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Synthesis of a Cobalt Complex of a Sulfonated Binucleating Schiff Base Ligand

Jieun Emily Hwang

Abstract: Current synthesis of cobalt (II) complexes of sulfonated binucleating Schiff base ligands requires the reaction be run under nitrogen.[1] This research introduces a novel process in which the complex can be prepared in open air. The cobalt (II) complexes are prepared with synthesized 5-sulfosalicylaldehyde, and then analyzed by IR and UV-Vis spectrophotometry.

Since the discovery of the anti-tumor activity of cisplatin, metal complexes have gained enormous attention from many scientists for their therapeutic applications. After considerable research, numerous metal complexes, including complexes of a binucleating Schiff base ligand or bis-salphen ligand, were found to have many different applications such as a treatment for cancer, antibacterial agents, antifungal agents, catalysts for reactions, and for chemical analysis.[2,3,4] The binucleating ligand describes the class of polydentate chelating ligands which can bind simultaneously with two metal ions.[2] These metal ions are covalently bound to two deprotonated phenolic oxygen atoms and two nitrogens. One of the better known bis-salphen ligands is tetrasalicylideneaminobenzene or TSAB (Figure 1) and its solubility is very low in almost all solvents except in dimethyl sulfoxide (DMSO) because it contains a large number of carbons. As large percentages of living beings are composed of water, medical applications of drugs are more efficient and safe when they dissolve in water; consequently, applications and formations of complexes of TSAB which only dissolve in DMSO are limited. Therefore, increased solubility of this ligand can aid the formation of these complexes and would allow a wider range of solvent choices for better synthesis and broader applications. Thus, the experiment is performed to synthesize the complexes of bis-salphen ligand for better solubility in water or other possible solvents. The bis-salphen ligand is synthesized from 5-sulfosalicylaldehyde instead of salicylaldehyde and the cobalt complex made to compare with reference standards.[1,5] The combination of the aromatic and planar characteristics of the compound, together with the unique properties of metal ions, indicates this metal complex may be able to intercalate rapidly replicating DNA, inhibit growing tumor cells, or induce apoptosis of cancer cells. The experimental procedures were modified to avoid the use of N_2 atmosphere and reduced pressure restrictions.
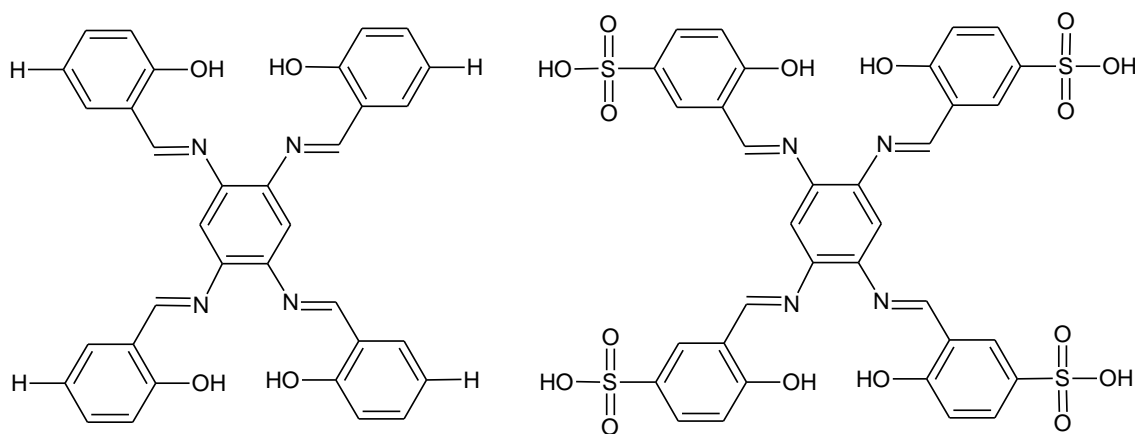
Figure 1. Structure of TSAB (left) and sulfonated bis-salphen ligand (right).

