1 of 1

Progress Report for Subcontract 9-X33-L0152-1

The P. I.'s (Dr. C. B. Storm, P. I., Dr. R. J. Butcher, Co-P. I.) have worked in the area of research outlined in the subcontract 9-X33-L0152-1 and a substantial body of preliminary data have been gathered and two publications, one manuscript in preparation, and several presentations at national American Chemical Society meetings have resulted. These are summarized below under various headings.

(a) Structural Studies.

X-ray structural studies were completed for the following compounds:

Data have been collected for the following structures:

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From the structural data obtained on the above complexes, the following conclusions can be drawn:

$[\text{Co}(\text{NH}_3)_5(4\text{-nitroimidazolato})](\text{ClO}_4)_2$; this was the first structure completed in this series and was determined to conclusively prove that imidazole had indeed been nitrated and the site of nitration. These results opened up a method for the facile and regiospecific nitration of coordinated heterocycles.

$[\text{Co}(\text{NH}_3)_5(\text{benzimidazole})](\text{ClO}_4)_3$; this structure was completed to determine the mode of attachment of the benzimidazole moiety, and as a benchmark structure to compare with the structure of the nitrated product and also as a test of the predictions from NMR methods outlined above.

$[\text{Co}(\text{NH}_3)_4(2,3\text{-dimethylimidazole})_2](\text{ClO}_4)_3$; this structure was completed to confirm the stoichiometry of the complex, confirm the cis geometry of the substituted imidazole groups, examine the mode of attachment of the imidazole groups, and check the assignments of the NMR resonances. These proved to be exactly as predicted.

$[\text{Co}(\text{en})_2(\text{aniline})(\text{Cl})]\text{Cl}_2$; this structure is of great interest as it is the first structurally characterized aniline complex of Co(III). The aniline and chloride groups are mutually cis to one another as predicted from their NMR resonances.

$[\text{Co}(\text{en})_2(\text{pyridine})(\text{Cl})]\text{Cl}_2$; this molecule has proved difficult to nitrate via the methods developed in this proposal for reasons that will be elaborated below in the section on "Synthesis and Nitration". The structural characterization was carried out to provide a comparison with the nitrated product and also as a test of whether the NMR method of structural assignment could also be applied to cobalt complexes of ethylenediamine and thus to confirm the expected cis arrangement of the pyridine and chloride moieties.

$[\text{Co}(\text{en})_2\text{Cl}_2]\text{Cl}\cdot 2\text{DMSO}$; this established the mutually cis geometry of the ligands and provided a benchmark structure for further structural studies on cis-bis ethylenediamine complexes of cobalt(III).

$\text{K}[\text{Co}(\text{en})(\text{CO}_3)_2]\cdot \text{H}_2\text{O}$; this analysis was carried out to confirm the structure of this compound first synthesized in our laboratories. It is a valuable precursor to complexes incorporating coordinated heterocycles via the reaction with perchloric acid in the presence of suitable heterocycle ligands.

$[\text{Co}(\text{NH}_3)_5(4\text{-nitropyrazole})](\text{ClO}_4)_2$; the structure of this molecule was carried out to confirm the site of nitration predicted from NMR studies and also to fully characterize this unique compound. The parent pyrazole complex was predicted to have similar properties to the analogous imidazole complex, i.e., that it would nitrate readily in the 4- position and this has proved to be correct (for more detailed analysis of this prediction see section "Synthesis and Nitration").

In particular, it is an unexplained phenomenon that in the process of nitrating both the imidazole and the pyrazole ligands in their respective complexes, reactions which, of necessity, are carried out in strongly acid media, both moieties are deprotonated. Further kinetic and mechanistic studies are in progress to identify the mechanism of this nitration and also whether the nitration and deprotonation occur simultaneously, or consecutively, and, if the latter, which comes first.

$[\text{Co}(\text{en})(\text{histidine})(\text{Cl})]\text{Cl}_2$; this structure demonstrated that histidine was bonded to the cobalt ion as a tridentate ligand.

$[\text{Co}(\text{en})(4\text{-nitrohistidine})(\text{Cl})]\text{Cl}$; this structure was completed to show that coordinated histidine could be nitrated as easily as imidazole. This result has potentially far reaching implications for the development of substituted histidines (e.g., fluorine) for NMR studies in biochemistry.

