measured. Hopefully, this will open up a new class of MRI contrast agents with increased ability to distinguish between tissue types.





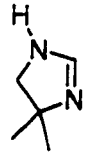
2.6 Experimental

Experimental Section

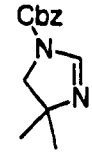
General Procedures: All NMR spectra (300 MHz for ^{1}H-NMR and 75 MHz, for ^{13}C-NMR) were recorded in $CDCl_3$ and chemical shifts were given in relative to TMS (0.00 for ^{1}H) and $CDCl_3$ (77.0 for ^{13}C) unless otherwise stated. The 300 MHz 1H-NMR and 75.5 MHz 13C-NMR were taken on a Varian Inova-300 spectometer and 400 MHz 1H-NMR and 100.6 13C-NMR were taken on a Varian Inova-500 spectometer. Mass specta were recorded on a Fisons Instraments VG autospec. X-ray crystallographic studies were performed on a Bruker Smart CCD diffractometer. The structures were solved using Bruker SHELXTL version 5.03 software. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR. Pentacarbonyl[(methyl)-{(tetramethylammonio)oxy}carbene]chromium(0)[31] was prepared by literature methods. The tri- and tetra(ethylene)glycols were dried over P_2O_5 and distilled under reduced pressure. THF was distilled from sodium-benzophenone ketyl; CH_2Cl_2 was distilled from CaH_2; MeOH was stored over 3 Å sieves prior to use. Column chromatography was performed with ICN 32-63 nm, 60 Å silica gel. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

4,4-Dimethyl-Δ^2-imidazoline.[32] Into a flame-dried, 100 mL round bottomed flask was placed 11.25 g (127.6 mmol) of 1,2-diamino-2-methylpropane and 14.70 g (127.6 mmol) of N,N-

dimethylformamide dimethylacetal This mixture was placed under Ar and heated to 60°C overnight. The solution was cooled to room temperature and distilled under vacuum (0.1 mm Hg). The fraction boiling at 40°C was collected to yield 10.10 g (102.9 mmol, 81%) of 4,4-dimethyl-Δ^2-imidazoline as a clear oil. ^{1}H-NMR δ 6.79 (s, 1H); 4.48 (bs, 1H); 3.32 (s, 2H); 1.29 (s, 6H). This material was converted to **17** without further purification.

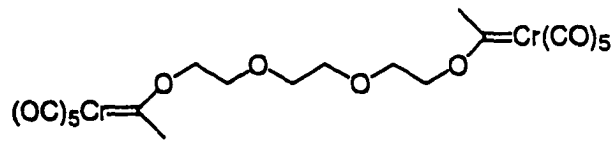


1-(Benzyloxycarbonyl)-4,4-dimethyl-Δ^2-imidazoline, 17.[32] Into a flame-dried, 500 mL round bottomed flask was placed 10.1 g (103 mmol) of 4,4-dimethyl-Δ^2-imidazoline, along with 52.0 g (575 mmol) triethylamine and 250 mL CH_2Cl_2. This was placed under Ar and cooled to 0°C. Benzyl chloroformate, (20.3 g, 119 mmol) was slowly added over 15 minutes. The solution was stirred at 0°C for 30 minutes and warmed to room temperature overnight. The solution was washed with sat. $NaHCO_3$ (aq) and water. The organic layer was separated and dried over Na_2SO_4. The solvent was removed under vacuum and the resulting yellowish oil was distilled under vacuum (0.01 mm Hg) at 105°C to give 16.8 g (72.4 mmol, 70%) of 1-(benzyloxycarbonyl)-4,4-dimethyl-Δ^2-imidazoline as a clear oil. The pressure at which the product is distilled is



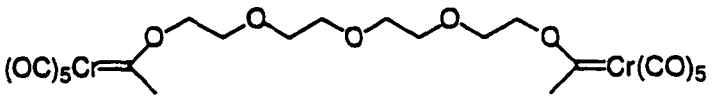
critical. The temperature cannot exceed 120°C or the yield will be decreased significantly. ^{1}H-NMR δ 7.42 (m, 5H); 5.26 (s, 2H); 3.47 (s, 2H); 1.34 (s, 6H). All other spectra were identical to those found in the literature.

Bis-carbene complex 16a.



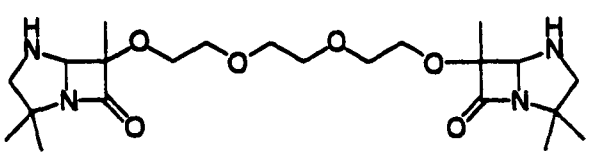
Into a flame-dried, 250 mL round bottomed flask was placed 3.8 g (12.6 mmol) of **15** and 63 mL of dry CH_2Cl_2. This solution was cooled to -40°C and 1.42 mL (11.5 mmol) of pivaloyl chloride was added. The mixture was stirred at -40°C for 20 minutes. Then, 0.67 mL (5.0 mmol) of dry tri(ethylene)glycol was added. The mixture was allowed to slowly warm to room temperature overnight. The reaction mixture was filtered and washed once with 5% $NaHCO_3$ (aq) and dried over $MgSO_4$. The solution was filtered and the solvent was removed under vacuum, adsorbing the product onto silica gel. The mixture was purified by column chromatography (silica gel) using 8:1 hexane:ethyl acetate until the excess pivalic acid had eluted and then with 2:1 hexane:ethyl acetate to collect 2.0 g (3.4 mmol, 68%) product as a yellow oil. ^{1}H-NMR δ 5.01 (bs, 4H); 4.04 (bs, 4H); 3.76 (bs, 4H); 2.97 (bs, 6H); ^{13}C-NMR δ 360.0, 223.1, 216.6, 71.0, 70.7, 69.1, 27.0; IR (thin film) ν 2064, 1899 cm^{-1}; HRMS FAB (M+) $C_{20}H_{18}O_{14}Cr_2$ Calc. 585.9507. Found 585.9510.

Bis-carbene complex 16b.



Into a flame-dried, 250 mL round bottomed flask was placed 4.0 g (12.9 mmol) of **15** and 120 mL of dry CH_2Cl_2. This solution was cooled to -40°C and 1.6 mL (12.9 mmol) of pivaloyl chloride was added. This solution was left to stir at -40°C for 1 hour. Then, 0.89 mL (5.16 mmol) of dry tetra(ethylene)glycol was added. This mixture was allowed to slowly warm to room temperature over 24 hours. The solution was filtered and the solvent removed under vacuum, adsorbing the product onto silica gel. Purification was accomplished using column chromatography (silica gel) and eluting with 4:1 hexane:ether until the excess pivalic acid had eluted and then with ether to collect 2.8 g (4.5 mmol, 87%) product as a yellow oil. ^{1}H-NMR δ 5.04 (bs, 4H); 4.05 (m, 4H); 3.74 (m, 8H); 2.99 (s, 6H); ^{13}C-NMR δ 359.4, 223.2, 216.3, 71.2, 70.9, 69.4, 27; IR (thin film) ν 2063, 1916 cm^{-1}; HRMS FAB (M+) $C_{22}H_{22}O_{15}Cr_2$ Calc. 629.9769. Found 629.9767.

Bis-azapenam 18a.

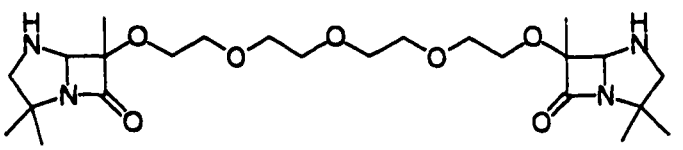


Into an oven dried 125 mL Ace pressure tube was placed 1.0 g (1.7 mmol) of bis-carbene complex **16a**, 57 mL of CH_2Cl_2, and 0.76 g (3.3 mmol) of 4,4'-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid benzyl ester. This mixture was freeze-pump-thaw degassed three times and flushed with CO (the pressure tube was filled with 80 psi of CO and slowly released) three times. The pressure tube was filled with 80 psi CO and irradiated (4 x 500 W halogen lamps) at 55°C. After 7 hours, the reaction was removed from the 55°C bath and irradiated at room temperature (450 W Conrad-Hanovia 7825, Pyrex well) for 2 days. The solvent was removed under vacuum and methanol was added to precipitate the $Cr(CO)_6$. This was removed by filtration and the methanol was removed under vacuum. The residue was dissolved in 1:1 hexane:ethyl acetate and placed into sunlight to oxidize any residual chromium complexes (usually one day), the mixture was filtered and the solvent was removed under vacuum. Purification was accomplished using column chromatography (silica gel) eluting with 3:1 hexane:ethyl acetate until the unreacted imidazoline was off and then with ethyl acetate to obtain 0.92 g (1.3 mmol, 74%) as a clear oil.

Cbz-protected **18a** 0.87 g (1.2 mmol), 500 mg of 10% Pd/C, 60 mL of dry methanol and 60 drops of triethylamine were added to an oven dried 125 mL Ace pressure tube. This was pressured with 80 psi H_2 and stirred at room temperature for 2 hours. The mixture was filtered and the solvent removed under vacuum. The residue was dissolved in CH_2Cl_2 and washed one time with 5% $NaHCO_3$ (aq). The aqueous layer was extracted three times with CH_2Cl_2 and the combined organic layers were dried over Na_2SO_4. The solvent was

removed under vacuum to yield 0.55 g (1.2 mmol, 100%) of free azapenam **18a** as a clear oil. ^{1}H-NMR δ 4.75 (s, 2H); 3.79-3.84 (m, 4H); 3.62-3.75 (m, 8H); 3.05 (d, J = 11.1Hz, 2H); 2.65 (d, J = 11.4Hz, 2H); 2.35 (bs, 2H); 1.54 (s, 6H); 1.30 (s, 6H); 1.08 (s, 6H); ^{13}C-NMR δ 175.5, 89.5, 77.9, 70.4, 65.3, 61.9, 60.8, 24.8, 21.6, 14.7; IR (thin film) ν 1747 cm^{-1}; HRMS FAB (M+1) $C_{22}H_{39}N_4O_6$ Calc. 455.2870. Found 455.2864.

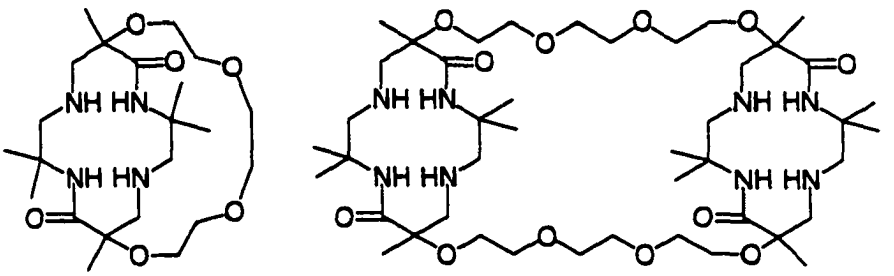
Bis-azapenam 18b.



Using a procedure similar to that of **18a**, 1.3 g (2.1 mmol) of bis-carbene complex **16b**, 0.94 g (4.1 mmol) of 4,4'-dimethyl-4,5-dihydro-imidazole-1-carboxylic acid benzyl ester, and 70 mL of CH_2Cl_2 were irradiated (4 x 500 W halogen lamps) at 55°C for 5 hours and then at room temperature (450 W Conrad-Hanovia 7825, Pyrex well) for 2 days, followed by isolation as with **18a** to give 1.4 g (1.8 mmol, 83%) of Cbz-protected azapenam **18b**. The Cbz group was removed under standard conditions using 1.1 g (1.4 mmol) of azapenam, 0.56 g of 10% Pd/C, 70 mL of methanol and 2 mL of triethylamine to yield 1.4 g (1.3 mmol, 91%) of free azapenam **18b**. ^{1}H-NMR δ 4.82 (s, 2H); 3.88 (m, 2H); 3.70-3.81 (m, 14H); 3.10 (d, J = 11.4Hz, 2H); 2.66 (d, J = 11.1Hz, 2H); 2.38 (bs, 2H); 1.60 (s, 6H); 1.36 (s, 6H); 1.14 (s, 6H); ^{13}C-NMR δ 175.5, 170.8, 89.5, 77.8, 70.5, 70.4, 70.3, 69.0, 65.2, 63.5, 61.9, 60.8, 24.9, 21.7, 20.9, 14.8. IR (thin film) ν

1745 cm^{-1}; HRMS FAB (M+1) $C_{24}H_{43}N_4O_7$ Calc. 499.3132. Found 499.3121.

Dioxocyclam 19, 20.



19 **20**

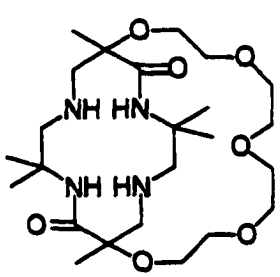
Into a 250 mL round bottomed flask was placed 0.50 g (1.1 mmol) of azapenam **18a**, 32 mg (0.14 mmol) of racemic camphor sulfonic acid and 110 mL dry of CH_2Cl_2. This was allowed to stir at room temperature for three days. The solution was then washed with 5% $NaHCO_3$ (aq), and the aqueous layer was extracted three times with CH_2Cl_2. The solution was dried over Na_2SO_4 and the solvent removed under vacuum. The residue was dissolved in 55 mL of CH_2Cl_2 and 55 mL of methanol. To this was added a small crystal of bromocresol green and 151 mg (2.4 mmol) of $NaCNBH_3$. The mixture was cooled to 0°C and sat. HCl/MeOH was added until a yellow-green color persisted (pH=6). The reaction was warmed to room temperature and stirred at this temperature overnight adding additional HCl/MeOH as needed to keep the pH=6. Saturated HCl/MeOH was added to give a pH=1. Then, 10% NaOH(aq) was added to give a pH=10. The aqueous layer was extracted three times with CH_2Cl_2, dried over Na_2SO_4 and the solvent was removed under vacuum.

Purification was accomplished using column chromatography (silica gel) eluting with 95:5 CH_2Cl_2:MeOH to yield 0.15 g (0.33 mmol, 30%) of basket cyclam **19**, and then 10:1 CH_2Cl_2:MeOH to yield 0.123 g (0.13 mmol, 25%) of bis-cyclam **20**.