Experimental method/Procedure

Synthesis of 5-sulfosalicylaldehyde sodium salt (Figure 2)

The experimental procedure was developed by Garry Kirker.[5] To perform the experiment on a smaller scale, all the masses and volumes of the substances were reduced by half the scale that was published. Sulfuric acid (Acros 98%, 125 mL) was reacted with salicylaldehye (Aldrich 98%, ~12.7mL) at an average temperature of 22℃, and the solution was stirred for about 24 hours. Then, the solution cooled in an ice bath, then was poured over 250 g of ice and then diluted with 250mL of reverse osmosis (RO) water. Sodium Carbonate (Aldrich 99.5+%, 125 g) was added to the solution while being stirred on a magnetic stirrer. A precipitate formed as the sodium carbonate was added. This solid was decanted and stored for future use (Trial 1b). The volume of the liquid was then reduced by about one-half using a rotary evaporator (Buchi RE 111 Rotavapor) at 40℃. Because of the rotary evaporator's limitation on the maximum volume of 250 mL, the solution made was divided into several portions. After solvent removal, a gel-like solid remained (Trial 1a). This gel was dried in a regular oven (Lindberd/blue M manufactured by Thermo Electron Corporation) instead of *in vacuo*. When the experiment was performed the second time, fresh salicylaldehyde (99%) was used instead due to a discoloration of salicyladehyde (98%). Also, the rotary evaporator was not used due to the reduction of the volume of the solution by half during the neutralization process. The product from the second trial (Trial 2) and solids stored from the first trial (Trial 1b) were recrystallized twice. Activated charcoal powder was added and filtered from the solution during the second recrystallization to increase the purity of the final product. The synthesized products were analyzed using IR spectroscopy (Nicolet IR 200 FT-IR).
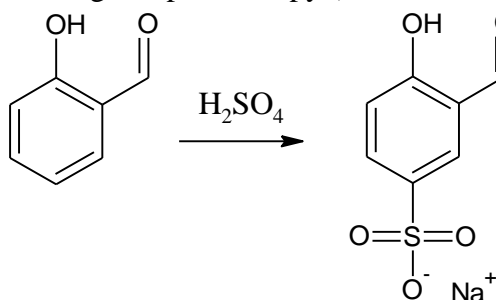

Figure 2. Synthesis of 5-sulfosalicylaldehyde.

Synthesis of cobalt complex of sulfonated binucleating Schiff base ligand

The experimental procedure was developed by Kirker.[1] In this experiment, sodium hydroxide (Fisher Scientific) was used instead of sodium methoxide. For the Trial 1a, masses and moles of the reagents were calculated based upon the total mass of synthesized 5-sulfosalicylaldehyde. About half of the total mass, 1.2000 g (5.353 mmol) of the synthesized 5-sulfosalicylaldehyde was used to react with 0.0537 g (1.338 mmol) of the sodium hydroxide and 0.3802 g (1.338 mmol) of the 1,2,4,5 – benzenetetramine tetrahydrochloride (Aldrich) in open air. The solution was refluxed overnight. Then 0.6667 g (2.676 mmol) of cobalt(II) acetate (J.T. Baker Chemical Co.) dissolved in DMSO (J.T. Baker Chemical Co., 150 ML) was added, and the solution was stirred for about eighteen hours. The precipitate was vacuum filtered, washed with ethanol and ether, and air dried. For both Trial 1b and Trial 2, the experiments were conducted using the same scale that was used in the article.[1] Trial 1b and Trial 2 were refluxed for 2 days and also used significantly less DMSO (71 and 65 mL respectively) to dissolve cobalt (II) acetate with stirring. Moreover, the cobalt complex from these trials was not air dried but dried in an oven at around 150℃. A UV-Visible spectrophotometer (UV-2450 manufactured by Shimadzu) was used to compare the spectrum of the compound to the previously reported data.[1]
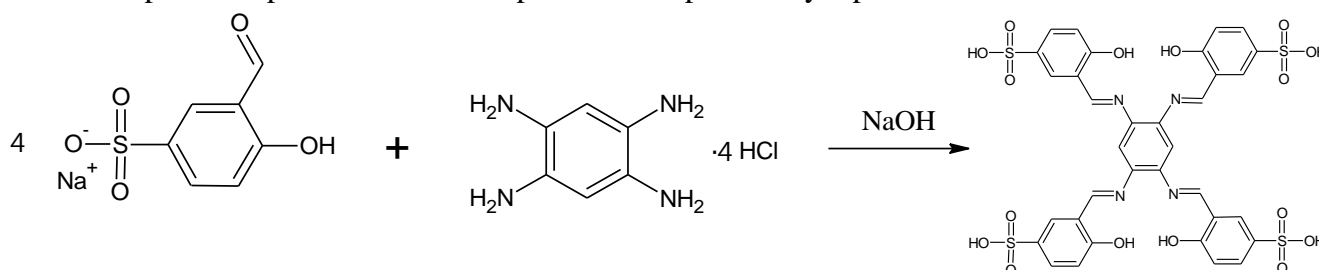