$[\text{Co}(\text{en})_2(4\text{-nitroimidazole})(\text{Cl})]\text{Cl}_2$; this structure demonstrated that the nitration of imidazole coordinated to a different moiety was equally facile to that of imidazole attached to the $[(\text{NH}_3)_5\text{Co}]^{3+}$ moiety.

$[\text{Co}(\text{en})_2(4\text{-chloroimidazole})(\text{Cl})]\text{Cl}_2$; this was one of the most surprising results as it demonstrated for the first time that electrophilic and/or nucleophilic substitutions other than nitration were being promoted by coordination to substitution inert centers such as Co(III). This result is to be exploited to a large degree in the proposed research.

(b) Synthesis and Nitration

A quantitative comparison of the nitration of methyl benzoate and $[\text{Co}(\text{NH}_3)_5(\text{benzoate})]^{2+}$ has been made, i.e., of the effect of replacing a methyl group, of known effect, by a $[\text{Co}(\text{NH}_3)_5]^{3+}$ group of unknown effect. In each case the nitration takes place in the meta position. For methyl benzoate, nitration takes place at a rate ca 20-fold faster than for the latter compound. This is a very effective demonstration of the fact that the rate enhancement observed in the case of the imidazole molecule must be via a π interaction.

In the case of the benzoate complex, the fact that the rate of nitration is less than that observed for the methyl benzoate molecule shows that the $[\text{Co}(\text{NH}_3)_5]^{3+}$ moiety displays the expected electron withdrawing effect and that this must therefore be expressed via a σ route as there is little, if any, π interaction between the carboxylate group and π cloud of the benzene ring.

This result thus requires that the activation of a nitrogenous heterocycle, such as imidazole or pyrazole, to electrophilic attack by a coordinated metal ion must be due to a specific $d-\pi^*$ interaction.

Examination of the LUMO's for pyridine and imidazole shows that the π^4^* orbital has a node at the ring nitrogen in the case of pyridine, while for imidazole there is an open orbital. Examination of the LUMO's for pyrazole shows that this molecule is completely analogous to imidazole in its electronic configuration and thus should have similar properties with respect to electrophilic substitution. This was confirmed by the facile nitration of coordinated pyrazole. This interpretation explains the ready reactivity of coordinated imidazole and pyrazole and also explains the lack of reactivity of coordinated pyridine.

Molecular Orbital diagrams for other nitrogenous heterocycles are being examined to choose suitable candidates for further nitrations. From this study it has already appeared that pyrazine has LUMO's available which should make it readily susceptible to nitration while coordinated to pentaamminecobalt(III). Accordingly the complex $[\text{Co}(\text{NH}_3)_5(\text{pyrazine})]\text{Cl}_3$ has been synthesized and nitration experiments are underway.

Further research on the complex $[\text{Co}(\text{en})_2(\text{aniline})\text{Cl}]\text{Cl}_2$, and in particular its reaction with the usual nitrating mixtures, have shown a very important difference with respect to the reaction of aniline itself with the same nitrating mixtures. In this complex (the fully characterized complex that has aniline ligated to cobalt(III)), it is found that the aniline moiety nitrates exclusively in the para position, in contrast with the expected meta substitution predicted from an examination of resonance structures.

Thus the $[\text{Co}(\text{en})_2\text{Cl}]^{2+}$ group not only enhances the rate of the reaction but also exerts a strong, and unexpected, directing effect on the incoming group. In addition to this, after the reaction is complete and the products worked up, it is found that the nitrated aniline is not attached to the cobalt(III) but "free". In light of the above arguments, it is obvious that

the aniline must first nitrate before coming off the cobalt(III) center. This unusual and important result makes this a potentially invaluable synthetic method for preparing nitrated isomers which have nitro groups in other places than that usually found from rules predicting directing effects. In addition the product of the nitration reaction is found in the reaction medium and is thus easily recovered.

Recent structural work have revealed that imidazole and histidine coordinated to the $[\text{Co}(\text{en})_2\text{Cl}]^{2+}$ moiety can be easily nitrated under mild conditions (0°C). In addition, the surprising discovery was made that by using nitronium tetrafluoroborate in sulfolane and treating the products with aqueous sodium chloride solution the species $[\text{Co}(\text{en})_2\text{Cl}(4\text{-Cl-imidazole})]^{2+}$ was obtained. This could be due to the formation of Cl^+ in situ which then attacked the activated coordinated imidazole. This would then be the first demonstration that electrophilic substitutions other than nitration might be promoted by metal-ion coordination, and this result is to be exploited in the proposed research (vide infra). However, it should be noted that the chlorination could have taken place via a nucleophilic displacement of the nitro group generated in the nitration step. This is potentially possible as it has been noted that the nitro group is a surprising good leaving group. Further studies are planned to clarify the nature of the chlorination in this instance and to see if it might be a general phenomenon.

