Synthesis and Characterization of a Chloro - Hydroxo Chromium [3+] Complex of Cross-Bridged Cyclam

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ABSTRACT

Another transition metal complex of cross-bridged cyclam, has been synthesized. The new chromium[3+] complex contains chloro and hydroxo ligands along with the macrocycle. Initial characterization of the ligand as well as the complex was done by mass spectrometry, ^{1}H NMR, ^{13}C NMR, and elemental analysis. A crystal structure of the complex has also been obtained and shows typical geometry for transition metals complexed to this ligand. The chromium[3+] center bound by ligands in a distorted octahedron and the Cr-OH bond length was found to be 1.965 angstroms.

Keywords: *cross-bridged cyclam, chromium, chloro, hydroxo*

INTRODUCTION

The use of oxidizing metal centers and their development as catalysts has attracted a good deal of attention in the past because of their important role in industrial and biochemical reactions (Sheldon, R.A.; Kochi, J.K., 1981). More recently, attention has been given new types of potential catalysts, as they can be more effective and efficient under a wide range of conditions. The transfer of an oxygen atom from an environmentally benign oxidant such as H_2O_2 to an organic compound via a homogeneous catalyst is desirable in many applications, including the laboratory, because of the ease and relative harmlessness of chemicals involved.

It has been shown that transition metal complexes of tetraazamacrocycles are quite stable, even under harsh conditions (Hubin, T.J.; et al, 1998). This is a consequence of the chelate effect, which simply means that the more rigid and better fitting the ligand is with the metal, the more stable the complex is. That the ligand will hold up under a wide array of conditions gives it promise as part of an oxidation catalyst. The ligand used in this research,4,11-dimethyl-1,4,8,11-tetraazabicyclo[6.6.2] hexadecane **(4)**, coordinates a metal ion in such a way as to leave an opening for redox reactions to occur. In past studies involving **(4)**, crystal structures have shown that the oxidizing metal center is coordinated in a cleft in the middle if the macrocycle (Hubin, T.J.; et al, 1998). Additionally, the ligand geometry changes dramatically upon complexation, which leaves coordination sites exposed and will allow reactions to proceed without steric interference with the ligand.

Many transition metal complexes of **(4)** have been synthesized. Among the metal ions to have been coordinated to the ligand are Iron(III), Manganese(II) as well as a variety of other first and second row transition metals (Hubin, T.J.; et al, 2000). It is the goal of this project to evaluate the promise of other transition metals for use as coordinating centers using **(4)** as the ligand. Hubin et al. have reported the Mn[II]**(4)** complex to be reasonably successful as an oxidation catalyst of carbamazepine. In this research, the syntheses of the Ru[III] and Cr[iii] complexes of **(4)** were attempted using published routes (Weisman, G.R.; et al, 1990)**.**

MATERIALS AND METHODS

All chemicals were either provided by Dr. Tim Hubin and the McPherson College Chemistry Department or purchased from Aldrich through McPherson College.

Cyclam (1)

Cyclam was prepared by dissolving $NiCl_2 \cdot H_2O$ (35.66 g, 0.15 mol) in 100 ml distilled water. 1,5,8,12 tetraazadodecane (26 g, 0.15 mol) was added to yield a purple solution, which was cooled to 0°C in an ice bath. 22.5 ml of a 40% glyoxal solution in acetonitrile was added and stirred for 4 hours. $NaBH_4$ (11g, 0.026 mol) was added slowly and the resulting solution was heated at 90°C for 20 minutes. The solution was then filtered through celite and a medium frit and stored in a refrigerator overnight. KCN (39 g, 0.6 mol) was dissolved and the solution was refluxed with a cold-water condenser for 2 hours. NaOH (15 g, 0.36 mol) was dissolved and the solution was evaporated using the rotovap. $CHCl_3$ (100 ml) was added and the solution was filtered through a medium frit. The solution was washed with $CHCl_3$ and extracted several times using $CHCl_3$. The organic layer was dried over Na_2SO_4 and then filtered with a coarse filter paper (Barefield, et al., 1976). The solvent was removed to yield pure Cyclam (16g, 0.080 mol, 53.30% yield).

Cantaurus
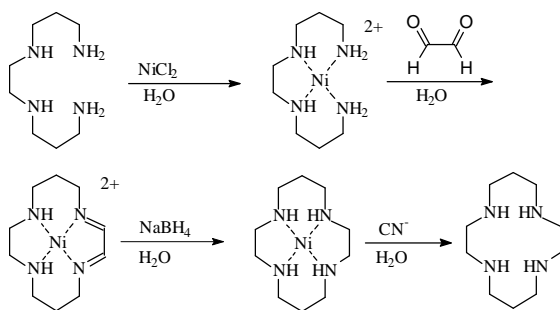
Figure 1. Synthesis of Cyclam.