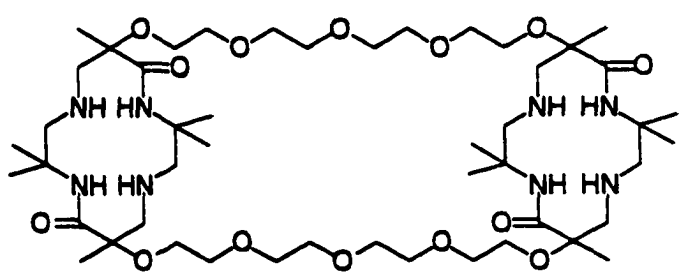
Dioxocyclam 19. ^{1}H-NMR (d^6-acetone) δ 7.57 (s, 2H); 3.45-3.72 (m, 12H); 3.03 (d, J = 11.3Hz, 2H); 2.80, (d, J = 11.7Hz, 2H); 2.65, (d, J = 11.8Hz, 2H); 2.11, (d, J = 11.3Hz, 2H); 1.97-2.02 (m, 2H); 1.32, (s, 6H); 1.20, (s, 6H); 1.14 (s, 6H); ^{13}C-NMR (d^6-acetone) δ 172.7, 80.3, 71.6, 71.3, 63.6, 58.2, 57.1, 53.5, 26.7, 25.0, 20.1; IR (thin film) ν 1667 cm^{-1}; Analysis Calculated for C: 57.62, H: 9.23, N: 12.22. Found: C: 57.44, H: 9.10, N: 12.27.

Dioxocyclam 20. ^{1}H-NMR δ 7.07 (s, 4H); 3.45-3.72 (m, 24H); 2.88 (d, J = 12.0Hz, 4H); 2.62 (d, J = 12.3Hz, 4H); 2.12 (d, J = 11.1Hz, 4H); 1.42 (s, 12H); 1.32 (s, 12H); 1.25 (s, 12H); ^{13}C-NMR δ 171.9, 80.1, 70.8, 70.7, 62.7, 56.9, 56.4, 52.9, 26.8, 25.2, 19.3; IR (thin film) ν 1670 cm^{-1}. This solid was recrystallized from MeOH:H_2O to give X-ray quality crystals.

Dioxocyclam 21, 22.



21

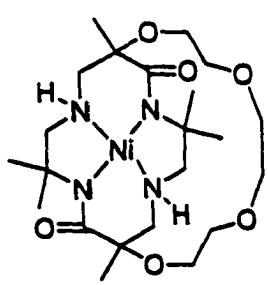


22

The dimerization and reduction of **18b** were accomplished using the general conditions for **19, 20**. Using 0.64 g (1.3 mmol) of free azapenam **18b**, after the reduction and purification, 0.23 g (0.45 mmol, 35%) of **21** and 0.10 g (0.10 mmol, 15%) of **22** were obtained.

Dioxocyclam 21. ^{1}H-NMR δ 7.05 (s, 2H); 3.72-3.85 (m, 2H); 3.67-3.70 (m, 12H); 3.57-3.66 (m, 4H); 2.92 (d, J = 11.7Hz, 2H); 2.57 (d, J = 11.7Hz, 2H); 2.04 (d, J = 10.8Hz, 2H); 1.43 (s, 6H); 1.33 (s, 6H); 1.29 (s, 6H); ^{13}C-NMR δ 172.1, 80.2, 71.0, 70.6, 70.3, 63.0, 57.3, 56.5, 53.1, 27.2, 25.4, 19.4; IR (thin film) ν 1668 cm^{-1}; HRMS FAB (M+1) $C_{24}H_{47}N_4O_7$ Calc. 503.3445. Found: 503.3434. This solid was recrystallized from MeOH:H_2O to give X-ray quality crystals.

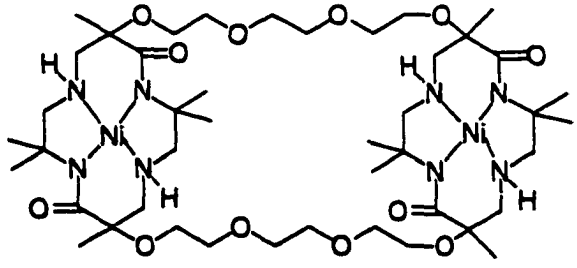
Dioxocyclam 22. ^{1}H-NMR δ 6.96 (s, 4H); 3.59-3.71 (m, 28H); 3.45-3.54 (m, 8H); 2.84 (d, J = 12.0Hz, 4H); 2.53 (d, J = 12.3Hz, 4H); 2.07 (d, J = 10.8Hz, 4H); 1.38 (s, 12H); 1.29 (s, 12H); 1.22 (s, 12H); ^{13}C-NMR δ 172.0, 80.4, 71.0, 70.8, 70.7, 63.0, 57.3, 56.4, 53.1, 27.0, 25.4, 19.3; IR (thin film) ν 1668 cm^{-1}; HRMS FAB (M+1) $C_{48}H_{93}N_8O_{14}$ Calc. 1005.6811. Found: 1005.6781.



Nickel complex 23. Into a flame-dried, 100 mL round bottomed flask under Ar was placed 0.11 g (0.25 mmol) of basket cyclam **19**, 0.54 g (1.2 mmol) of $NiBr_2$•3DMF, one drop of triethylamine and 30 ml of MeOH. This mixture was heated to reflux overnight. The solution

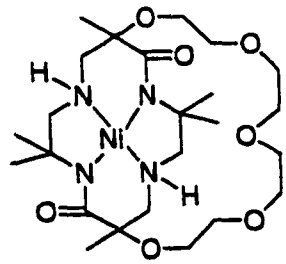
was cooled to room temperature, filtered through Celite and the solvent was removed under vacuum. The residue was dissolved in CH_2Cl_2 and washed once with water. The aqueous layer was extracted 3 X 50 mL CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was removed under vacuum. Purification was accomplished using column chromatography (silica gel) eluting with 8:1 ethyl acetate: methanol to yield 0.07 g (0.14 mmol, 55%) of **23** as a pink solid ^{1}H-NMR δ 4.18-4.11 (m, 2H); 3.99-3.75 (m, 8H); 3.54 (d, J = 10.4 Hz , 2H); 3.22 (t, J = 12.6 Hz, 2H); 2.78 (dd, J = 10.8 Hz, 13.8 Hz, 2H); 2.52 (t, J = 11.6 Hz, 2H); 2.13 (dd J = 11.1, 1.6 Hz, 2H); 1.84, (dd, J = 10.5, 2.7 Hz, 2H); 1.40 (s, 6H); 1.29, (s, 6H); 1.20, (s, 6H); ^{13}C-NMR δ 172.7, 70.3, 69.5, 65.6, 62.1, 58.5, 57.1, 25.1, 22.7, 20.1; IR (thin film) ν 1550 cm^{-1}. This solid was recrystallized from CH_2Cl_2:MeOH to give X-ray quality crystals.

Nickel complex 25.



Into a flame-dried, 50 mL round bottomed flask under Ar was placed 0.57 g (2.9 mmol) of $AgBF_4$, 0.63 mg (2.9 mmol) of $NiBr_2$, and 29 mL of THF. This solution was heated to reflux for 1 hour. The resulting pale green solution was filtered hot through Celite into an oven-dried, 125 mL Ace pressure tube containing 0.27 mg (0.29

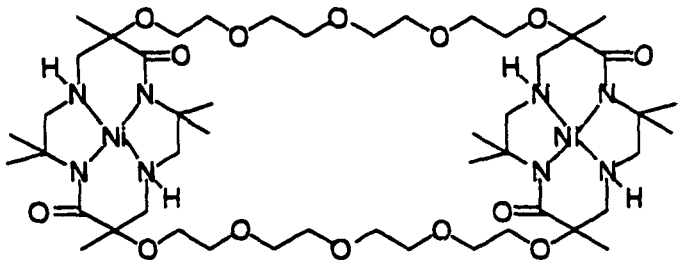
mmol) of bis-cyclam **20**, 0.15 mL of triethylamine, and 10 mL of THF. The tube was sealed and heated to 80°C for 2 days. The resulting pink solution was cooled to room temperature and 20 mL 5% $NaHCO_3$ (aq) was added. This solution was extracted 3 X 20 mL CH_2Cl_2, dried over Na_2SO_4, and the solvent was removed under vacuum to yield 0.18 g (0.18 mmol, 60%) of **25** as a pink solid. ^{1}H-NMR δ 3.65-3.87 (m, 28H); 3.06 (t, J = 12.6 Hz ,6H); 2.75 (dd, J = 10.8, 13.5Hz. 4H); 2.50 (t, J = 11.7 Hz, 4H); 2.13, (d, J = 9.9 Hz, 4H); 1.84 (d, J = 10.5 Hz, 4H); 1.35 (s, 12H); 1.26 (s, 12H); 1.17 (s, 12H); ^{13}C-NMR δ 172.5, 76.8, 70.9, 70.5, 65.3, 62.8, 58.4, 56.5, 24.8, 22.6, 20.3; IR (thin film) ν1574 cm^{-1}. This solid was recrystallized from $CHCl_3$:pentane to give X-ray quality crystals.



Nickel complex 24. Nickel complex **24** was synthesized under the conditions for **25** using 0.21 g (1.1 mmol) of $AgBF_4$, 0.23 g (1.1 mmol) of $NiBr_2$, and 10 mL of THF. This was filtered hot through Celite into an oven-dried, 40 mL Ace pressure tube containing 0.13 g (0.26 mmol) of cyclam **21**, 0.15 mL of triethylamine, and 5 mL of THF. This mixture was heated to 80°C for 2 days and isolated as for **25**, to yield 0.145 g (0.26 mmol, 100%) of **24** as a pink solid. ^{1}H-NMR δ 3.55-4.06 (m, 16H); 3.11 (t, J = 12.9Hz, 2H); 2.69 (t, J = 11.7Hz, 4H); 2.21 (dd, J = 2.4, 12.0Hz, 2H); 1.85 (dd, J = 3.3, 10.5Hz, 2H); 1.40 (s, 6H); 1.35 (s, 6H); 1.24 (s, 6H); ^{13}C-NMR δ 172.8, 71.1,

70.9, 70.5, 66.0, 63.2, 58.7, 57.1, 24.9, 22.6, 20.3; IR (thin film) ν 1574 cm^{-1}. This solid was recrystallized from $CHCl_3$:hexane to give X-ray quality crystals

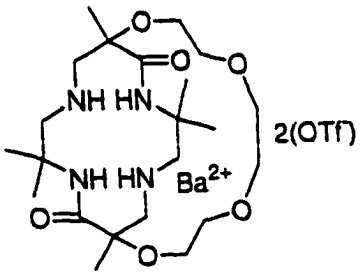
Nickel complex 26b.



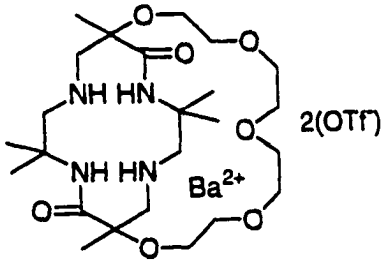
Nickel complex **26b** was synthesized under the conditions for **25** using 0.21 g (1.1 mmol) of $AgBF_4$, 0.13 g (0.58 mmol) of $NiBr_2$, and 10 mL of THF. This was filtered through Celite into an oven-dried, 40 mL Ace pressure tube containing 53 mg (0.05 mmol) of bis-cyclam **22** and 5 mL of THF and heated to 80°C overnight. The product was isolated as for **25** to yield 45 mg (0.04 mmol, 80%) of bis-nickel complex **26b**. ^{1}H-NMR δ 3.75-4.01 (m, 28H); 3.17 (t, J = 12.9 Hz, 4H); 2.82 (dd, J = 10.5, 13.2 Hz, 4H); 2.61 (t, J = 11.7 Hz, 4H); 2.23 (dd, J = 1.8, 11.1 Hz, 4H); 1.91 (dd, J = 3.3, 10.5 Hz, 4H); 1.43 (s, 12H); 1.35 (s, 12H); 1.26 (s, 12H); ^{13}C-NMR δ 172.9, 76.9, 71.3, 70.9, 70.5, 65.5, 63.2, 58.6, 56.8, 24.8, 22.7, 20.6; IR (thin film) ν 1579 cm^{-1}; HRMS FAB (M+1) $C_{48}H_{89}N_8O_{14}Ni_2$ Calc. 1117.5205. Found: 1117. 5205.

Barium complex 27. Into a 100 mL round bottomed flask was placed 0.17 g (0.36 mmol) of basket cyclam **19**, 0.18 g (0.41 mmol)

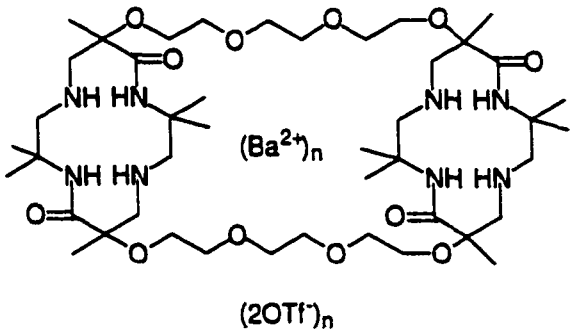
of $Ba(OTf)_2$ and 37 mL of MeOH. This was heated to reflux overnight. The solution was cooled to room temperature and the solvent was removed under reduced pressure to yield a white solid. ^{1}H-NMR (CD_3OD) δ 3.84-5.56 (m, 12H); 3.08 (d, J = 11.7 Hz, 2H); 2.91 (q, J1 = 12.3 Hz, J2 = 12.0 Hz, 4H); 2.37 (d, J = 12.0 Hz, 2H); 1.44 (s, 6H); 1.34, (s, 6H); 1.31, (s, 6H); ^{13}C-NMR (CD_3OD) δ 174.8, 81.1, 71.6, 71.4, 63.9, 58.3, 57.3, 54.7, 26.8, 24.7, 19.8; IR (thin film) ν 1668 cm^{-1}; MS FAB ((**19**•$Ba(OTf)_2$)-OTf) $C_{23}H_{42}BaF_3N_4O_9S$ calc. 745.17, found 745.32.



Barium complex 28. Into a 50 mL round bottomed flask was placed 60 mg (0.12 mmol) of basket cyclam **21**, 72 mg (0.17 mmol) of $Ba(OTf)_2$ and 17 mL of MeOH. This was heated to reflux overnight. The solution was cooled to room temperature and the solvent was removed under reduced pressure to yield a white solid. ^{1}H-NMR (CD_3OD) δ 3.55-3.76 (m, 16H); 3.35 (bd, 2H); 2.79 (d, J = 11.7 Hz, 1H); 2.67 (d, J = 12.0 Hz, 1H); 2.19 (bs, 2H); 1.36 (s, 6H); 1.31 (s, 6H); 1.29 (s, 6H); ^{13}C-NMR (DMSO-d^6) δ 171.5, 120.7 (q J = 319 Hz); 79.0, 72.4, 69.9, 69.4, 62.9, 56.2, 56.1, 55.5, 52.1, 26.4, 24.9, 18.8; IR (thin film) ν 1654 cm^{-1}; MS FAB (**21**•($Ba(OTf)_2$)-OTf)) $C_{25}H_{46}BaF_3N_4O_{10}S$ calc. 789.19, found 789.37.