Synthetic Procedures:

The following complexes were prepared by following various literature procedures: $[(\text{NH}_3)_5\text{Co}(\text{H}_2\text{O})](\text{ClO}_4)_3$, $[(\text{NH}_3)_5\text{CoCl}]\text{Cl}_2$, $[(\text{NH}_3)_5\text{Co}(\text{CF}_3\text{SO}_3)](\text{CF}_3\text{SO}_3)_2$, $[\text{Co}(\text{dien})\text{Cl}_3]$, $[\text{Co}(\text{dien})(\text{CF}_3\text{SO}_3)_3]$, $[(\text{NH}_3)_5\text{CrCl}]\text{Cl}_2$, and $[(\text{NH}_3)_5\text{Cr}(\text{CF}_3\text{SO}_3)](\text{CF}_3\text{SO}_3)_2$.

Synthesis of $[(\text{NH}_3)_5\text{Co}(\text{TriNO}_2)]\text{Cl}_2$. This complex was prepared

by following literature procedures for analogous complexes. To $[(\text{NH}_3)_5\text{Co}(\text{H}_2\text{O})](\text{ClO}_4)_3$ (20.0 g) in a 250 mL round bottom flask was added 30.0 mL of DMSO. The mixture was placed on a rotary evaporator and heated to 70°C for 1.0 hour to produce $[(\text{NH}_3)_5\text{Co}(\text{DMSO})](\text{ClO}_4)_3$. After cooling the mixture to room temperature, 1,2,4-triazole (6.0 g) was dissolved in 20.0 mL of DMSO and then poured into the mixture containing the $[(\text{NH}_3)_5\text{Co}(\text{DMSO})]^{3+}$ ion. The resulting mixture was placed on a rotary evaporator and heated to 75°C for 1.0 hour or until the solution turned orange-brown. After the solution cooled, excess NO_2BF_4 in sulfolane was added and allowed stand stoppered for 30 minutes. The solution was transferred to a 1.0 liter volumetric flask and diluted to 1.0 liter with distilled water. The complex was slowly absorbed onto a column of CM-Sephadex C-25-125 ion exchange resin. The eluent was an aqueous solution of NaCl (0.1 - 1.0 M). After elution with 0.1M NaCl to remove any Co^{2+} that might be present, the desired orange band was removed by eluding with 1.0 M NaCl. The complex was precipitated by the addition of acetone or ethanol and gravity filtered. The precipitate was then washed repeatedly with acetone and allowed to dry overnight in a desiccator.

Synthesis of $[(\text{NH}_3)_5\text{Co}(\text{ImNO}_2)]\text{Cl}_2$. The method for the preparation of this complex was essentially the same as that described above for $[(\text{NH}_3)_5\text{Co}(\text{TriNO}_2)]\text{Cl}_2$.

Synthesis of $[(\text{NH}_3)_5\text{Co}(\text{PyNO}_2)]\text{Cl}_2$. The method for the preparation of this complex was essentially the same as that described above for $[(\text{NH}_3)_5\text{Co}(\text{TriNO}_2)]\text{Cl}_2$.

Synthesis of $[(\text{dien})\text{Co}(\text{ImH})_3](\text{CF}_3\text{SO}_3)_3$. To 20.0 millimoles of $[(\text{dien})\text{Co}(\text{CF}_3\text{SO}_3)_3]$ dissolved in acetone in a 250 mL round bottom flask was added excess imidazole (> 20 millimoles). The mixture was stirred

continuously for nearly 20 minutes or until there was a distinct color change from purple to orange. The solvent was allowed to evaporate slowly from the mixture; orange-yellow crystals were obtained.

Synthesis of $[(\text{NH}_3)_5\text{Cr}(\text{Im})](\text{CF}_3\text{SO}_3)_3$. An equimolar mixture of $[(\text{NH}_3)_5\text{Cr}(\text{CF}_3\text{SO}_3)](\text{CF}_3\text{SO}_3)_2$ and imidazole was dissolved in acetone and stirred for 30 minutes. The resulting solution was allowed to slowly evaporate, however, no crystalline product formed for this complex, i.e., the product was an oil.