### *cis*-Decahydro-1H, 6H-3a,5a, 8a, 10a-tetraazapyrene (2)

   Cyclam (9.8 g, 0.049 mol) was added to two-neck round-bottomed flask and flushed with N_2 for 15 min. CH_2CN (40ml) was added and stirred, followed by a 40% solution of glyoxal (7.6 mL) in acetonitrile. The solution was stirred at 50-65°C for 3 hours under N_2. The solvent was removed using the rotovap and the solution was extracted 5 times with $CHCl_3$ (40 ml). The crude product was filtered and stored overnight in a refrigerator. The product was purified in 6" alumina in a 1-inch diameter column using a 1% solution of CH_3OH in CH_2Cl_2. Chromatography was complete when a yellow band reached the bottom of the column. The solvent was removed with the rotovap to yield a white solid **(2)** (10.46 g, 0.047 mol, 96% yield)**.**
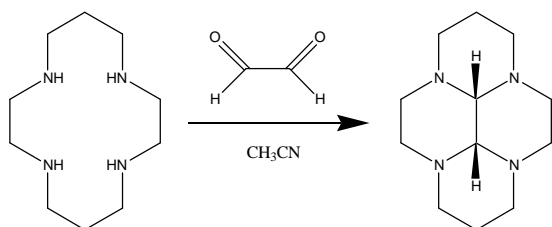
Figure 2. Condensation of glyoxal into the macrocycle.

### 3a,8a-Dimethyl-decahydro-3a,5a,8a,10a-tetraaza-pyrene (3)

   (2) (10.46 g, 0.047 mol) was dissolved in CH_3CN (300 ml) and put under N_2 in a two-necked round-bottomed flask. Methyl iodide (40 mL) was added to the reaction flask and the solution was stirred for 72 hrs. under N_2. Following completion of the reaction, the product was collected on a medium frit and allowed to dry. This reaction had a 60% yield (14.25 g, 0.028 mol).
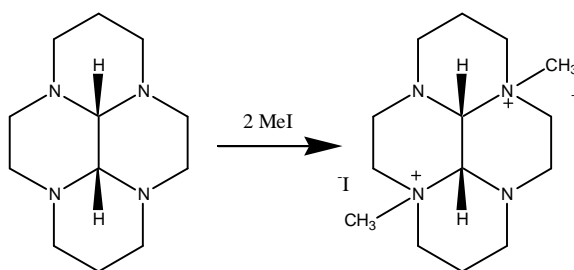
Figure 3. Dimethylation of the tetracycle.

4,11-Dimethyl-1,4,8,11-tetraaza-bicyclo[6.6.2] hexadecane (4)

   (3) (6.997 g) was added to 609 ml 95% EtOH solution in a large round-bottomed flask. $NaBH_4$ (14.078 g) was added slowly and the solution was stirred for 5 days. Following completion of this reaction, 10% aqueous HCl was added until the pH was between 1 and 2. 450 ml EtOH was then added and the solvent was then removed with the rotovap. The residue was dissolved in 150 ml distilled H_2O and then made strongly basic, first with a 30% solution of KOH (50 ml), then by adding KOH pellets until the pH was approximately 14. The product was extracted 4 times using benzene (225 ml) and then dried over Na_2SO_4. Approximately 3 ground KOH pellets and 2 small boiling chips were added to the crude product in a small round-bottomed flask. Purification was done by short-path vacuum distillation at 70-75° C to give a 33.8% yield of pure **(4)** (4.01 g, 0.016 mol)**.**
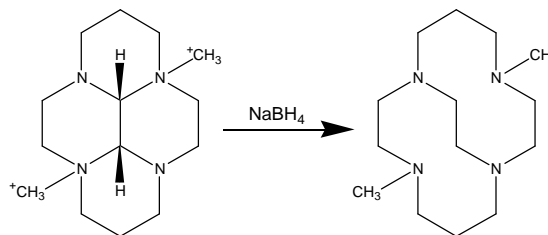
Figure 4. Reduction of the tetracycle to yield **(4)**.

Metallation with RuCl₃ (5)
   In the glove box, **(4)** (0.254 g, 0.001 mol) was dissolved in 20 ml DMF in a 50 ml round-bottomed flask equipped with a condenser. Anhydrous $RuCl_3$ (0.207 g, 0.001 mol) was added and the solution was stirred for 2 days under low heat (≈40-50°C).