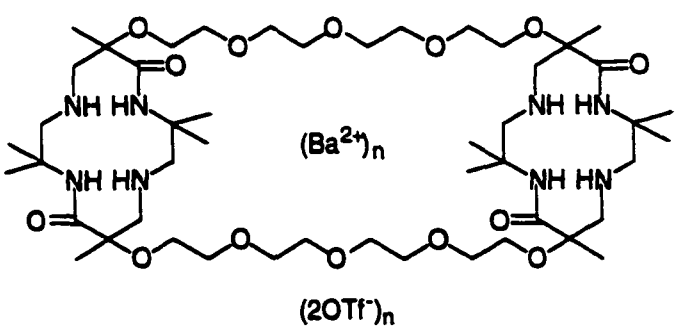


Barium complex 29.



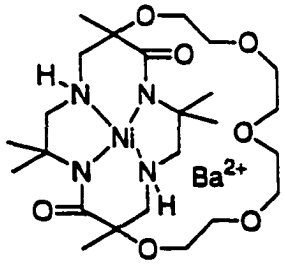
Into a 50 mL round bottomed flask was placed 0.10 g (0.11 mmol) of bis-cyclam **20**, 0.50 g (1.1 mmol) of $Ba(OTf)_2$ and 15 mL of MeOH. This was heated to reflux overnight. The solution was cooled to room temperature and the solvent was removed under reduced pressure to yield a white solid. ^{1}H-NMR (CD_3OD) δ 3.73-3.77 (m, 32H); 2.9 (bs, 10H); 1.33-1.50 (bm, 36H); ^{13}C-NMR (DMSO-d^6, CD_3OD) δ 173.5, 121.5 (q, J = 317 Hz); 80.7, 71.0, 70.8, 63.4, 57.0, 56.8. 53.5, 27.1, 25.4, 19.4. IR (thin film) ν 1650 cm^{-1}, MS FAB (**20**•(2($Ba(OTf)_2$)-(OTf)) $C_{47}H_{84}Ba_2F_9N_8O_{21}S_3$ calc. 1639.29 found 1639.30 and (**20**•($Ba(OTf)_2$)) $C_{46}H_{84}BaF_6N_8O_{18}S_2$ calc. 1352.43 found 1353.28 and (**20**•($Ba(OTf)_2$)-(OTf)) $C_{45}H_{84}BaF_3N_8O_{15}S$ calc. 1203.48 found 1203.37.

Barium complex 30.



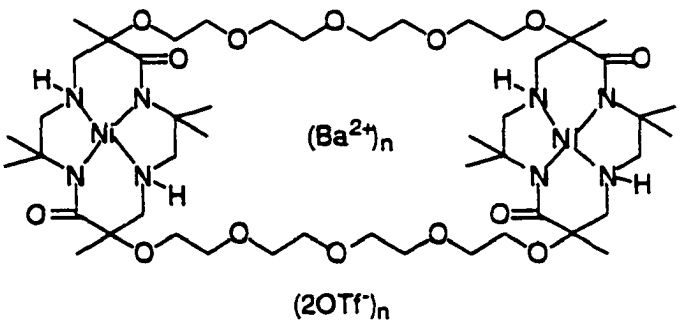
Into a 100 mL round bottomed flask was placed 0.31 g (0.31 mmol) of bis-cyclam **22**, 1.1 g (2.5 mmol) of $Ba(OTf)_2$ and 31 mL of MeOH. This was heated to reflux overnight. The solution was cooled to room temperature and the solvent was removed under reduced pressure to yield a white solid. ^{1}H-NMR (CD_3OD) δ 3.68-3.82 (m, 36H); 2.91-2.94 (bm, 10H); 2.53 (bs, 4H); 1.37-1.42 (m, 36H); ^{13}C-NMR (DMSO-d^6); δ 171.6, 120.8, 79.4, 69.9, 69.5, 62.8, 56.4, 55.7, 52.3, 48.8, 26.5, 25.0, 19.1; IR (thin film) ν 1634 cm^{-1}; MS FAB (**22**•(2($Ba(OTf)_2$)-(OTf))) $C_{51}H_{92}Ba_2F_9N_8O_{23}S_3$ calc.1727.3 found 1727.1 (**22**•($Ba(OTf)_2$-(OTf) $C_{49}H_{92}BaF_3N_8O_{17}S$ calc. 1291.5 found 1291.5

Barium complex 31. Into a 50 mL round bottomed flask was placed 0.12 g (0.21 mmol) of nickel cyclam **24**, 0.19 g (0.43 mmol) of $Ba(OTf)_2$ and 21 mL of MeOH. This was heated to reflux over-night. The solution was cooled to room temperature and the solvent was removed under reduced pressure to yield a white solid. ^{1}H-NMR (CD_3OD) δ 3.94-4.06 (m, 4H); 3.67-3.87 (m, 12H); 3.54-3.61 (m, 2H); 3.14 (t, J = 12.9 Hz, 2H); 2.78 (dd, J = 10.5, 13.8 Hz, 2H); 2.64 (t, J = 11.7 Hz, 2H); 2.26 (dd J = 2.4, 12.3 Hz, 2H); 1.98 (dd, J = 3.9, 11.1 Hz, 2H); 1.39 (s, 6H); 1.37 (s, 6H); 1.20 (s, 6H); ^{13}C-NMR (CD_3OD) δ 175.4, 120.3, 78.4, 72.4, 72.0, 71.6, 66.9, 64.3, 60.3, 57.5, 25.3, 23.2, 20.5; IR (thin film) ν 1573 cm^{-1}; MS FAB (**24**•($Ba(OTf)_2$)-(OTf) $C_{25}H_{44}BaF_3N_4NiO_{10}S$ calc. 845.11 found 845.31.



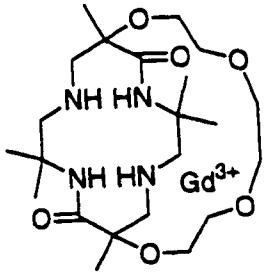
2(OTf)

Barium complex 32.

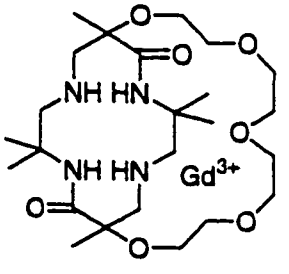


Into a 40 mL Ace pressure tube was placed 45 mg (0.04 mmol) of bis-nickel cyclam **26b**, 60 mg (0.14 mmol) of $Ba(OTf)_2$ and 10 mL of MeOH. The tube was sealed and heated to 70°C overnight. The solution was cooled to room temperature and the solvent was removed under reduced pressure to yield a white solid. ^{1}H-NMR (CD_3OD) δ 3.71-4.02 (m, 32H); 3.15 (t, J = 12.0 Hz, 4H); 2.89 (d, J = 11.1 Hz, 2H); 2.84 (d, J = 10.2 Hz, 2H); 2.66 (t, J = 11.7 Hz, 4H); 2.33 (dd, J = 2.1, 12.3 Hz, 4H); 2.06, (dd, J = 3.0, 11.1 Hz, 4H); 1.40, (s, 12H); 1.38 (s, 12H); 1.22 (s, 12H); ^{13}C-NMR δ (CD_3OD) 175.7, 121.9 9 (q J = 316); 79.1, 72.3, 71.9, 71.8, 66.6, 64.1, 60.5, 57.0, 25.2, 23.3, 20.8; IR (thin film) ν 1556 cm^{-1}; MS FAB (**26b**•(2($Ba(OTf)_2$)-(OTf) $C_{51}H_{88}Ba_2N_8F_9Ni_2O_{23}S_3$ calc. 1839.18, found 1838.61 and (**26b**•($Ba(OTf)_2$)-(OTf)) $C_{49}H_{88}BaF_3Ni_2O_{17}S$ calc. 1403.37 found 1403.36.

Gadolinium complex 34. Into a 100 mL round bottomed flask was placed 0.15 g (0.33 mmol) of the basket-cyclam **19**, 0.31 g (0.70 mmol) of $Gd(NO_3)_3$•$6H_2O$, and 30 mL of MeOH. This mixture was heated to reflux overnight. The solution was cooled to room

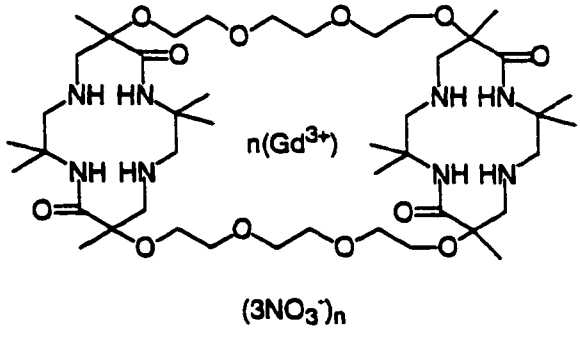


temperature and the solvent was removed under vacuum to give **34** as a white solid. IR (thin film) ν 1635 cm^{-1}. MS FAB (**19**•($Gd(NO_3)_3$)-(NO_3)) $C_{22}H_{42}GdN_6O_{12}$ calc. 740.21, found 740.36.



Gadolinium complex 33 Into a 100 mL round bottomed flask was placed 0.06 g (0.12 mmol) of the basket-cyclam **21**, 0.10 g (0.22 mmol) of $Gd(NO_3)_3•6H_2O$, and 30 mL of MeOH. This mixture was heated to reflux overnight. The solution was cooled and the solvent was removed under vacuum to give **35** as a white solid. IR (thin film) ν 1635 cm^{-1}. MS FAB (**21**•($Gd(NO_3)_3$)-(NO_3)) $C_{24}H_{46}GdN_6O_{13}$ calc. 784.24 found 784.37.

Gadolinium complex 35.



Into a 10 mL round bottomed flask was placed 0.04 g (0.04 mmol) of the bis-cyclam **20**, 0.04 g (0.08 mmol) of $Gd(NO_3)_3 \bullet 6H_2O$ and 5 mL of MeOH. This mixture was heated to reflux overnight. The solution was cooled to room temperature and the solvent was removed under vacuum to yield **35** as a white solid. IR (thin film) v 1654 cm-1. MS FAB (**20**•(2($Gd(NO_3)_3$))-(NO_3)) $C_{44}H_{84}Gd_2N_{13}O_{27}$ calc. 1542.41, found 1541.46 and (**20**•($Gd(NO_3)_3$)-(NO_3)) $C_{44}H_{84}GdN_{10}O_{18}$ calc. 1198.52, found 1198.42.

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Appendix A: Tables of X-Ray Crystal Structure Data

Table A.1 Crystal data and structure refinement for 21.

Identification code	lshccd27
Empirical formula	$C_{24}H_{50}N_4O_9$
Formula weight	538.68
Temperature	169(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 10.5027(3) Å alpha = 90° b = 20.5456(6) Å beta = 92.5100(10)° c = 13.5525(3) Å gamma = 90°
Volume, Z	2921.61(14) $Å^3$, 4
Density (calculated)	1.225 Mg/m^3
Absorption coefficient	0.093 mm^{-1}
F(000)	1176
Crystal size	0.08 x 0.08 x 0.50 mm
θ range for data collection	1.80 to 28.33°
Limiting indices	$-13 \le h \le 13$, $-27 \le k \le 21$, $-16 \le l \le 17$
Reflections collected	18744
Independent reflections	6941 (R_{int} = 0.0690)
Absorption correction	SADABS
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6941 / 0 / 364
Goodness-of-fit on F^2	1.045
Final R indices [I>2σ(I)]	R1 = 0.0786, wR2 = 0.1594
R indices (all data)	R1 = 0.1640, wR2 = 0.2014
Largest diff. peak and hole	0.706 and -0.315 $eÅ^{-3}$

Table A.2 Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 21. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
O(1)	571(2)	2232(1)	7698(2)	35(1)
O(2)	5186(2)	2285(1)	6911(2)	37(1)
O(3)	-87(2)	949(1)	5926(2)	31(1)
O(4)	-259(3)	-273(1)	6899(2)	57(1)
O(5)	2101(3)	-1005(1)	7561(2)	62(1)
O(6)	4533(3)	-501(1)	8516(2)	53(1)
O(7)	5717(2)	699(1)	7866(2)	35(1)
N(1)	677(2)	1121(1)	7808(2)	28(1)
N(2)	2410(2)	1528(1)	5804(2)	29(1)
N(3)	5079(2)	1266(1)	6237(2)	25(1)
N(4)	3344(3)	1280(2)	8364(2)	30(1)
C(1)	466(3)	1683(2)	7319(2)	26(1)
C(2)	91(3)	1621(2)	6202(2)	27(1)
C(3)	1209(3)	1879(2)	5623(2)	27(1)
C(4)	3399(3)	1833(2)	5213(2)	27(1)
C(5)	4652(3)	1445(1)	5214(2)	24(1)
C(6)	5276(3)	1686(2)	6987(2)	27(1)
C(7)	5636(3)	1393(2)	8011(2)	29(1)
C(8)	4569(3)	1562(2)	8697(2)	30(1)
C(9)	2360(3)	1439(2)	9058(2)	29(1)
C(10)	1110(3)	1065(2)	8866(2)	29(1)
C(11)	-1075(3)	2046(2)	5939(2)	38(1)
C(12)	4470(3)	813(2)	4632(2)	32(1)
C(13)	5675(3)	1854(2)	4733(2)	32(1)
C(14)	6904(3)	1688(2)	8400(2)	39(1)
C(15)	1302(3)	339(2)	9076(2)	38(1)
C(16)	102(3)	1347(2)	9529(2)	38(1)
C(17)	-1283(3)	657(2)	6148(2)	41(1)
C(18)	-1141(4)	-65(2)	6126(3)	47(1)
C(19)	23(5)	-969(2)	6785(3)	81(2)
C(20)	823(5)	-1221(2)	7590(4)	76(2)
C(21)	2911(5)	-1299(2)	8321(3)	64(1)
C(22)	4265(5)	-1158(2)	8227(3)	59(1)
C(23)	5867(4)	-374(2)	8473(3)	54(1)
C(24)	6130(4)	317(2)	8709(3)	50(1)
O(9)	2866(3)	3045(1)	7426(2)	58(1)
O(8A)	3028(8)	167(4)	6633(8)	66(2)
O(8B)	2709(9)	5(4)	6116(6)	54(2)

Table A.3 Bond lengths [Å] and angles [°] for 21.