Synthesis of $[(\text{NH}_3)_5\text{Cr}(\text{Py})](\text{CF}_3\text{SO}_3)_3$. An equimolar mixture of $[(\text{NH}_3)_5\text{Cr}(\text{CF}_3\text{SO}_3)](\text{CF}_3\text{SO}_3)_2$ and pyrazole was dissolved in acetone and stirred for 30 minutes. The solvent of the resulting solution was allowed to slowly evaporate yielding orange crystals.

Synthesis of $[(\text{NH}_3)_5\text{Cr}(\text{Tri})](\text{CF}_3\text{SO}_3)_3$. An equimolar mixture of $[(\text{NH}_3)_5\text{Cr}(\text{CF}_3\text{SO}_3)](\text{CF}_3\text{SO}_3)_2$ and pyrazole was dissolved in acetone and stirred for 30 minutes. The solvent of the resulting solution was allowed to slowly evaporate yielding orange-yellow crystals.

Synthesis of $[(\text{NH}_3)_5\text{Co}(\mu, \mu\text{-Im})\text{Co}(\text{NH}_3)_5]\text{Cl}_5$. To 20 millimoles of $[(\text{NH}_3)_5\text{Co}(\text{H}_2\text{O})](\text{ClO}_4)_3$ dissolved in DMSO was added 10 millimoles of sodium imidazolate. The mixture was placed on a rotary and heated to 75°C for 1.0 hour. After the solution was a distinct orange color, the solution was cooled and transferred to a 1.0 liter volumetric flask and diluted to 1.0 liter with distilled water. The complex was slowly absorbed onto a column of CM-Sephadex C-25-125 ion exchange resin. The eluent was an aqueous solution of NaCl (0.1 - 1.0 M). After elution with 0.1M NaCl to remove any Co^{2+} that might be present, the desired orange band was removed by eluting with 1.0 M NaCl. The complex was precipitated by the addition of acetone or ethanol and gravity filtered. The precipitate was then washed repeatedly with

acetone and allowed to dry overnight in a desiccator.

Synthesis of $[(\text{NH}_3)_5\text{Co}-\mu,\mu'-(\text{ImNO}_2)\text{Co}(\text{NH}_3)_5]\text{Cl}_5$. To 20 millimoles of $[(\text{NH}_3)_5\text{Co}(\text{H}_2\text{O})](\text{ClO}_4)_3$ dissolved in DMSO was added 10 millimoles of sodium imidazolate. The mixture was placed on a rotary and heated to 75°C for 1.0 hour. After the solution was a distinct orange color, the solution was cooled and excess NO_2BF_4 in sulfolane was added and allowed stand stoppered for 30 minutes. The solution was transferred to a 1.0 liter volumetric flask and diluted to 1.0 liter with distilled water. The complex was slowly absorbed onto a column of CM-Sephadex C-25-125 ion exchange resin. The eluent was an aqueous solution of NaCl (0.1 - 1.0 M). After elution with 0.1M NaCl to remove any Co^{2+} that might be present, the desired orange band was removed by eluding with 1.0 M NaCl. The complex was precipitated by the addition of acetone or ethanol and gravity filtered. The precipitate was then washed repeatedly with acetone and allowed to dry overnight in a desiccator.

Some of these molecules are being synthesized as precursors for the synthesis of hetero- and homobinuclear imidazole bridged complexes. The method to be used for the synthesis of such compounds is given below.

Molecular Modeling

By use of ChemX Molecular Modeling software, the following complexes were built (modeled). Electron density maps were placed around the molecular ions in order to observe the radii of each atom. Electrostatic potential was also placed about each structure to determine the active site, i.e., to determine where nitration would occur in the molecular ion. The following complexes were modeled:..

Several other complexes were modeled and studied thus revealing where substitution would occur, such that, the metal with the highest

electron density about it would favor substitution at the carbon nearest to itself.

Publications

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Electrophilic Substitution Reactions in Heterocycles Complexed to Exchange-Inert Metal Ions: Part 3, by J. P. Jasinski, W. L. Darby, E. Sinn, R. J. Butcher, and F. R. Jackson, to be submitted to *Inorg. Chem.*

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