Metallation with CrCl₂ (6)
   The procedure for this step was identical to the preparation of **(5)**, using anhydrous $CrCl_2$ (0.123g, 0.001 mol) rather than $RuCl_3$. Since this step was thought to be successful, several small ether diffusion chambers were set up to grow crystals of **(6).**

RESULTS AND DISCUSSION

Mass spectra of all compounds except **(2)** were taken aby the Analtical Service at the University of Kansas using a VG ZAB HS spectrometer equipped with a xenon gun. The mass spectrum of **(2)** was taken at McPherson College using a Varian Saturn 2100D GC/MS. ^1H and ^{13}C NMR spectra were also taken at the University of Kansas on a 500 MHz spectrometer. Elemental analyses were perfomed at Quantitative Technologies Inc. in Whitehouse, NJ. X-Ray crystal structure data were obtained by Dr. Stephen Archibald at the University of Hull, England using a Stoe IPDS-II imaging plate diffractometer. NMR peak assignments are available upon request.

Synthesis 1 (Cyclam **(1)**)
The yield for this step was 53.3%, which is about average for this reaction. Synthesizing cyclam in the lab is more cost-effective than purchasing it ($50/gram) and was therefore chosen. Characterization of cyclam by melting point and infrared spectroscopy has been performed in literature (Barefield, et al., 1976).

Synthesis 2 (*cis*-Decahydro-1H, 6H-3a,5a, 8a, 10a-tetraazapyrene **(2)**)
This reaction yielded 10.46 g of product, which is equivalent to a 96% yield. However, this mass is believed to have been taken prematurely, before the product was completely dry, so the calculated percent yield is probably high. Still, there was an adequate amount of product for the purposes of this research. The condensation of the two-carbon glyoxal unit into the macrocycle is the foundation for the cross-bridge necessary for ligand rigidity. Mass spectrometry showed a large peak at m/z =222, which is consistent with the mass of this molecule.

Synthesis 3 (3a,8a-Dimethyl-decahydro-3a,5a,8a,10a-tetraaza-pyrene **(3)**)
The tetracycle was methylated in 300ml dry acetonitrile with fifteen equivalents of methyl iodide. The reaction proceeded for 72 hours under N_2 to give an 60% yield. This is lower than what was expected and it is believed that undried solvents and reagents may be partly to blame. ^{13}C NMR shows carbon atoms in seven different environments, as expected. Furthermore, analysis of the ^1H NMR supports the existence of the dimethylated tetracycle. The theoretical elemental analysis for $C_{14}N_4H_{28}I_2$ is C, 33.23%; H, 5.53%; N, 11.07%. The experimental analysis found these percentages to be C, 32.61%; H, 5.61%; N, 10.62%.
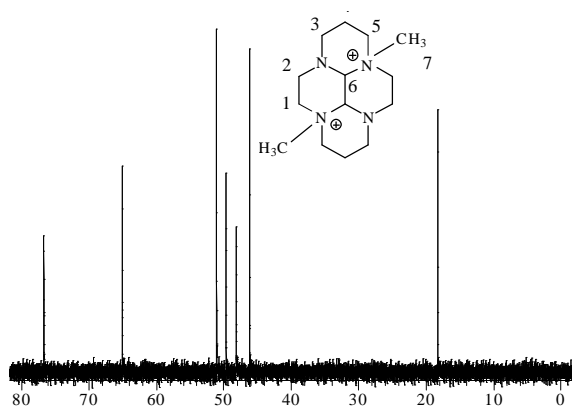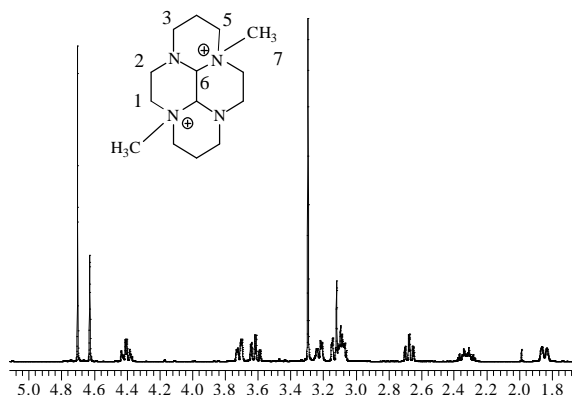

Figure 5. ^{13}C NMR of **(3)**.

Figure 6. ^1H NMR of **(3)**.