O(1)-C(1)	1.242(4)	O(2)-C(6)	1.239(4)
O(3)-C(17)	1.436(4)	O(3)-C(2)	1.441(4)
O(4)-C(18)	1.433(4)	O(4)-C(19)	1.470(5)
O(5)-C(20)	1.416(5)	O(5)-C(21)	1.440(5)
O(6)-C(23)	1.428(5)	O(6)-C(22)	1.431(4)
O(7)-C(24)	1.437(4)	O(7)-C(7)	1.443(4)
N(1)-C(1)	1.344(4)	N(1)-C(10)	1.489(4)
N(2)-C(3)	1.464(4)	N(2)-C(4)	1.478(4)
N(3)-C(6)	1.343(4)	N(3)-C(5)	1.484(4)
N(4)-C(8)	1.464(4)	N(4)-C(9)	1.465(4)
C(1)-C(2)	1.553(4)	C(2)-C(11)	1.532(4)
C(2)-C(3)	1.535(4)	C(4)-C(5)	1.538(4)
C(5)-C(12)	1.525(4)	C(5)-C(13)	1.532(4)
C(6)-C(7)	1.544(4)	C(7)-C(8)	1.527(4)
C(7)-C(14)	1.536(4)	C(9)-C(10)	1.534(4)
C(10)-C(15)	1.531(4)	C(10)-C(16)	1.532(4)
C(17)-C(18)	1.491(5)	C(19)-C(20)	1.443(6)
C(21)-C(22)	1.462(6)	C(23)-C(24)	1.479(5)
O(8A)-O(8B)	0.833(9)		

C(17)-O(3)-C(2)	116.8(2)	C(18)-O(4)-C(19)	109.9(3)
C(20)-O(5)-C(21)	112.3(3)	C(23)-O(6)-C(22)	110.0(3)
C(24)-O(7)-C(7)	116.7(2)	C(1)-N(1)-C(10)	125.3(3)
C(3)-N(2)-C(4)	108.7(2)	C(6)-N(3)-C(5)	125.4(2)
C(8)-N(4)-C(9)	110.4(2)	O(1)-C(1)-N(1)	124.5(3)
O(1)-C(1)-C(2)	119.4(3)	N(1)-C(1)-C(2)	116.1(3)
O(3)-C(2)-C(11)	113.1(2)	O(3)-C(2)-C(3)	106.9(2)
C(11)-C(2)-C(3)	107.8(2)	O(3)-C(2)-C(1)	110.8(2)
C(11)-C(2)-C(1)	110.3(2)	C(3)-C(2)-C(1)	107.6(2)
N(2)-C(3)-C(2)	114.7(2)	N(2)-C(4)-C(5)	113.7(2)
N(3)-C(5)-C(12)	107.4(2)	N(3)-C(5)-C(13)	110.1(2)
C(12)-C(5)-C(13)	108.7(2)	N(3)-C(5)-C(4)	110.6(2)
C(12)-C(5)-C(4)	110.7(2)	C(13)-C(5)-C(4)	109.3(2)
O(2)-C(6)-N(3)	124.5(3)	O(2)-C(6)-C(7)	118.5(3)
N(3)-C(6)-C(7)	117.0(3)	O(7)-C(7)-C(8)	110.9(3)
O(7)-C(7)-C(14)	112.4(3)	C(8)-C(7)-C(14)	110.4(2)
O(7)-C(7)-C(6)	106.1(2)	C(8)-C(7)-C(6)	107.6(2)
C(14)-C(7)-C(6)	109.2(3)	N(4)-C(8)-C(7)	112.3(2)
N(4)-C(9)-C(10)	113.7(2)	N(1)-C(10)-C(15)	106.7(2)
N(1)-C(10)-C(16)	110.2(2)	C(15)-C(10)-C(16)	110.3(3)
N(1)-C(10)-C(9)	110.3(2)	C(15)-C(10)-C(9)	110.6(3)
C(16)-C(10)-C(9)	108.6(2)	O(3)-C(17)-C(18)	108.8(3)
O(4)-C(18)-C(17)	110.1(3)	C(20)-C(19)-O(4)	112.5(3)
O(5)-C(20)-C(19)	112.8(4)	O(5)-C(21)-C(22)	113.6(3)
O(6)-C(22)-C(21)	110.1(3)	O(6)-C(23)-C(24)	109.9(3)
O(7)-C(24)-C(23)	107.7(3)		

Symmetry transformations used to generate equivalent atoms:

Table A.4 Anisotropic displacement parameters [$Å^2 \times 10^3$] for 21.
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)	38(1)	33(1)	33(1)	-5(1)	1(1)	3(1)
O(2)	43(1)	28(1)	41(1)	-3(1)	0(1)	0(1)
O(3)	27(1)	37(1)	28(1)	-4(1)	0(1)	-6(1)
O(4)	69(2)	50(2)	51(2)	5(1)	-17(1)	-26(1)
O(5)	96(2)	41(2)	49(2)	8(1)	-5(2)	-27(2)
O(6)	88(2)	29(1)	41(1)	-1(1)	-3(1)	2(1)
O(7)	43(1)	36(1)	26(1)	4(1)	-5(1)	12(1)
N(1)	31(2)	30(1)	23(1)	-2(1)	-2(1)	-5(1)
N(2)	19(1)	40(2)	29(2)	7(1)	2(1)	3(1)
N(3)	27(1)	26(1)	22(1)	2(1)	-1(1)	4(1)
N(4)	24(2)	36(2)	31(2)	-7(1)	2(1)	-5(1)
C(1)	18(2)	36(2)	26(2)	1(1)	2(1)	-2(1)
C(2)	23(2)	31(2)	27(2)	0(1)	-3(1)	1(1)
C(3)	22(2)	34(2)	25(2)	3(1)	1(1)	2(1)
C(4)	25(2)	30(2)	26(2)	7(1)	3(1)	1(1)
C(5)	21(2)	28(2)	25(2)	6(1)	1(1)	2(1)
C(6)	19(2)	32(2)	31(2)	-1(1)	3(1)	0(1)
C(7)	25(2)	33(2)	28(2)	-2(1)	-2(1)	4(1)
C(8)	23(2)	40(2)	27(2)	-7(1)	-2(1)	-1(1)
C(9)	30(2)	35(2)	20(2)	-3(1)	0(1)	-2(1)
C(10)	27(2)	38(2)	20(2)	0(1)	-1(1)	-6(1)
C(11)	25(2)	54(2)	35(2)	4(2)	1(1)	5(2)
C(12)	36(2)	35(2)	25(2)	2(1)	2(1)	3(2)
C(13)	25(2)	38(2)	34(2)	6(2)	2(1)	2(1)
C(14)	24(2)	59(2)	34(2)	-7(2)	-2(1)	4(2)
C(15)	41(2)	42(2)	29(2)	4(2)	-2(1)	-10(2)
C(16)	28(2)	58(2)	27(2)	-2(2)	4(1)	-3(2)
C(17)	28(2)	59(2)	35(2)	-3(2)	0(1)	-14(2)
C(18)	53(2)	53(2)	34(2)	-2(2)	-6(2)	-23(2)
C(19)	128(5)	47(3)	65(3)	3(2)	-22(3)	-50(3)
C(20)	107(4)	49(3)	72(3)	9(2)	3(3)	-30(3)
C(21)	95(4)	33(2)	67(3)	15(2)	23(3)	5(2)
C(22)	87(3)	38(2)	54(2)	0(2)	9(2)	2(2)
C(23)	70(3)	48(2)	44(2)	9(2)	-9(2)	14(2)
C(24)	69(3)	46(2)	33(2)	8(2)	-14(2)	10(2)
O(9)	58(2)	41(2)	77(2)	-10(2)	14(2)	-5(1)
O(8A)	64(5)	42(5)	93(7)	31(5)	20(5)	-1(4)
O(8B)	66(5)	46(5)	50(5)	16(4)	16(4)	3(4)

Table A.5 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 21.

	x	y	z	U(eq)
H(1A)	549(2)	757(1)	7477(2)	34
H(2D)	2667(41)	1539(21)	6388(32)	71(15)
H(3A)	5213(2)	851(1)	6361(2)	30
H(3B)	973(3)	1857(2)	4909(2)	33
H(3C)	1347(3)	2343(2)	5795(2)	33
H(4B)	3582(3)	2274(2)	5476(2)	32
H(4C)	3062(3)	1881(2)	4524(2)	32
H(8A)	4800(3)	1400(2)	9369(2)	36
H(8B)	4483(3)	2041(2)	8734(2)	36
H(9A)	2180(3)	1912(2)	9018(2)	34
H(9B)	2692(3)	1344(2)	9737(2)	34
H(11A)	-1804(3)	1891(2)	6300(2)	57
H(11B)	-1276(3)	2019(2)	5227(2)	57
H(11C)	-889(3)	2498(2)	6122(2)	57
H(12A)	3817(3)	547(2)	4934(2)	48
H(12B)	5276(3)	573(2)	4642(2)	48
H(12C)	4199(3)	914(2)	3948(2)	48
H(13A)	5800(3)	2261(2)	5101(2)	48
H(13B)	5401(3)	1952(2)	4049(2)	48
H(13C)	6478(3)	1611(2)	4743(2)	48
H(14A)	7578(3)	1575(2)	7953(2)	59
H(14B)	7121(3)	1514(2)	9060(2)	59
H(14C)	6823(3)	2162(2)	8438(2)	59
H(15A)	1948(3)	165(2)	8647(2)	56
H(15B)	495(3)	107(2)	8947(2)	56
H(15C)	1585(3)	278(2)	9769(2)	56
H(16A)	-12(3)	1811(2)	9386(2)	57
H(16B)	381(3)	1291(2)	10223(2)	57
H(16C)	-708(3)	1119(2)	9402(2)	57
H(17A)	-1953(3)	795(2)	5655(2)	49
H(17B)	-1538(3)	798(2)	6809(2)	49
H(18A)	-1980(4)	-273(2)	6211(3)	56
H(18B)	-830(4)	-201(2)	5479(3)	56
H(19A)	-787(5)	-1216(2)	6746(3)	97
H(19B)	453(5)	-1036(2)	6158(3)	97
H(20A)	471(5)	-1084(2)	8223(4)	91
H(20B)	808(5)	-1702(2)	7567(4)	91
H(21A)	2785(5)	-1777(2)	8302(3)	77
H(21B)	2648(5)	-1143(2)	8973(3)	77
H(22A)	4782(5)	-1460(2)	8650(3)	71
H(22B)	4496(5)	-1224(2)	7534(3)	71
H(23A)	6152(4)	-475(2)	7803(3)	65
H(23B)	6345(4)	-657(2)	8951(3)	65
H(24A)	5665(4)	450(2)	9296(3)	60
H(24B)	7054(4)	382(2)	8855(3)	60
HB	2260(41)	2776(22)	7555(31)	70
HA	3523(43)	2801(21)	7237(31)	70
HC	2548(43)	-150(23)	6712(37)	65

HD	2415 (70)	381 (38)	6239 (59)	156 (33)
H (4A)	3457 (51)	946 (24)	8309 (40)	100 (22)

Table A.6 Crystal data and structure refinement for 20.

Identification code	lshccd17
Empirical formula	$C_{44}H_{96}N_8O_{16}$
Formula weight	993.29
Temperature	165(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/n$
Unit cell dimensions	a = 10.6507(2) Å alpha = 90° b = 15.2681(3) Å beta = 104.4090(10)° c = 17.3856(2) Å gamma = 90°
Volume, Z	2738.24(8) $Å^3$, 2
Density (calculated)	1.205 Mg/m^3
Absorption coefficient	0.091 mm^{-1}
F(000)	1088
Crystal size	0.20 x 0.30 x 0.50 mm
θ range for data collection	1.80 to 28.35°
Limiting indices	$-13 \le h \le 14$, $-20 \le k \le 17$, $-23 \le l \le 22$
Reflections collected	17678
Independent reflections	6564 (R_{int} = 0.0584)
Absorption correction	SADABS
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6564 / 0 / 316
Goodness-of-fit on F^2	1.041
Final R indices [$I>2\sigma(I)$]	R1 = 0.0911, wR2 = 0.2173
R indices (all data)	R1 = 0.1728, wR2 = 0.2711
Largest diff. peak and hole	0.568 and -0.487 $eÅ^{-3}$

Table A.7 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)
C(1)	8144(3)	6764(3)	2532(2)	39(1)
C(2)	5972(3)	6213(2)	2333(2)	34(1)
C(3)	4615(3)	6082(2)	1780(2)	35(1)
C(4)	3848(3)	7629(2)	1865(2)	32(1)
C(5)	3402(3)	8466(2)	1370(2)	32(1)
C(6)	4600(3)	9023(2)	1367(2)	34(1)
C(7)	6515(4)	9296(2)	929(2)	35(1)
C(8)	7649(3)	8960(2)	610(2)	32(1)
C(9)	8646(3)	8092(3)	1828(2)	35(1)
C(10)	9133(4)	7173(3)	2136(2)	38(1)
C(11)	3759(4)	5648(3)	2262(3)	51(1)
C(12)	4649(4)	5506(3)	1076(3)	48(1)
C(13)	7195(4)	8719(3)	-269(2)	41(1)
C(14)	8661(4)	9693(3)	717(3)	43(1)
C(15)	2516(4)	9020(3)	1746(3)	42(1)
C(16)	10457(4)	7263(3)	2734(3)	56(1)
C(17)	1540(4)	7875(3)	405(3)	45(1)
C(18)	1163(4)	7555(3)	-415(3)	54(1)
C(19)	1582(5)	6421(3)	-1258(3)	54(1)
C(20)	2278(5)	5585(3)	-1225(3)	60(1)
C(21)	700(7)	4710(3)	-815(3)	75(2)
C(22)	9829(4)	5832(3)	1556(3)	62(1)
N(1)	6868(3)	6698(2)	1981(2)	34(1)
N(2)	4066(3)	6931(2)	1454(2)	30(1)
N(3)	5552(3)	8623(2)	986(2)	31(1)
N(4)	8215(3)	8162(2)	1031(2)	31(1)
O(1)	4014(3)	7641(2)	2591(2)	47(1)
O(2)	8646(3)	8685(2)	2299(2)	50(1)
O(3)	2817(2)	8261(2)	561(1)	34(1)
O(4)	1964(3)	6841(2)	-483(2)	56(1)
O(5)	2015(4)	4948(2)	-693(2)	67(1)
O(6)	9191(3)	6665(2)	1447(2)	43(1)
O(11)	3364(4)	8711(3)	3770(2)	87(1)
O(12)	1910(4)	8421(2)	4849(2)	69(1)
O(13)	4550(3)	7407(2)	-323(2)	65(1)

Table A.8 Bond lengths [Å] and angles [°] for 20.

