Synthesis of a Cobaltoxime Derivatives

Cobaloximes have been prepared\textsuperscript{2,3} and studied extensively as model compounds for the coenzyme vitamin B\textsubscript{12}. These compounds exist at the interface of classical coordination chemistry, organometallic chemistry, and bioinorganic chemistry.

The metal site of vitamin B\textsubscript{12} consists of a cobalt atom coordinated by a tetrapyrrole macrocyclic ligand called a corrin (see structures below). One of the axial sites is occupied by a 5,6-dimethylbenzimidazole nucleotide. The key feature of the vitamin’s biochemical activity is its ability to form metal-alkyl (Co–C) bonds in the second axial site. The N4 macrocycle in the cobaloxime model complexes is made up of two monodeprotonated dioxime molecules linked at two points by hydrogen bonding. The result is an essentially planar macrocyclic ligand. The most common cobaloximes utilize the dimethylglyoxime ligand. The structure shows a typical cobaloxime model complex. A very large number of model complexes have been prepared in which both the neutral ligand and the alkyl ligand are varied\textsuperscript{2,3}.

Structural comparison of vitamin B\textsubscript{12} derivative (left) and a cobaloxime model complex (right).

Alkyl or aryl derivatives of cobaloximes (CbCoX) are routinely prepared by two general routes. A carbanionic reagent (such as PhMgBr) reacting with a Co(III) halide results in a nucleophilic displacement of the halide ion. In the second method, Co(III) is converted to Co(I) using a variety of reducing agents (such as NaBH\textsubscript{4}). In acidic or neutral solution, a cobalt
hydride species exists, while under sufficiently basic conditions, the Co(I) species has significant
anionic character and behaves as an exceedingly powerful nucleophile. Reaction of the Co(I)
species with a wide variety of electrophiles generates an organocobaloxime (RX). In the
organocobaloxime compounds, the cobalt formally exists in a +3 oxidation state, with the carbon
ligand being assigned a charge of −1.

\[ \text{CbCoBr} + \text{PhMgBr} \rightarrow \text{CbCoPh} + \text{MgBr}_2 \]  \hspace{1cm} (1)

\[ \text{NaBH}_4 \rightarrow \text{CbCo}^- \] \hspace{1cm} (2)

\[ \text{CbCo}^- + \text{CH}_3\text{I} \rightarrow \text{CbCoCH}_3 + \text{I}^- \] \hspace{1cm} (3)

The reversal of reactivity displayed by this organometallic system has parallels in classical
organic chemistry. Alkyl halides (carbon in a higher oxidation state) behave as electrophiles and
readily undergo nucleophilic displacement of the halide atom (eq 4). This sense of reactivity can
be reversed by reducing the alkyl halide (for instance by conversion to a Grignard reagent using
elemental magnesium; eq 5). These reagents (where carbon is now in a lower oxidation state)
are very nucleophilic and can react with a variety of electrophiles (eq 6). Seebach has coined the
term “\textit{umpolung}” to describe this reversal of reactivity.\(^4\)

\[ \text{RX} + \text{R}^- \rightarrow \text{R} - \text{R}' \] \hspace{1cm} (4)

\[ \text{RX} + \text{M}^0 \rightarrow \text{RMX} \] \hspace{1cm} (5)

\[ \text{RMX} + \text{R}^-\text{X}' \rightarrow \text{R} - \text{R}' + \text{MXX}' \] \hspace{1cm} (6)