Synthesis 4 (4,11-Dimethyl-1,4,8,11-tetraaza - bicyclo[6.6.2] hexadecane **(4)**)
The dimethlyated tetracycle was reduced to (**4**) using sodium borohydride. The reaction proceeded under N_2 for five days to give a 69.7% yield. Due to the proton-sponge behavior of this ligand, strongly basic conditions are required to remove protons so as to reduce complications during metal complexation (Hubin, T.J.; et al, 1998). The addition of several grams of KOH pellets provided the aprotic environment necessary to remove protons from the ligand. After purification by short-path vacuum distillation, the ligand exists as a clear, oily liquid. Mass spec shows a strong peak at m/z=255, as expected for this ligand. Analyses of ^1H NMR and ^{13}C NMR spectra further support the successful synthesis of **(4)** and show a high degree of purity.

Synthesis 5 (Metallation with $RuCl_3$ **(5)**)
The synthesis of the Ru^{III} complex of this ligand was attempted in the glove box. The ruthenium salt was successfully dissolved in DMF, however, the lack of a color change after hours of stirring hinted that no reaction had occurred. FAB^+ mass spectrometry
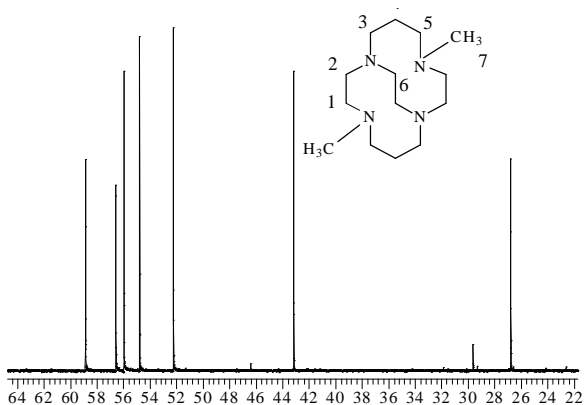
Figure 7. ^{13}C NMR of **(4)**.

confirmed the lack of a successful reaction as no significant peak corresponded to a possible metal complex. Additionally, there was a large amount of unreacted ligand present at m/z =255.
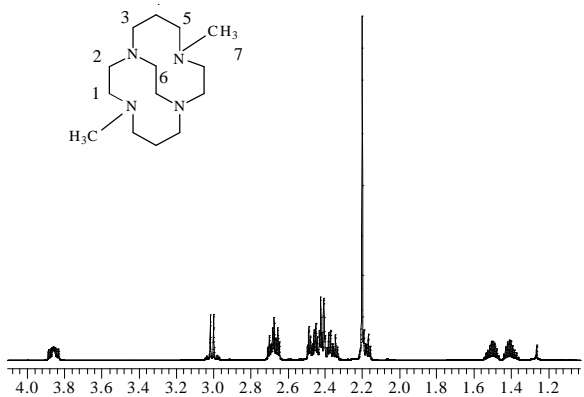

Figure 8. ^{1}H NMR of **(4)**.

Synthesis 6 (Metallation with $CrCl_2$ **(6)**)

Chromium had more promise as a metal for this ligand due mainly to its smaller size. A color change from green to blue was almost immediately observed upon the combination of reagents. The mixture was left to react overnight. Mass spectrometry supports the successful formation of a chromium complex. The theoretical mass of the complex not including the 1.5 water molecules and the chloride counterion is 358.6 g/mol and a strong peak appears in the mass spectrum at m/z=358.1. The percent yield for this reaction was at least 22.73% (2.27×10^{-4} mol). This data is consistent with a large peak in the mass spectrum at m/z=255 due to a large amount of unreacted ligand. Crystals were grown using ether diffusion chambers and a crystal structure was obtained. According to the crystal structure, the chromium complex was unintentionally oxidized to Cr^{III} during the course of the reaction. Is possibly due to an undesirable presence of water in the DMF. There is also the small possibility that trace amounts of oxygen were present in the glove box. The crystal structure shows that a chloro-hydroxo