C(1)-N(1)	1.459(5)	C(1)-C(10)	1.528(5)
C(2)-N(1)	1.457(4)	C(2)-C(3)	1.537(5)
C(3)-N(2)	1.475(4)	C(3)-C(12)	1.515(6)
C(3)-C(11)	1.534(5)	C(4)-O(1)	1.230(4)
C(4)-N(2)	1.336(5)	C(4)-C(5)	1.548(5)
C(5)-O(3)	1.426(4)	C(5)-C(15)	1.529(5)
C(5)-C(6)	1.534(5)	C(6)-N(3)	1.473(4)
C(7)-N(3)	1.473(4)	C(7)-C(8)	1.537(5)
C(8)-N(4)	1.472(4)	C(8)-C(13)	1.528(5)
C(8)-C(14)	1.532(5)	C(9)-O(2)	1.220(5)
C(9)-N(4)	1.352(5)	C(9)-C(10)	1.545(5)
C(10)-O(6)	1.441(5)	C(10)-C(16)	1.536(6)
C(17)-O(3)	1.445(5)	C(17)-C(18)	1.466(6)
C(18)-O(4)	1.407(5)	C(19)-O(4)	1.456(5)
C(19)-C(20)	1.470(6)	C(20)-O(5)	1.417(6)
C(21)-O(5)	1.411(7)	C(21)-C(22)#1	1.518(8)
C(22)-O(6)	1.431(5)	C(22)-C(21)#1	1.518(8)

N(1)-C(1)-C(10)	111.5(3)	N(1)-C(2)-C(3)	114.5(3)
N(2)-C(3)-C(12)	106.6(3)	N(2)-C(3)-C(11)	110.9(3)
C(12)-C(3)-C(11)	109.1(3)	N(2)-C(3)-C(2)	110.3(3)
C(12)-C(3)-C(2)	111.9(3)	C(11)-C(3)-C(2)	108.0(3)
O(1)-C(4)-N(2)	124.1(3)	O(1)-C(4)-C(5)	120.3(3)
N(2)-C(4)-C(5)	115.5(3)	O(3)-C(5)-C(15)	112.3(3)
O(3)-C(5)-C(6)	106.1(3)	C(15)-C(5)-C(6)	107.3(3)
O(3)-C(5)-C(4)	111.4(3)	C(15)-C(5)-C(4)	110.8(3)
C(6)-C(5)-C(4)	108.6(3)	N(3)-C(6)-C(5)	116.0(3)
N(3)-C(7)-C(8)	114.5(3)	N(4)-C(8)-C(13)	106.6(3)
N(4)-C(8)-C(14)	110.8(3)	C(13)-C(8)-C(14)	109.6(3)
N(4)-C(8)-C(7)	111.0(3)	C(13)-C(8)-C(7)	111.1(3)
C(14)-C(8)-C(7)	107.7(3)	O(2)-C(9)-N(4)	125.0(4)
O(2)-C(9)-C(10)	119.8(3)	N(4)-C(9)-C(10)	115.1(3)
O(6)-C(10)-C(1)	109.4(3)	O(6)-C(10)-C(16)	112.9(3)
C(1)-C(10)-C(16)	110.5(3)	O(6)-C(10)-C(9)	106.4(3)
C(1)-C(10)-C(9)	108.5(3)	C(16)-C(10)-C(9)	109.0(3)
O(3)-C(17)-C(18)	109.6(4)	O(4)-C(18)-C(17)	108.3(4)
O(4)-C(19)-C(20)	108.8(4)	O(5)-C(20)-C(19)	116.3(4)
O(5)-C(21)-C(22)#1	114.4(4)	O(6)-C(22)-C(21)#1	107.9(4)
C(2)-N(1)-C(1)	111.1(3)	C(4)-N(2)-C(3)	126.8(3)
C(7)-N(3)-C(6)	108.0(3)	C(9)-N(4)-C(8)	124.6(3)
C(5)-O(3)-C(17)	115.7(3)	C(18)-O(4)-C(19)	112.5(3)
C(21)-O(5)-C(20)	115.4(4)	C(22)-O(6)-C(10)	119.0(3)

Symmetry transformations used to generate equivalent atoms:

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

Table A.9 Anisotropic displacement parameters [$Å^2 \times 10^3$] 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
C(1)	24(2)	49(2)	43(2)	18(2)	6(2)	2(2)
C(2)	28(2)	33(2)	42(2)	12(2)	11(2)	3(2)
C(3)	27(2)	28(2)	51(2)	7(2)	9(2)	3(2)
C(4)	26(2)	33(2)	39(2)	1(2)	11(2)	2(2)
C(5)	29(2)	28(2)	41(2)	2(2)	15(2)	6(2)
C(6)	34(2)	29(2)	40(2)	0(2)	12(2)	5(2)
C(7)	32(2)	28(2)	46(2)	1(2)	11(2)	-1(2)
C(8)	32(2)	27(2)	37(2)	5(2)	9(2)	3(2)
C(9)	27(2)	39(2)	40(2)	6(2)	7(2)	-6(2)
C(10)	26(2)	47(2)	40(2)	12(2)	5(2)	1(2)
C(11)	33(2)	45(2)	75(3)	22(2)	15(2)	-3(2)
C(12)	45(2)	33(2)	63(3)	-5(2)	6(2)	4(2)
C(13)	42(2)	39(2)	42(2)	11(2)	12(2)	10(2)
C(14)	36(2)	36(2)	59(3)	6(2)	16(2)	-5(2)
C(15)	42(2)	35(2)	56(2)	1(2)	25(2)	10(2)
C(16)	27(2)	76(3)	60(3)	27(2)	3(2)	-4(2)
C(17)	27(2)	42(2)	63(3)	1(2)	5(2)	2(2)
C(18)	42(2)	44(3)	69(3)	-3(2)	-2(2)	2(2)
C(19)	52(3)	46(3)	59(3)	0(2)	4(2)	-1(2)
C(20)	65(3)	47(3)	66(3)	-2(2)	13(3)	4(2)
C(21)	118(5)	45(3)	85(4)	20(3)	70(4)	40(3)
C(22)	41(3)	47(3)	103(4)	27(3)	31(3)	16(2)
N(1)	22(2)	40(2)	38(2)	16(1)	5(1)	-2(1)
N(2)	28(2)	29(2)	33(2)	4(1)	7(1)	5(1)
N(3)	27(2)	23(2)	45(2)	-5(1)	14(1)	-1(1)
N(4)	26(2)	30(2)	37(2)	5(1)	9(1)	3(1)
O(1)	57(2)	49(2)	37(2)	3(1)	16(1)	14(1)
O(2)	58(2)	48(2)	41(2)	-4(1)	6(1)	-6(2)
O(3)	26(1)	37(1)	37(1)	2(1)	7(1)	4(1)
O(4)	45(2)	49(2)	69(2)	-12(2)	4(2)	3(1)
O(5)	94(3)	42(2)	61(2)	2(2)	13(2)	13(2)
O(6)	37(2)	37(2)	59(2)	16(1)	19(1)	12(1)
O(11)	72(3)	108(3)	86(3)	-31(2)	28(2)	-17(2)
O(12)	85(3)	57(2)	72(2)	-8(2)	33(2)	-10(2)
O(13)	53(2)	77(2)	68(2)	-20(2)	22(2)	-6(2)

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

	x	y	z	U(eq)
H(15A)	8443(3)	6172(3)	2729(2)	47
H(15B)	8082(3)	7125(3)	2994(2)	47
H(21A)	5882(3)	6528(2)	2815(2)	41
H(21B)	6350(3)	5631(2)	2502(2)	41
H(20A)	4304(3)	9582(2)	1093(2)	40
H(20B)	5046(3)	9165(2)	1923(2)	40
H(12A)	6869(4)	9550(2)	1463(2)	42
H(12B)	6072(4)	9772(2)	578(2)	42
H(11A)	3733(4)	6018(3)	2718(3)	76
H(11B)	4118(4)	5073(3)	2450(3)	76
H(11C)	2878(4)	5575(3)	1925(3)	76
H(9A)	5195(4)	5781(3)	766(3)	72
H(9B)	3768(4)	5434(3)	741(3)	72
H(9C)	5007(4)	4932(3)	1266(3)	72
H(13A)	6548(4)	8251(3)	-336(2)	61
H(13B)	7937(4)	8518(3)	-460(2)	61
H(13C)	6809(4)	9235(3)	-574(2)	61
H(6A)	8951(4)	9846(3)	1281(3)	65
H(6B)	8276(4)	10208(3)	413(3)	65
H(6C)	9404(4)	9492(3)	527(3)	65
H(10A)	1738(4)	8683(3)	1758(3)	63
H(10B)	2265(4)	9554(3)	1432(3)	63
H(10C)	2978(4)	9179(3)	2289(3)	63
H(5A)	11078(4)	7526(3)	2470(3)	84
H(5B)	10767(4)	6683(3)	2937(3)	84
H(5C)	10370(4)	7638(3)	3175(3)	84
H(8A)	907(4)	8317(3)	488(3)	54
H(8B)	1542(4)	7383(3)	777(3)	54
H(7A)	243(4)	7369(3)	-551(3)	65
H(7B)	1264(4)	8026(3)	-786(3)	65
H(4A)	1796(5)	6806(3)	-1666(3)	65
H(4B)	635(5)	6316(3)	-1404(3)	65
H(3A)	2068(5)	5329(3)	-1765(3)	72
H(3B)	3220(5)	5709(3)	-1076(3)	72
H(1A)	174(7)	5250(3)	-848(3)	90
H(1B)	596(7)	4373(3)	-348(3)	90
H(2A)	9664(4)	5532(3)	2026(3)	74
H(2B)	10777(4)	5912(3)	1642(3)	74
H(1C)	6665(3)	6922(2)	1500(2)	41
H(3C)	3861(3)	6983(2)	933(2)	36
H(2C)	5546(3)	8078(2)	822(2)	37
H(4C)	8278(3)	7697(2)	744(2)	37

Table A.11 Crystal data and structure refinement for 23.

Identification code	lshccd18
Empirical formula	$C_{22}H_{40}N_4NiO_6$
Formula weight	515.29
Temperature	173(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	a = 19.784(2) Å alpha = 90° b = 8.2259(7) Å beta = 97.484(2)° c = 15.4990(14) Å gamma = 90°
Volume, Z	2500.8(4) $Å^3$, 4
Density (calculated)	1.369 Mg/m^3
Absorption coefficient	0.819 mm^{-1}
F(000)	1104
Crystal size	0.08 x 0.18 x 0.40 mm
θ range for data collection	2.08 to 28.31°
Limiting indices	$-26 \le h \le 22$, $-10 \le k \le 10$, $-20 \le l \le 19$
Reflections collected	7773
Independent reflections	3011 (R_{int} = 0.0770)
Absorption correction	SADABS
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3011 / 0 / 150
Goodness-of-fit on F^2	1.050
Final R indices [$I>2\sigma(I)$]	R1 = 0.0691, wR2 = 0.1479
R indices (all data)	R1 = 0.1295, wR2 = 0.1765
Largest diff. peak and hole	0.900 and -0.850 $eÅ^{-3}$

Table A.12 Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 23. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
C(1)	-739(2)	17511(5)	3976(2)	17(1)
C(2)	-9(2)	18090(5)	4196(2)	18(1)
C(3)	1147(2)	17702(5)	3848(2)	17(1)
C(4)	1606(2)	16665(5)	3350(3)	16(1)
C(5)	-1472(2)	16948(5)	2653(3)	18(1)
C(6)	-838(2)	15878(5)	4430(3)	22(1)
C(7)	-1194(2)	18819(5)	4299(3)	24(1)
C(8)	2346(2)	16997(6)	3689(3)	26(1)
C(9)	1667(2)	13788(5)	3031(3)	22(1)
C(10)	1442(2)	12167(5)	3360(3)	26(1)
C(11)	366(2)	11950(7)	2475(3)	40(1)
N(1)	-834(2)	17316(4)	3006(2)	14(1)
N(2)	435(2)	17185(4)	3666(2)	14(1)
O(1)	-1971(1)	16770(4)	3053(2)	22(1)
O(2)	722(2)	12009(4)	3333(2)	25(1)
O(3)	1416(1)	15025(3)	3548(2)	20(1)
Ni(1)	0	17239(1)	2500	18(1)

Table A.13 Bond lengths [Å] and angles [°] for 23.

C(1)-N(1)	1.500(5)	C(1)-C(2)	1.517(6)
C(1)-C(7)	1.528(5)	C(1)-C(6)	1.541(5)
C(2)-N(2)	1.479(5)	C(3)-N(2)	1.464(5)
C(3)-C(4)	1.527(5)	C(4)-O(3)	1.444(5)
C(4)-C(8)	1.515(6)	C(4)-C(5)#1	1.560(5)
C(5)-O(1)	1.241(5)	C(5)-N(1)	1.343(5)
C(5)-C(4)#1	1.560(5)	C(9)-O(3)	1.424(5)
C(9)-C(10)	1.515(6)	C(10)-O(2)	1.425(5)
C(11)-O(2)	1.423(5)	C(11)-C(11)#1	1.461(10)
N(1)-Ni(1)	1.918(3)	N(2)-Ni(1)	1.899(3)
Ni(1)-N(2)#1	1.899(3)	Ni(1)-N(1)#1	1.918(3)
N(1)-C(1)-C(2)	104.5(3)	N(1)-C(1)-C(7)	113.7(3)
C(2)-C(1)-C(7)	106.8(3)	N(1)-C(1)-C(6)	111.0(3)
C(2)-C(1)-C(6)	110.1(3)	C(7)-C(1)-C(6)	110.4(3)
N(2)-C(2)-C(1)	109.5(3)	N(2)-C(3)-C(4)	111.2(3)
O(3)-C(4)-C(8)	111.2(3)	O(3)-C(4)-C(3)	103.1(3)
C(8)-C(4)-C(3)	109.6(3)	O(3)-C(4)-C(5)#1	109.6(3)
C(8)-C(4)-C(5)#1	110.5(3)	C(3)-C(4)-C(5)#1	112.6(3)
O(1)-C(5)-N(1)	126.1(4)	O(1)-C(5)-C(4)#1	115.9(4)
N(1)-C(5)-C(4)#1	118.0(3)	O(3)-C(9)-C(10)	107.5(3)
O(2)-C(10)-C(9)	114.0(3)	O(2)-C(11)-C(11)#1	109.0(5)
C(5)-N(1)-C(1)	114.9(3)	C(5)-N(1)-Ni(1)	129.7(3)
C(1)-N(1)-Ni(1)	114.3(2)	C(3)-N(2)-C(2)	111.9(3)
C(3)-N(2)-Ni(1)	118.8(2)	C(2)-N(2)-Ni(1)	106.8(2)
C(11)-O(2)-C(10)	113.7(3)	C(9)-O(3)-C(4)	115.4(3)
N(2)-Ni(1)-N(2)#1	177.3(2)	N(2)-Ni(1)-N(1)#1	94.74(13)
N(2)#1-Ni(1)-N(1)#1	85.35(13)	N(2)-Ni(1)-N(1)	85.35(13)
N(2)#1-Ni(1)-N(1)	94.74(13)	N(1)#1-Ni(1)-N(1)	176.2(2)

Symmetry transformations used to generate equivalent atoms:

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

Table A.14 Anisotropic displacement parameters [$Å^2$ x 10^3] for 23.