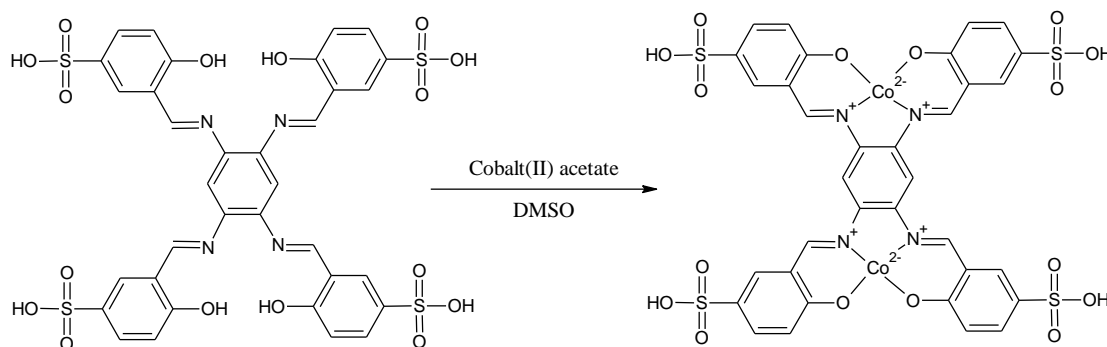Figure 3. Synthesis of the sulfonated bis-salphen ligand.

Figure 4. Synthesis of the cobalt complex of a sulfonated bis-salphen ligand.

Results and Discussion

Throughout the experiment, the colors of the products were not the same as those reported by Kirker. Unlike the gray precipitate mentioned by Kirker,[5] the crystals of the 5-sulfosalicylaldehyde from Trial 1a were a mixture of dark purple, pink, and white. During the second trial, newly synthesized 5-sulfosalicylaldehyde (Trial 2) had a red/pink color before recrystallization and was light pink with white spots after recrystallization. The product from the stored solids (Trial 1b) had a lighter pink color even before recrystallization, and white crystals with a tint of pink after recrystallization. Similarly, the color of the mixture with 1,2,4,5 – benzenetetramine tetrahydrochloride and sodium hydroxide was a clear solvent with purple solute

rather than a yellow solution. The reaction that occurred under nitrogen did not seem to occur under atmospheric conditions. The color of the solution after reflux was a light tan for Trial 2 and a medium brown color for Trial 1b, and both of the solutions became black after the cobalt solution was added. The color of the cobalt complex prepared by 5-sulfosalicylaldehyde is not mentioned in the reference.[1]

Interestingly, the textures of the final products were different for each of the three experiments. The cobalt complex from Trial 1a, had a dull, dark brown, tightly packed appearance of the product, which eventually became completely dried after it was washed with anhydrous ethanol. The color became slightly lighter brown after washing with anhydrous ether. Apparently, this product did not dissolve well in any solvents, including water, which defeats the purpose. The other two products (Trial 1b and Trial 2) had a black color with a dense appearance. Both products then turned greasy and appeared to be slightly more brown after being washed with anhydrous ether. These dissolved completely in water and were slightly soluble in methanol. Unexpectedly, those products did not air dry well and held moisture that seemed to require heating in order to dry completely. Such an incident possibly happened because of the large mass of the product. When one of them (Trial 2) was heated in the oven (150℃), a thick, white smoke was evident with an unrecognizable smell and it also produced black shiny powder. The greasy texture had completely disappeared. Trial 1b was put into the oven for only 30 minutes recognizing the possible hydrolytic decomposition that was mentioned in the reference.[1] The IR spectra were compared between the products from the Trial 1a, Trial 1b, and Trial 2. Within Trial 1b, the IR spectra of before and after heating were also compared. No clear evidence of differences due to heating was found, other than a weaker peak or two in the fingerprint areas, which will be explained in detail later. All three products cracked into separate pieces as they dried.