complex was formed, with chloride acting as a counterion and 1.5 water molecules elsewhere in the structure. The theoretical elemental analysis for $[Cr(C_{14}H_{30}N_4)]Cl \bullet 1.5\ H_2O$ is C, 39.84%; H, 8.29%; N, 13.27%. The experimental values were C, 39.87%; H, 8.37%, N, 12.82%.
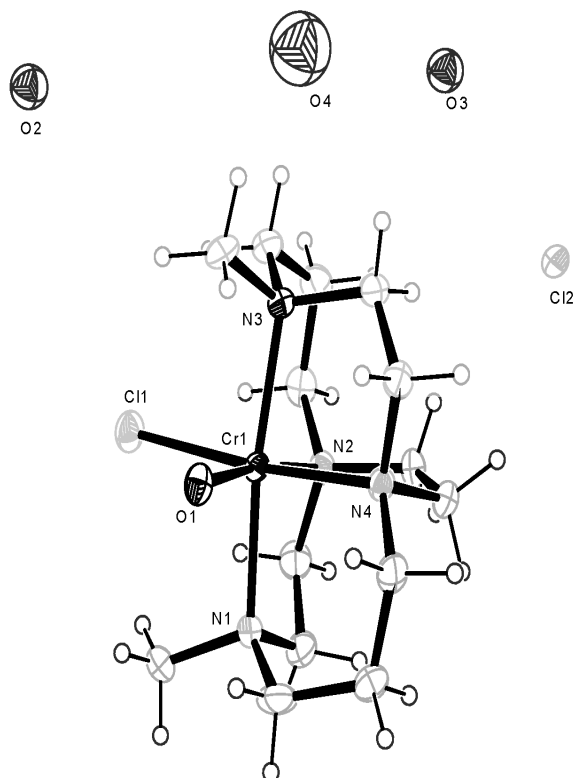

Figure 9. X-Ray Crystal structure of **(6)**.

Table 1. Atomic coordinates (x 10^4) for **(6)**.

	x	y	z
Cr(1)	948(1)	2656(1)	1429(1)
Cl(1)	642(1)	3302(1)	3402(1)
N(3)	1143(1)	1555(2)	2807(4)
N(1)	843(1)	3744(2)	-52(4)
N(2)	1626(1)	3179(2)	2103(4)
N(4)	1273(1)	1998(2)	-174(4)
O(1)	329(1)	2213(2)	513(3)
C(5)	1397(2)	1728(3)	4330(5)
C(7)	1260(2)	1073(3)	293(5)
C(1)	1312(2)	4209(3)	127(6)
C(14)	711(2)	1058(3)	3012(6)
C(4)	1850(2)	2242(3)	4422(6)
C(6)	1434(2)	988(3)	1944(5)
C(13)	494(2)	4365(3)	440(7)
C(3)	1809(2)	3129(3)	3759(6)
C(10)	659(2)	3530(4)	-1624(6)

C(2)	1574(2)	4113(3)	1727(6)
C(9)	952(2)	2930(3)	-2401(5)
C(12)	1772(1)	2294(3)	-139(5)
C(8)	1017(2)	2044(3)	-1744(5)
C(11)	1980(2)	2773(3)	1277(5)
Cl(2)	2806(1)	1060(1)	2482(1)
O(2)	37(1)	732(2)	5954(4)
O(3)	2285(1)	23(2)	4782(4)
O(4)	2018(3)	921(4)	7268(9)

Table 2. Selected bond lengths for **(6)**.

Cr(1)-O(1)	1.965(3)
Cr(1)-N(4)	2.110(4)
Cr(1)-N(2)	2.115(4)
Cr(1)-N(3)	2.145(4)
Cr(1)-N(1)	2.153(4)
Cr(1)-Cl(1)	2.3341(14)

Table 3. Selected bond angles for **(6)**.

O(1)-Cr(1)-N(4)	90.57(13)
O(1)-Cr(1)-N(2)	171.93(14)
N(4)-Cr(1)-N(2)	84.07(14)
O(1)-Cr(1)-N(3)	95.75(14)
N(4)-Cr(1)-N(3)	84.45(14)
N(2)-Cr(1)-N(3)	89.75(14)
O(1)-Cr(1)-N(1)	89.26(14)
N(4)-Cr(1)-N(1)	89.58(14)
N(2)-Cr(1)-N(1)	84.68(14)
N(3)-Cr(1)-N(1)	172.23(14)
O(1)-Cr(1)-Cl(1)	92.85(9)
N(4)-Cr(1)-Cl(1)	173.70(11)
N(2)-Cr(1)-Cl(1)	93.06(10)
N(3)-Cr(1)-Cl(1)	89.94(11)
N(1)-Cr(1)-Cl(1)	95.76(11)

The x-ray crystal structure data show a typical geometry for this class of transition metal complexes. The chromium^{3+} center is bonded to ligands in a distorted octahedron, leaving the equatorial sites (bonded by the hydroxo and chloro ligands) available for potential redox reactions. The Cr-OH bond length is also typical for this type of complex (Goodson, P. R.; et al, 1998).

ACKNOWLEDGEMENTS

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