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
C(1)	22(2)	18(2)	12(2)	-2(2)	6(2)	4(2)
C(2)	27(2)	16(2)	11(2)	-3(2)	3(2)	3(2)
C(3)	23(2)	17(2)	11(2)	-3(2)	2(2)	-1(2)
C(4)	23(2)	12(2)	15(2)	0(2)	6(2)	1(2)
C(5)	27(2)	10(2)	17(2)	0(2)	7(2)	5(2)
C(6)	26(2)	23(2)	16(2)	6(2)	5(2)	3(2)
C(7)	28(2)	22(2)	22(2)	-6(2)	9(2)	5(2)
C(8)	23(2)	35(3)	19(2)	-2(2)	0(2)	0(2)
C(9)	31(2)	14(2)	23(2)	0(2)	11(2)	2(2)
C(10)	34(3)	16(2)	29(3)	5(2)	10(2)	7(2)
C(11)	40(3)	54(4)	25(3)	-5(2)	8(2)	-2(2)
N(1)	22(2)	14(2)	8(2)	0(1)	7(1)	1(2)
N(2)	23(2)	9(2)	10(2)	0(1)	6(1)	1(1)
O(1)	22(2)	27(2)	19(2)	-2(1)	8(1)	2(1)
O(2)	31(2)	24(2)	22(2)	4(1)	9(1)	1(1)
O(3)	30(2)	13(2)	17(2)	1(1)	9(1)	6(1)
Ni(1)	25(1)	15(1)	15(1)	0	4(1)	0

Table A.15 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 23.

	x	y	z	U(eq)
H(2A)	18(2)	19269(5)	4076(2)	22
H(2C)	146(2)	17911(5)	4822(2)	22
H(3A)	1301(2)	17611(5)	4480(2)	20
H(3B)	1185(2)	18856(5)	3680(2)	20
H(6A)	-1311(2)	15516(5)	4284(3)	32
H(6B)	-736(2)	16017(5)	5062(3)	32
H(6C)	-530(2)	15064(5)	4234(3)	32
H(7A)	-1673(2)	18490(5)	4168(3)	35
H(7B)	-1125(2)	19850(5)	4006(3)	35
H(7C)	-1077(2)	18954(5)	4928(3)	35
H(8A)	2640(2)	16330(6)	3369(3)	39
H(8B)	2431(2)	16726(6)	4310(3)	39
H(8C)	2447(2)	18150(6)	3609(3)	39
H(9A)	2170(2)	13837(5)	3082(3)	26
H(9B)	1480(2)	13935(5)	2411(3)	26
H(10A)	1609(2)	11288(5)	3006(3)	31
H(10B)	1657(2)	12017(5)	3968(3)	31
H(11A)	494(2)	10955(7)	2176(3)	47
H(11B)	489(2)	12905(7)	2139(3)	47
H(2B)	424(2)	16106(4)	3844(2)	17

Table A.16 Crystal data and structure refinement for 24.

Identification code	lshccd28
Empirical formula	$C_{24}H_{44}N_4NiO_7$
Formula weight	559.34
Temperature	172(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1/c$
Unit cell dimensions	a = 14.3690(5) Å alpha = 90° b = 13.1776(5) Å beta = 112.3020(10)° c = 15.5299(6) Å gamma = 90°
Volume, Z	2720.6(2) $Å^3$, 4
Density (calculated)	1.366 Mg/m^3
Absorption coefficient	0.762 mm^{-1}
F(000)	1200
Crystal size	0.10 x 0.15 x 0.20 mm (dichromatic red/yellow)
θ range for data collection	1.53 to 28.35°
Limiting indices	$-18 \le h \le 16$, $-17 \le k \le 17$, $-10 \le l \le 20$
Reflections collected	17413
Independent reflections	6637 (R_{int} = 0.0745)
Absorption correction	SADABS
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	6636 / 0 / 332
Goodness-of-fit on F^2	1.025
Final R indices [I>2σ(I)]	R1 = 0.0637, wR2 = 0.1207
R indices (all data)	R1 = 0.1282, wR2 = 0.1472
Extinction coefficient	0.0003(3)
Largest diff. peak and hole	0.929 and -0.829 $eÅ^{-3}$

Table A.17 Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 24. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Ni(1)	3312(1)	9469(1)	3640(1)	19(1)
N(1)	2237(2)	10319(2)	3643(2)	21(1)
N(2)	2728(2)	8454(2)	4126(2)	23(1)
N(3)	4360(2)	8603(2)	3598(2)	22(1)
N(4)	3928(2)	10501(2)	3193(2)	24(1)
O(1)	1066(2)	11575(2)	2966(2)	39(1)
O(2)	4847(2)	7047(2)	3234(2)	38(1)
O(3)	2577(2)	11699(2)	2014(2)	30(1)
O(4)	1440(2)	10682(2)	284(2)	36(1)
O(5)	1422(3)	8482(2)	39(3)	60(1)
O(6)	1839(3)	7011(4)	1473(3)	90(2)
O(7)	2823(2)	6645(2)	3412(2)	28(1)
C(1)	1501(3)	9780(3)	3944(3)	22(1)
C(2)	2115(3)	8930(3)	4567(3)	28(1)
C(3)	3424(3)	7670(3)	4705(2)	23(1)
C(4)	3771(3)	7007(3)	4086(3)	23(1)
C(5)	4366(3)	7579(3)	3590(3)	26(1)
C(6)	5035(3)	9117(3)	3202(3)	23(1)
C(7)	4996(3)	10224(3)	3458(3)	26(1)
C(8)	3787(3)	11536(3)	3485(3)	26(1)
C(9)	2698(3)	11859(3)	2970(3)	25(1)
C(10)	1928(3)	11212(3)	3197(3)	27(1)
C(11)	1098(3)	10433(3)	4538(3)	30(1)
C(12)	624(3)	9339(3)	3110(3)	35(1)
C(13)	4405(3)	6138(3)	4655(3)	32(1)
C(14)	6141(3)	8781(3)	3664(3)	30(1)
C(15)	4647(3)	8990(3)	2139(3)	34(1)
C(16)	2588(3)	12971(3)	3184(3)	34(1)
C(17)	1713(4)	12101(3)	1289(3)	38(1)
C(18)	1762(4)	11707(3)	397(3)	40(1)
C(19)	1570(4)	10186(4)	-475(3)	45(1)
C(20)	1040(4)	9209(3)	-676(3)	46(1)
C(21)	1068(4)	8525(4)	741(4)	59(2)
C(22)	1029(6)	7566(4)	1158(6)	97(3)
C(23)	1828(4)	6069(4)	1922(3)	43(1)
C(24)	2821(3)	5956(3)	2703(3)	32(1)

Table A.18 Bond lengths [Å] and angles [°] for 24.

Ni(1)-N(2)	1.883(3)	Ni(1)-N(4)	1.893(3)
Ni(1)-N(1)	1.910(3)	Ni(1)-N(3)	1.910(3)
N(1)-C(10)	1.352(5)	N(1)-C(1)	1.489(5)
N(2)-C(2)	1.448(5)	N(2)-C(3)	1.481(4)
N(3)-C(5)	1.349(5)	N(3)-C(6)	1.493(5)
N(4)-C(8)	1.474(5)	N(4)-C(7)	1.475(5)
O(1)-C(10)	1.247(5)	O(2)-C(5)	1.252(4)
O(3)-C(17)	1.424(5)	O(3)-C(9)	1.443(4)
O(4)-C(18)	1.417(5)	O(4)-C(19)	1.422(5)
O(5)-C(21)	1.366(6)	O(5)-C(20)	1.411(6)
O(6)-C(22)	1.302(7)	O(6)-C(23)	1.427(6)
O(7)-C(24)	1.426(4)	O(7)-C(4)	1.447(4)
C(1)-C(2)	1.523(5)	C(1)-C(11)	1.528(5)
C(1)-C(12)	1.537(5)	C(3)-C(4)	1.518(5)
C(4)-C(13)	1.520(5)	C(4)-C(5)	1.545(5)
C(6)-C(7)	1.518(5)	C(6)-C(14)	1.539(5)
C(6)-C(15)	1.539(5)	C(8)-C(9)	1.523(5)
C(9)-C(16)	1.524(5)	C(9)-C(10)	1.539(5)
C(17)-C(18)	1.506(6)	C(19)-C(20)	1.468(6)
C(21)-C(22)	1.431(7)	C(23)-C(24)	1.488(6)

N(2)-Ni(1)-N(4)	178.1(2)	N(2)-Ni(1)-N(1)	86.08(13)
N(4)-Ni(1)-N(1)	94.05(13)	N(2)-Ni(1)-N(3)	93.80(13)
N(4)-Ni(1)-N(3)	86.14(13)	N(1)-Ni(1)-N(3)	178.09(13)
C(10)-N(1)-C(1)	116.3(3)	C(10)-N(1)-Ni(1)	128.2(3)
C(1)-N(1)-Ni(1)	113.1(2)	C(2)-N(2)-C(3)	114.1(3)
C(2)-N(2)-Ni(1)	109.0(2)	C(3)-N(2)-Ni(1)	115.9(2)
C(5)-N(3)-C(6)	116.3(3)	C(5)-N(3)-Ni(1)	127.3(3)
C(6)-N(3)-Ni(1)	112.7(2)	C(8)-N(4)-C(7)	113.2(3)
C(8)-N(4)-Ni(1)	114.4(2)	C(7)-N(4)-Ni(1)	107.5(2)
C(17)-O(3)-C(9)	119.2(3)	C(18)-O(4)-C(19)	113.6(3)
C(21)-O(5)-C(20)	116.7(4)	C(22)-O(6)-C(23)	120.0(5)
C(24)-O(7)-C(4)	119.6(3)	N(1)-C(1)-C(2)	104.0(3)
N(1)-C(1)-C(11)	113.4(3)	C(2)-C(1)-C(11)	106.9(3)
N(1)-C(1)-C(12)	111.7(3)	C(2)-C(1)-C(12)	110.5(3)
C(11)-C(1)-C(12)	110.1(3)	N(2)-C(2)-C(1)	109.2(3)
N(2)-C(3)-C(4)	109.0(3)	O(7)-C(4)-C(3)	101.7(3)
O(7)-C(4)-C(13)	111.4(3)	C(3)-C(4)-C(13)	109.4(3)
O(7)-C(4)-C(5)	110.3(3)	C(3)-C(4)-C(5)	114.3(3)
C(13)-C(4)-C(5)	109.6(3)	O(2)-C(5)-N(3)	124.7(4)
O(2)-C(5)-C(4)	116.7(3)	N(3)-C(5)-C(4)	118.5(3)
N(3)-C(6)-C(7)	103.5(3)	N(3)-C(6)-C(14)	113.3(3)
C(7)-C(6)-C(14)	106.8(3)	N(3)-C(6)-C(15)	111.4(3)
C(7)-C(6)-C(15)	110.5(3)	C(14)-C(6)-C(15)	111.0(3)
N(4)-C(7)-C(6)	107.7(3)	N(4)-C(8)-C(9)	109.4(3)
O(3)-C(9)-C(8)	101.4(3)	O(3)-C(9)-C(16)	112.5(3)
C(8)-C(9)-C(16)	109.0(3)	O(3)-C(9)-C(10)	109.8(3)
C(8)-C(9)-C(10)	114.1(3)	C(16)-C(9)-C(10)	109.9(3)
O(1)-C(10)-N(1)	125.3(4)	O(1)-C(10)-C(9)	116.4(3)
N(1)-C(10)-C(9)	118.4(3)	O(3)-C(17)-C(18)	105.6(4)
O(4)-C(18)-C(17)	108.4(3)	O(4)-C(19)-C(20)	111.0(4)
O(5)-C(20)-C(19)	114.4(4)	O(5)-C(21)-C(22)	114.5(5)
O(6)-C(22)-C(21)	118.9(6)	O(6)-C(23)-C(24)	107.5(4)
O(7)-C(24)-C(23)	106.6(3)		

Symmetry transformations used to generate equivalent atoms:

Table A.19 Anisotropic displacement parameters [$Å^2$ x 10^3] for 24.
The anisotropic displacement factor exponent takes the form:
$-2\pi^2$ [$(ha^*)^2U_{11}$ + ... + 2hka*b*U_{12}]

	U11	U22	U33	U23	U13	U12
Ni(1)	23(1)	16(1)	22(1)	2(1)	13(1)	1(1)
N(1)	26(2)	16(2)	27(2)	3(1)	16(1)	2(1)
N(2)	26(2)	20(2)	25(2)	5(1)	13(2)	3(1)
N(3)	22(2)	19(2)	26(2)	1(1)	11(1)	3(1)
N(4)	27(2)	21(2)	26(2)	4(2)	13(1)	4(2)
O(1)	35(2)	35(2)	54(2)	19(2)	25(2)	13(1)
O(2)	45(2)	23(2)	58(2)	-5(1)	33(2)	3(1)
O(3)	39(2)	27(2)	28(2)	7(1)	17(1)	7(1)
O(4)	40(2)	33(2)	37(2)	-1(1)	17(1)	-3(1)
O(5)	86(3)	37(2)	81(3)	4(2)	59(2)	10(2)
O(6)	65(3)	145(4)	74(3)	74(3)	42(2)	50(3)
O(7)	31(2)	25(1)	27(2)	-5(1)	11(1)	-1(1)
C(1)	24(2)	21(2)	27(2)	3(2)	15(2)	1(2)
C(2)	32(2)	23(2)	34(2)	9(2)	19(2)	3(2)
C(3)	28(2)	20(2)	21(2)	2(2)	9(2)	2(2)
C(4)	26(2)	18(2)	24(2)	1(2)	8(2)	0(2)
C(5)	24(2)	20(2)	33(2)	-1(2)	12(2)	2(2)
C(6)	26(2)	22(2)	27(2)	0(2)	17(2)	0(2)
C(7)	22(2)	27(2)	32(2)	2(2)	16(2)	-1(2)
C(8)	34(2)	16(2)	33(2)	1(2)	18(2)	-1(2)
C(9)	33(2)	20(2)	26(2)	4(2)	15(2)	5(2)
C(10)	33(2)	25(2)	29(2)	5(2)	19(2)	4(2)
C(11)	31(2)	35(2)	33(2)	6(2)	22(2)	4(2)
C(12)	29(2)	37(3)	37(2)	0(2)	10(2)	-4(2)
C(13)	39(3)	22(2)	32(2)	6(2)	11(2)	7(2)
C(14)	23(2)	31(2)	39(2)	5(2)	16(2)	5(2)
C(15)	40(3)	39(3)	28(2)	-2(2)	19(2)	1(2)
C(16)	48(3)	20(2)	42(3)	4(2)	26(2)	5(2)
C(17)	45(3)	29(2)	37(3)	5(2)	13(2)	2(2)
C(18)	56(3)	32(2)	33(3)	5(2)	17(2)	-10(2)
C(19)	56(3)	45(3)	40(3)	-2(2)	25(2)	0(2)
C(20)	58(3)	38(3)	51(3)	-5(2)	29(3)	2(2)
C(21)	70(4)	66(4)	49(3)	7(3)	33(3)	25(3)
C(22)	155(8)	43(4)	163(7)	2(4)	141(7)	10(4)
C(23)	44(3)	50(3)	35(3)	-11(2)	16(2)	-6(2)
C(24)	46(3)	18(2)	34(2)	-5(2)	16(2)	1(2)