Syntheses of cobaloxime derivatives have been reported in two volumes of \textit{Inorganic
Synthesis}\(^5,6\) and there are at least five published laboratory experiments based on the preparation
of cobaloximes\(^7-11\). The original \textit{Inorganic Synthesis} preparation of cobaloxime derivatives\(^5\)
suffers drawbacks that preclude its conversion to a useful laboratory exercise. Several of the
derivatives are of such low solubility that characterization by NMR is difficult. Subsequent
work by Marzilli has shown\(^12\) that the procedure for preparation of Co(dmgH)\(_2\)(Py)Cl leads to
large amounts of a salt, [Co(dmgH)\(_2\)(Py)\(_2\)][Co(dmgH)\(_2\)Cl\(_2\)], in addition to the desired complex.
In that same paper, Mazilli describes a more reliable, two-step procedure for preparing
Co(dmgH)\(_2\)(RPy)Cl. Both Marzilli\(^12\) and Bulkowski et al.\(^6\), in the second \textit{Inorganic Synthesis
procedure, have used 4-\textit{tert}-butylpyridine as the axial base, thus increasing the solubility and
facilitating characterization by NMR. The final refinement of the original \textit{Inorganic Synthesis
procedure is to prepare organocobaloximes via alkylation of a Co(I) intermediate prepared by
reduction of the Co(III) precursor. Although Bulkowski et al.\(^6\) state that this procedure gives
more reproducible yields and higher quality product, it is still common practice to prepare
organocobaloximes in situ from mixtures of cobalt(II) salt, dioxime ligand, sodium borohydride,
and electrophile\(^13\). Three of the published experiments describe the in situ preparation of
organocobaloximes without adding NaBH\(_4\)\(^8-10\). In this case, the Co(II) intermediate
disproportionates to the reactive Co(I) and Co(III). This method, while very rapid and
technically straightforward, is seldom encountered in the research literature because it suffers the
obvious disadvantage of a maximum 50% yield based on cobalt and ligand. The procedure described here incorporates all of the aforementioned improvements.

The following scheme will be used to form a methylcobaloxime model of vitamin B₁₂.

Scheme I: Synthesis of cobaloxime derivatives
The Co(I) intermediate generated in the course of preparing the very stable Co(dmgH)2(4-t-BuPy)Et is very air-sensitive and failure to maintain strictly anaerobic conditions will result in greatly diminished yields and very impure product.

Compounds 1 and 2 (Scheme I) may be made in a single day, and compound 3 (Scheme I) may be prepared during the second lab period.

These low-spin d⁶ compounds can be characterized by IR and NMR spectroscopy.

**Experimental procedure**

**Synthesis of Dibromo(dimethylglyoxime)(dimethylglyoximato)cobalt(III) (1)**

Add 1.10 g dimethylglyoxime (9.5 mmole) to a stirred solution of 1.50 g of cobalt(II) bromide hydrate (4.59 mmole) in 25 mL of acetone. As a very gentle stream of air is played over the solution a green solid will be deposited. After 30 min, chill the solution on ice, filter, and wash with 2 x 10 mL of cold acetone. The yield of green microcrystalline product is 1.8-2.0 g (85-95% yield based on CoBr₂). The compound can be characterized with IR.

**Synthesis of Bromo(4-tert-butylpyridine)cobaloxime (2)**

Suspend 1.8 g (3.89 mmole) of the green product (1) from the first step in 40 mL of methanol. Add 1.10 g (1.21 mL, 8.1 mmole) of 4-tert-butylpyridine. Stir the mixture until the green solid disappears and is replaced by a brown crystalline solid (20-30 min). Add water (60 mL) with stirring and cool the suspension in ice for 10 min. Collect the product by suction filtration and wash with 3 x 10 mL of 2:1 water/methanol and 2 x 10 mL of diethyl ether. The yield of the brown microcrystalline solid is about 1.8 g (89%).

**Synthesis of Ethyl(4-tert-butylpyridine)cobaloxime (3)**

Dissolve 0.2 g KOH in 20 mL of methanol in a 100 mL round-bottom flask. Fit the flask with a Claisen-head that has a stopper on the straight arm and a septum, with a needle outlet, on the curved arm. Add 0.75 g (1.50 mmole) of bromo(4-tert-butyl-pyridine)cobaloxime (2) as a solid through the stopper end. Chill the homogenous mixture in an ice/salt bath (to about –10 °C) and thoroughly deaerated with N₂ (~10 min). Add sodium borohydride (0.15 g, 3.9 mmole) carefully through the stopper end against a positive nitrogen flow. The mixture should turn rapidly to a dark blue-green color. Stir the solution for 5 min and add 0.50 mL (0.98 g, 6.3 mmole) of ethyl iodide using a syringe (against a positive nitrogen flow). The mixture will immediately turned red-brown. Stir in the ice bath for 20 to 30 min. Quench the reaction with acetone (3 mL) and water (30 mL). Reduce the volume to 50 mL with nitrogen, giving an orange crystalline solid. Chill the flask in an ice bath, filter the orange solid and wash with water. The yield for this step is 1.0-1.2 g (73-88%). The compound is sufficiently pure (by NMR), but it may be recrystallized by dissolving in methanol, adding an equal volume of water, and reducing to half volume by evaporation.
Literature Cited