Table A.20 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for 24.

	x	y	z	U(eq)
H(2C)	2292(29)	8127(29)	3648(28)	27
H(4A)	3627(30)	10529(30)	2621(28)	28
H(2A)	2550(3)	9210(3)	5179(3)	33
H(2B)	1659(3)	8422(3)	4668(3)	33
H(3B)	3079(3)	7250(3)	5022(2)	28
H(3C)	4012(3)	7999(3)	5187(2)	28
H(7A)	5365(3)	10322(3)	4135(3)	31
H(7B)	5310(3)	10656(3)	3121(3)	31
H(8A)	4241(3)	12013(3)	3343(3)	31
H(8B)	3953(3)	11550(3)	4164(3)	31
H(11A)	696(3)	10991(3)	4161(3)	45
H(11B)	1662(3)	10711(3)	5067(3)	45
H(11C)	676(3)	10017(3)	4768(3)	45
H(12A)	236(3)	9895(3)	2717(3)	52
H(12B)	186(3)	8941(3)	3336(3)	52
H(12C)	889(3)	8901(3)	2747(3)	52
H(13A)	4629(3)	5709(3)	4255(3)	48
H(13B)	4002(3)	5733(3)	4915(3)	48
H(13C)	4992(3)	6413(3)	5163(3)	48
H(14A)	6200(3)	8067(3)	3516(3)	45
H(14B)	6369(3)	8863(3)	4340(3)	45
H(14C)	6557(3)	9200(3)	3429(3)	45
H(15A)	4677(3)	8273(3)	1986(3)	51
H(15B)	5067(3)	9390(3)	1893(3)	51
H(15C)	3950(3)	9228(3)	1860(3)	51
H(16A)	1889(3)	13186(3)	2854(3)	51
H(16B)	3031(3)	13387(3)	2979(3)	51
H(16C)	2773(3)	13057(3)	3855(3)	51
H(17A)	1728(4)	12852(3)	1300(3)	46
H(17B)	1090(4)	11869(3)	1358(3)	46
H(18A)	1321(4)	12117(3)	-136(3)	48
H(18B)	2459(4)	11754(3)	421(3)	48
H(19A)	2296(4)	10073(4)	-325(3)	54
H(19B)	1309(4)	10625(4)	-1033(3)	54
H(20A)	322(4)	9329(3)	-794(3)	56
H(20B)	1077(4)	8927(3)	-1253(3)	56
H(21A)	383(4)	8820(4)	491(4)	70
H(21B)	1503(4)	8989(4)	1229(4)	70
H(22A)	810(6)	7693(4)	1681(6)	116
H(22B)	496(6)	7157(4)	692(6)	116
H(23A)	1716(4)	5501(4)	1476(3)	51
H(23B)	1281(4)	6065(4)	2162(3)	51
H(24A)	2912(3)	5251(3)	2941(3)	38
H(24B)	3373(3)	6120(3)	2492(3)	38

Table A.21 Crystal data and structure refinement for 25.

Identification code	lshccd30
Empirical formula	$C_{44}H_{80}N_8Ni_2O_{12}$
Formula weight	1030.58
Temperature	166(2) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions	a = 13.2981(4) Å alpha = 84.7600(10)° b = 13.5327(5) Å beta = 88.7940(10)° c = 15.2904(6) Å gamma = 63.6840(10)°
Volume, Z	2455.6(2) Å^3, 2
Density (calculated)	1.394 Mg/m^3
Absorption coefficient	0.834 mm^{-1}
F(000)	1104
Crystal size	0.20 x 0.30 x 0.40 mm
θ range for data collection	1.34 to 28.32°
Limiting indices	$-17 \le h \le 17$, $-17 \le k \le 17$, $-20 \le l \le 8$
Reflections collected	16511
Independent reflections	11370 (R_{int} = 0.0379)
Absorption correction	SADABS
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	11368 / 0 / 588
Goodness-of-fit on F^2	1.023
Final R indices [I>2σ(I)]	R1 = 0.0690, wR2 = 0.1290
R indices (all data)	R1 = 0.1330, wR2 = 0.1658
Extinction coefficient	0.0001(2)
Largest diff. peak and hole	1.027 and -0.780 eÅ^{-3}

Table A.22 Atomic coordinates [x 10^4] and equivalent isotropic displacement parameters [$Å^2$ x 10^3] for 25. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
Ni(1)	13290(1)	1355(1)	801(1)	24(1)
Ni(2)	7008(1)	4400(1)	4450(1)	22(1)
O(1)	11263(3)	78(3)	-59(2)	37(1)
O(2)	14611(4)	2870(3)	2297(3)	53(1)
O(3)	8140(3)	1628(3)	6161(2)	36(1)
O(4)	6815(3)	6493(3)	2283(2)	37(1)
O(5)	14759(3)	629(3)	3024(2)	36(1)
O(6)	12656(4)	1907(3)	3751(4)	95(2)
O(7)	10475(3)	3574(3)	3285(3)	44(1)
O(8)	8823(2)	5738(3)	3610(2)	29(1)
O(9)	10271(3)	2550(3)	-102(2)	31(1)
O(10)	9185(3)	2243(3)	1559(2)	39(1)
O(11)	8699(3)	1480(4)	3252(2)	55(1)
O(12)	7050(3)	1487(3)	4474(2)	33(1)
N(1)	12252(3)	2624(3)	111(3)	25(1)
N(2)	14312(3)	90(3)	1498(3)	26(1)
N(3)	13856(3)	2313(3)	1214(3)	27(1)
N(4)	12726(3)	399(3)	389(2)	24(1)
N(5)	7485(3)	3405(3)	5497(2)	24(1)
N(6)	6536(3)	5392(3)	3399(2)	23(1)
N(7)	6179(3)	3708(3)	4010(2)	23(1)
N(8)	7831(3)	5089(3)	4907(2)	23(1)
C(1)	12714(4)	3440(4)	-1(3)	33(1)
C(2)	13184(4)	3510(4)	875(3)	33(1)
C(3)	14531(4)	2135(4)	1910(3)	34(1)
C(4)	15289(4)	927(4)	2281(3)	33(1)
C(5)	15407(4)	65(4)	1668(3)	30(1)
C(6)	14407(4)	-912(4)	1116(3)	28(1)
C(7)	13243(4)	-736(4)	862(3)	27(1)
C(8)	11757(4)	672(4)	-48(3)	27(1)
C(9)	11194(4)	1804(4)	-595(3)	26(1)
C(10)	11928(4)	2397(4)	-735(3)	30(1)
C(11)	12236(5)	4100(4)	1506(4)	44(1)
C(12)	13880(5)	4150(4)	681(4)	44(1)
C(13)	16442(4)	803(5)	2516(4)	44(1)
C(14)	12575(4)	-789(4)	1680(3)	36(1)
C(15)	13401(4)	-1675(4)	289(3)	34(1)
C(16)	10813(4)	1663(4)	-1486(3)	34(1)
C(17)	8273(4)	3603(4)	6068(3)	26(1)
C(18)	7929(4)	4837(4)	5869(3)	27(1)
C(19)	7424(4)	6271(4)	4631(3)	27(1)
C(20)	7632(4)	6432(4)	3663(3)	24(1)
C(21)	6943(4)	6081(4)	3051(3)	24(1)
C(22)	5876(4)	5090(4)	2784(3)	23(1)
C(23)	5327(4)	4516(4)	3372(3)	26(1)
C(24)	5689(4)	3233(4)	4689(3)	25(1)
C(25)	6588(4)	2210(4)	5174(3)	26(1)

C(26)	7495(4)	2407(4)	5645(3)	28(1)
C(27)	9502(4)	2920(4)	5824(3)	35(1)
C(28)	8116(4)	3404(4)	7053(3)	34(1)
C(29)	7363(4)	7641(4)	3412(3)	33(1)
C(30)	6647(4)	4307(4)	2135(3)	31(1)
C(31)	4924(4)	6082(4)	2275(3)	31(1)
C(32)	6048(4)	1703(4)	5851(3)	31(1)
C(33)	14587(5)	1228(5)	3776(3)	42(1)
C(34)	13625(5)	1199(4)	4259(4)	45(1)
C(35)	11779(7)	1760(6)	3794(7)	112(4)
C(36)	10811(5)	2419(5)	3254(4)	51(2)
C(37)	9585(4)	4231(4)	2689(4)	40(1)
C(38)	9280(4)	5413(4)	2774(3)	36(1)
C(39)	9276(4)	2389(4)	-47(3)	33(1)
C(40)	8677(4)	2877(4)	766(3)	38(1)
C(41)	8937(6)	1326(5)	1720(4)	58(2)
C(42)	9348(5)	758(5)	2616(4)	50(2)
C(43)	8996(5)	980(5)	4129(4)	49(1)
C(44)	8162(4)	610(4)	4516(4)	39(1)

Table A.23 Bond lengths [Å] and angles [°] for 25.

Ni(1)-N(2)	1.892(4)	Ni(1)-N(1)	1.897(4)
Ni(1)-N(4)	1.913(4)	Ni(1)-N(3)	1.920(4)
Ni(2)-N(8)	1.899(4)	Ni(2)-N(7)	1.900(4)
Ni(2)-N(5)	1.915(4)	Ni(2)-N(6)	1.919(4)
O(1)-C(8)	1.243(5)	O(2)-C(3)	1.247(6)
O(3)-C(26)	1.243(5)	O(4)-C(21)	1.235(5)
O(5)-C(33)	1.422(6)	O(5)-C(4)	1.444(6)
O(6)-C(35)	1.265(9)	O(6)-C(34)	1.412(7)
O(7)-C(37)	1.409(6)	O(7)-C(36)	1.428(6)
O(8)-C(38)	1.424(6)	O(8)-C(20)	1.444(5)
O(9)-C(39)	1.432(5)	O(9)-C(9)	1.448(5)
O(10)-C(40)	1.412(6)	O(10)-C(41)	1.419(7)
O(11)-C(42)	1.427(7)	O(11)-C(43)	1.426(7)
O(12)-C(44)	1.426(6)	O(12)-C(25)	1.452(5)
N(1)-C(10)	1.472(6)	N(1)-C(1)	1.479(6)
N(2)-C(5)	1.470(6)	N(2)-C(6)	1.478(6)
N(3)-C(3)	1.340(6)	N(3)-C(2)	1.507(6)
N(4)-C(8)	1.347(5)	N(4)-C(7)	1.496(6)
N(5)-C(26)	1.344(6)	N(5)-C(17)	1.503(5)
N(6)-C(21)	1.339(5)	N(6)-C(22)	1.497(5)
N(7)-C(24)	1.461(6)	N(7)-C(23)	1.478(5)
N(8)-C(19)	1.466(6)	N(8)-C(18)	1.473(6)
C(1)-C(2)	1.519(7)	C(2)-C(12)	1.531(7)
C(2)-C(11)	1.534(7)	C(3)-C(4)	1.551(7)
C(4)-C(13)	1.514(6)	C(4)-C(5)	1.514(6)
C(6)-C(7)	1.512(6)	C(7)-C(14)	1.534(7)
C(7)-C(15)	1.544(6)	C(8)-C(9)	1.544(6)
C(9)-C(10)	1.515(6)	C(9)-C(16)	1.520(6)
C(17)-C(18)	1.525(6)	C(17)-C(28)	1.531(6)
C(17)-C(27)	1.537(6)	C(19)-C(20)	1.513(6)
C(20)-C(29)	1.525(6)	C(20)-C(21)	1.563(6)
C(22)-C(23)	1.514(6)	C(22)-C(31)	1.534(6)
C(22)-C(30)	1.531(6)	C(24)-C(25)	1.509(6)
C(25)-C(32)	1.528(6)	C(25)-C(26)	1.550(6)
C(33)-C(34)	1.477(8)	C(35)-C(36)	1.424(9)
C(37)-C(38)	1.484(7)	C(39)-C(40)	1.503(7)
C(41)-C(42)	1.495(8)	C(43)-C(44)	1.498(7)

N(2)-Ni(1)-N(1)	179.3(2)	N(2)-Ni(1)-N(4)	86.0(2)
N(1)-Ni(1)-N(4)	93.8(2)	N(2)-Ni(1)-N(3)	94.0(2)
N(1)-Ni(1)-N(3)	86.2(2)	N(4)-Ni(1)-N(3)	180.0(2)
N(8)-Ni(2)-N(7)	179.1(2)	N(8)-Ni(2)-N(5)	85.8(2)
N(7)-Ni(2)-N(5)	93.5(2)	N(8)-Ni(2)-N(6)	94.2(2)
N(7)-Ni(2)-N(6)	86.5(2)	N(5)-Ni(2)-N(6)	179.7(2)
C(33)-O(5)-C(4)	117.5(4)	C(35)-O(6)-C(34)	120.9(6)
C(37)-O(7)-C(36)	112.2(4)	C(38)-O(8)-C(20)	118.7(3)
C(39)-O(9)-C(9)	117.7(3)	C(40)-O(10)-C(41)	111.5(4)
C(42)-O(11)-C(43)	112.4(4)	C(44)-O(12)-C(25)	122.5(4)
C(10)-N(1)-C(1)	112.0(4)	C(10)-N(1)-Ni(1)	114.7(3)
C(1)-N(1)-Ni(1)	108.3(3)	C(5)-N(2)-C(6)	112.9(4)
C(5)-N(2)-Ni(1)	115.2(3)	C(6)-N(2)-Ni(1)	108.8(3)
C(3)-N(3)-C(2)	115.3(4)	C(3)-N(3)-Ni(1)	128.8(3)
C(2)-N(3)-Ni(1)	113.2(3)	C(8)-N(4)-C(7)	115.2(4)
C(8)-N(4)-Ni(1)	128.7(3)	C(7)-N(4)-Ni(1)	113.0(3)

C(26)-N(5)-C(17)	115.6(4)	C(26)-N(5)-Ni(2)	127.9(3)
C(17)-N(5)-Ni(2)	113.1(3)	C(21)-N(6)-C(22)	116.0(4)
C(21)-N(6)-Ni(2)	128.9(3)	C(22)-N(6)-Ni(2)	112.4(3)
C(24)-N(7)-C(23)	112.3(3)	C(24)-N(7)-Ni(2)	114.3(3)
C(23)-N(7)-Ni(2)	108.1(3)	C(19)-N(8)-C(18)	113.3(4)
C(19)-N(8)-Ni(2)	115.6(3)	C(18)-N(8)-Ni(2)	108.3(3)
N(1)-C(1)-C(2)	109.2(4)	N(3)-C(2)-C(1)	103.3(4)
N(3)-C(2)-C(12)	114.6(4)	C(1)-C(2)-C(12)	106.7(4)
N(3)-C(2)-C(11)	110.2(4)	C(1)-C(2)-C(11)	110.9(4)
C(12)-C(2)-C(11)	110.8(4)	O(2)-C(3)-N(3)	125.4(5)
O(2)-C(3)-C(4)	115.7(4)	N(3)-C(3)-C(4)	118.9(4)
O(5)-C(4)-C(13)	112.2(4)	O(5)-C(4)-C(5)	101.6(4)
C(13)-C(4)-C(5)	109.3(4)	O(5)-C(4)-C(3)	109.5(4)
C(13)-C(4)-C(3)	109.9(4)	C(5)-C(4)-C(3)	114.1(4)
N(2)-C(5)-C(4)	110.6(4)	N(2)-C(6)-C(7)	108.4(4)
N(4)-C(7)-C(6)	103.9(4)	N(4)-C(7)-C(14)	110.7(4)
C(6)-C(7)-C(14)	110.8(4)	N(4)-C(7)-C(15)	114.6(4)
C(6)-C(7)-C(15)	106.4(4)	C(14)-C(7)-C(15)	110.2(4)
O(1)-C(8)-N(4)	125.4(4)	O(1)-C(8)-C(9)	115.8(4)
N(4)-C(8)-C(9)	118.8(4)	O(9)-C(9)-C(10)	103.0(4)
O(9)-C(9)-C(16)	112.2(4)	C(10)-C(9)-C(16)	108.8(4)
O(9)-C(9)-C(8)	108.4(4)	C(10)-C(9)-C(8)	114.5(4)
C(16)-C(9)-C(8)	109.9(4)	N(1)-C(10)-C(9)	110.7(4)
N(5)-C(17)-C(18)	103.4(3)	N(5)-C(17)-C(28)	113.5(4)
C(18)-C(17)-C(28)	107.2(4)	N(5)-C(17)-C(27)	111.4(4)
C(18)-C(17)-C(27)	110.4(4)	C(28)-C(17)-C(27)	110.6(4)
N(8)-C(18)-C(17)	108.0(4)	N(8)-C(19)-C(20)	110.0(4)
O(8)-C(20)-C(19)	102.4(4)	O(8)-C(20)-C(29)	110.3(4)
C(19)-C(20)-C(29)	109.5(4)	O(8)-C(20)-C(21)	111.5(3)
C(19)-C(20)-C(21)	113.7(4)	C(29)-C(20)-C(21)	109.3(4)
O(4)-C(21)-N(6)	126.2(4)	O(4)-C(21)-C(20)	115.5(4)
N(6)-C(21)-C(20)	118.3(4)	N(6)-C(22)-C(23)	104.8(3)
N(6)-C(22)-C(31)	114.6(3)	C(23)-C(22)-C(31)	106.6(4)
N(6)-C(22)-C(30)	110.9(4)	C(23)-C(22)-C(30)	110.4(4)
C(31)-C(22)-C(30)	109.4(4)	N(7)-C(23)-C(22)	108.5(3)
N(7)-C(24)-C(25)	110.8(4)	O(12)-C(25)-C(24)	101.9(3)
O(12)-C(25)-C(32)	109.8(3)	C(24)-C(25)-C(32)	109.6(4)
O(12)-C(25)-C(26)	112.2(4)	C(24)-C(25)-C(26)	114.5(4)
C(32)-C(25)-C(26)	108.7(4)	O(3)-C(26)-N(5)	125.9(4)
O(3)-C(26)-C(25)	116.0(4)	N(5)-C(26)-C(25)	118.1(4)
O(5)-C(33)-C(34)	108.6(4)	O(6)-C(34)-C(33)	106.3(5)
O(6)-C(35)-C(36)	122.2(8)	O(7)-C(36)-C(35)	111.7(5)
O(7)-C(37)-C(38)	108.6(4)	O(8)-C(38)-C(37)	111.8(4)
O(9)-C(39)-C(40)	107.5(4)	O(10)-C(40)-C(39)	114.4(4)
O(10)-C(41)-C(42)	110.5(5)	O(11)-C(42)-C(41)	108.6(5)
O(11)-C(43)-C(44)	112.4(5)	O(12)-C(44)-C(43)	112.0(4)

Symmetry transformations used to generate equivalent atoms:

Table A.24 Anisotropic displacement parameters [$Å^2$ x 10^3] for 25.

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
Ni(1)	25(1)	23(1)	24(1)	-3(1)	-3(1)	-10(1)
Ni(2)	22(1)	24(1)	22(1)	-1(1)	-3(1)	-12(1)
O(1)	40(2)	34(2)	43(2)	4(2)	-14(2)	-22(2)
O(2)	74(3)	40(2)	55(3)	-7(2)	-24(2)	-32(2)
O(3)	40(2)	34(2)	35(2)	7(2)	-15(2)	-20(2)
O(4)	41(2)	49(2)	28(2)	9(2)	-8(2)	-28(2)
O(5)	47(2)	41(2)	29(2)	-8(2)	-3(2)	-25(2)
O(6)	41(3)	35(2)	197(6)	-2(3)	-31(3)	-7(2)
O(7)	38(2)	32(2)	59(3)	-9(2)	-12(2)	-12(2)
O(8)	22(2)	36(2)	28(2)	-3(2)	-1(1)	-13(1)
O(9)	25(2)	35(2)	34(2)	-10(2)	3(1)	-13(2)
O(10)	45(2)	43(2)	39(2)	-11(2)	8(2)	-26(2)
O(11)	42(2)	82(3)	28(2)	0(2)	1(2)	-17(2)
O(12)	31(2)	31(2)	33(2)	-9(2)	1(2)	-11(2)
N(1)	26(2)	24(2)	27(2)	-1(2)	-2(2)	-12(2)
N(2)	26(2)	26(2)	25(2)	-5(2)	-3(2)	-12(2)
N(3)	29(2)	23(2)	31(2)	-1(2)	-3(2)	-14(2)
N(4)	24(2)	27(2)	22(2)	-3(2)	-1(2)	-12(2)
N(5)	27(2)	28(2)	21(2)	-1(2)	-6(2)	-15(2)
N(6)	21(2)	24(2)	22(2)	-2(2)	-3(2)	-9(2)
N(7)	23(2)	24(2)	24(2)	-4(2)	-3(2)	-11(2)
N(8)	25(2)	26(2)	20(2)	0(2)	-2(2)	-14(2)
C(1)	33(3)	23(2)	42(3)	2(2)	-2(2)	-13(2)
C(2)	35(3)	27(3)	40(3)	-4(2)	-5(2)	-16(2)
C(3)	38(3)	34(3)	35(3)	-6(2)	-6(2)	-18(2)
C(4)	30(3)	37(3)	36(3)	-7(2)	-8(2)	-18(2)
C(5)	24(2)	30(3)	35(3)	-2(2)	-7(2)	-10(2)
C(6)	32(3)	22(2)	28(3)	-3(2)	-3(2)	-10(2)
C(7)	31(3)	24(2)	25(2)	-1(2)	-5(2)	-11(2)
C(8)	27(2)	24(2)	28(3)	-1(2)	-6(2)	-10(2)
C(9)	24(2)	32(3)	23(2)	-4(2)	-1(2)	-11(2)
C(10)	31(3)	33(3)	24(3)	6(2)	-6(2)	-14(2)
C(11)	45(3)	35(3)	52(4)	-15(3)	2(3)	-15(3)
C(12)	48(3)	32(3)	56(4)	-4(3)	-6(3)	-20(3)
C(13)	42(3)	54(3)	44(3)	-2(3)	-13(3)	-29(3)
C(14)	42(3)	39(3)	30(3)	4(2)	-5(2)	-22(3)
C(15)	39(3)	25(3)	35(3)	-3(2)	-8(2)	-13(2)
C(16)	33(3)	39(3)	27(3)	-4(2)	-5(2)	-14(2)
C(17)	26(2)	34(3)	23(2)	0(2)	-8(2)	-18(2)
C(18)	28(2)	35(3)	26(2)	-2(2)	-5(2)	-20(2)
C(19)	32(3)	22(2)	31(3)	-2(2)	-6(2)	-15(2)
C(20)	23(2)	23(2)	32(3)	-1(2)	0(2)	-13(2)
C(21)	20(2)	27(2)	26(3)	-3(2)	1(2)	-10(2)
C(22)	20(2)	26(2)	24(2)	-4(2)	-5(2)	-9(2)
C(23)	18(2)	29(2)	28(3)	-1(2)	-6(2)	-9(2)
C(24)	25(2)	29(2)	27(2)	0(2)	-5(2)	-18(2)
C(25)	30(3)	24(2)	24(2)	-3(2)	-1(2)	-14(2)

C(26)	28(3)	35(3)	25(3)	-1(2)	-4(2)	-18(2)
C(27)	28(3)	39(3)	41(3)	-3(2)	-6(2)	-18(2)
C(28)	37(3)	38(3)	30(3)	0(2)	-7(2)	-20(2)
C(29)	36(3)	28(3)	36(3)	-2(2)	1(2)	-16(2)
C(30)	29(3)	33(3)	26(3)	-5(2)	1(2)	-9(2)
C(31)	26(2)	32(3)	33(3)	1(2)	-11(2)	-10(2)
C(32)	38(3)	33(3)	27(3)	0(2)	-3(2)	-20(2)
C(33)	52(3)	45(3)	32(3)	-13(3)	-4(3)	-21(3)
C(34)	46(3)	33(3)	50(4)	-12(3)	-1(3)	-11(3)
C(35)	79(6)	40(4)	208(11)	19(5)	-72(7)	-22(4)
C(36)	47(4)	41(3)	70(4)	-20(3)	8(3)	-20(3)
C(37)	25(3)	54(3)	37(3)	-14(3)	-2(2)	-12(2)
C(38)	29(3)	46(3)	27(3)	1(2)	2(2)	-14(2)
C(39)	29(3)	40(3)	32(3)	-8(2)	-2(2)	-16(2)
C(40)	31(3)	44(3)	40(3)	-14(3)	6(2)	-15(2)

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

	x	y	z	U(eq)
H(1)	11643(41)	2898(39)	372(32)	30
H(2)	13997(42)	157(42)	1933(33)	31
H(7)	6630(40)	3177(39)	3748(32)	28
H(8)	8432(40)	4803(39)	4672(31)	27
H(1A)	12115(4)	4175(4)	-216(3)	40
H(1B)	13314(4)	3211(4)	-440(3)	40
H(5A)	15723(4)	210(4)	1106(3)	36
H(5B)	15931(4)	-679(4)	1935(3)	36
H(6A)	14757(4)	-1565(4)	1550(3)	34
H(6B)	14884(4)	-1045(4)	592(3)	34
H(10A)	12610(4)	1934(4)	-1050(3)	36
H(10B)	11515(4)	3103(4)	-1103(3)	36
H(11A)	12559(5)	4136(4)	2065(4)	66
H(11B)	11790(5)	3688(4)	1607(4)	66
H(11C)	11755(5)	4851(4)	1247(4)	66
H(12A)	14201(5)	4214(4)	1232(4)	66
H(12B)	13397(5)	4890(4)	404(4)	66
H(12C)	14486(5)	3754(4)	285(4)	66
H(13A)	16368(4)	1359(5)	2913(4)	66
H(13B)	16813(4)	909(5)	1980(4)	66
H(13C)	16890(4)	61(5)	2806(4)	66
H(14A)	11825(4)	-674(4)	1501(3)	54
H(14B)	12508(4)	-211(4)	2052(3)	54
H(14C)	12965(4)	-1516(4)	2011(3)	54
H(15A)	12665(4)	-1595(4)	106(3)	51
H(15B)	13811(4)	-2392(4)	629(3)	51
H(15C)	13828(4)	-1633(4)	-232(3)	51
H(16A)	10338(4)	1280(4)	-1403(3)	50
H(16B)	11471(4)	1226(4)	-1824(3)	50
H(16C)	10386(4)	2392(4)	-1804(3)	50
H(18A)	7202(4)	5275(4)	6141(3)	33
H(18B)	8500(4)	5026(4)	6110(3)	33
H(19A)	7816(4)	6583(4)	4977(3)	33
H(19B)	6610(4)	6668(4)	4740(3)	33
H(23A)	4699(4)	5067(4)	3687(3)	31
H(23B)	5023(4)	4132(4)	3015(3)	31
H(24A)	5139(4)	3040(4)	4415(3)	30
H(24B)	5286(4)	3787(4)	5109(3)	30
H(27A)	9710(4)	2130(4)	5954(3)	52
H(27B)	9988(4)	3121(4)	6165(3)	52
H(27C)	9591(4)	3074(4)	5196(3)	52
H(28A)	8328(4)	2616(4)	7205(3)	51
H(28B)	7328(4)	3842(4)	7196(3)	51
H(28C)	8592(4)	3625(4)	7387(3)	51
H(29A)	7499(4)	7744(4)	2786(3)	49
H(29B)	7844(4)	7844(4)	3758(3)	49
H(29C)	6575(4)	8112(4)	3531(3)	49
H(30A)	6995(4)	4689(4)	1759(3)	46

H(30B)	6207(4)	4075(4)	1771(3)	46
H(30C)	7233(4)	3654(4)	2461(3)	46
H(31A)	5241(4)	6482(4)	1884(3)	47
H(31B)	4423(4)	6579(4)	2689(3)	47
H(31C)	4498(4)	5818(4)	1925(3)	47
H(32A)	6633(4)	1039(4)	6165(3)	47
H(32B)	5529(4)	1503(4)	5552(3)	47
H(32C)	5635(4)	2242(4)	6271(3)	47
H(33A)	14431(5)	2004(5)	3592(3)	51
H(33B)	15268(5)	889(5)	4159(3)	51
H(34A)	13697(5)	435(4)	4330(4)	54
H(34B)	13588(5)	1460(4)	4848(4)	54
H(35A)	11534(7)	1833(6)	4411(7)	134
H(35B)	12010(7)	980(6)	3684(7)	134
H(36A)	10974(5)	2230(5)	2640(4)	62
H(36B)	10187(5)	2248(5)	3452(4)	62
H(37A)	8930(4)	4082(4)	2821(4)	48
H(37B)	9816(4)	4051(4)	2082(4)	48
H(38A)	9957(4)	5538(4)	2691(3)	43
H(38B)	8725(4)	5879(4)	2307(3)	43
H(39A)	9475(4)	1589(4)	-13(3)	40
H(39B)	8789(4)	2760(4)	-574(3)	40
H(40A)	8636(4)	3624(4)	779(3)	46
H(40B)	7898(4)	2965(4)	731(3)	46
H(41A)	9299(6)	797(5)	1273(4)	69
H(41B)	8116(6)	1583(5)	1671(4)	69
H(42A)	9270(5)	61(5)	2691(4)	60
H(42B)	10151(5)	575(5)	2693(4)	60
H(43A)	9052(5)	1518(5)	4499(4)	58
H(43B)	9743(5)	334(5)	4134(4)	58
H(44A)	8180(4)	-1(4)	4195(4)	47
H(44B)	8375(4)	321(4)	5137(4)	47