The masses and percent yields are found in Table 1. The percent yields of 5-sulfosalicylaldehyde from Kirker's research were 27%, starting with 29 g of salicylaldehyde, and 45%, starting from 5 g.[5] Thus, a yield of 47.58% in Trial 2 is quite reasonable. Since the products from Trial 1a and 1b are technically from the same solution, adding the two yields gives a combined yield of 47.16 %. Although there was no record of the yield of a cobalt complex of sulfonated bis-salphen ligand, the article mentioned that TSAB had a percent yield of 90% with a melting point of 270-290℃.[1] According to this result, the cobalt complex from Trial 1b had reasonable yield; however, the lower yield of the cobalt complex from Trial 2 was because of the heating process. Consequently, it leads to the question of identifying the gas that was being released, and whether or not it should have occurred. Because of similar IR spectra before and after getting dried in the oven, and the greasy texture observed after washing, an assumption can be made that the gas can be a mixture of ethanol, anhydrous ether, and water. Moreover, the significantly smaller yield of the cobalt complex from Trial 1a may be because of large amounts of impurities in the synthesized 5-sulfosalicylaldehyde.

Table 1. Analysis of three products from three sets of experiments

	Trial 1a	Trial 1b	Trial 2
Mass of synthesized 5-sulfosalicylaldehyde (g)	2.5431	10.0561	12.7123
Percent Yield (%)	9.519	37.64	47.58
Melting Point (°C)	Above 260	Above 260	Above 260
Mass of synthesized cobalt complex (g)	0.2180	2.70829	1.9396
Percent Yield (%)	17.47	87.99	63.02
Melting Point (°C)	Above 260	N/A	Above 260

At first, IR spectroscopy could not be used to identify the product in solution due to the insolubility of the product in alcohols. Later, implementation of a new technique led to the successful usage of IR spectroscopy: the products were mixed with potassium bromide and made into a clear pellet. The peaks that were given by Kirker[5] were 3530, 3440, 2900, 1660, 1180, and 1035 (cm^{-1}) for his 5-sulfosalicylaldehyde. The major peaks obtained from synthesized 5-sulfosalicylaldehyde from Trial 2 were 3431, 3223, 3075, 2892, 1678, 1186, and 1038 (cm^{-1}). About 3650 - 3300 region determines an O-H bond. About two different peaks at this region are determined because of the two different O-H bonds present in the 5-sulfosalicylaldehyde. The peak nearby 1725 determines the C=O of the aldehyde functional group; however, the determined peak is slightly lower because of the conjugation of a benzene ring. About 1350 and about 1175 are the regions to determine the S=O bond of the product, and between 1000 to 700 determines the S-O bond; thus, the presence of functional groups such as alcohol, aldehyde, benzene, and sulfonate were all evident. The product from Trial 1b had weaker peaks overall near 3000 area that seem to be missing major peaks at around 3450 and 2900. The result may suggest a possibility of absence of two distinct O-H groups; however, such error seemed to be human error occurred during process of making a pellet of the product. The major peaks were 3226, 1686, 1187, and 1040.

The IR spectra of the cobalt complex from trials are also analyzed including the IR spectrum of the Trial 1b before heating. The Trial 1a had strong peaks on 3413, 1602, 1316, 1174, and 1032 (cm^{-1}). The Trial 2 had 3400, 1625, 1604, 1318, 1172, and 1024 (cm^{-1}). The Trial 1b before heating had 3415, 1625, 1318, 1174, and 1024 (cm^{-1}). The Trial 1b after heating had 3469, 1637, 1606, 1319, 1187, and 1034 (cm^{-1}). All four IR spectrums included more than four peaks on the area identifying benzene. The cobalt complex from Trial 1b before heating did not have a strong 1600 peak, but it was evident; therefore, that no hydrolytic decomposition seemed to have occurred. However, the cobalt complex from Trial 1a's peak nearby 1630 was significantly smaller than others. This manifests the possibility of the absence of imines. Thus, one can conclude that products have a slight difference between Trial 1a from Trial 1b and Trial 2.

To compare those cobalt complexes with the literature[1], the UV-visible spectra (Figure 4) has been obtained. The spectra was measured between 190 to 500 nm, and the maximum peaks were between 373 to 345 nm for all three cobalt complexes. More accurately, the region of the maximum absorbance (λ_{max}) of the cobalt complex from Trial 2 is at 373.8 nm with 1.783 absorbance, the cobalt complex from Trial 1a is at 374.6 nm with 1.792 absorbance, and the cobalt complex from Trial 1b is at 374.2 nm with 2.008 absorbance. Moreover, small bumps between 460 to 470 nm are evident for Trial 2 and Trial 1b cobalt complexes, but not for Trial 1a. Because the λ_{max} values of the $(Co^{II})_2(5\text{-}SO_3sal_4bz)^{4-}$ given in the literature have two peaks at 416 nm and 310 nm, and for $(Co^{III})_2(5\text{-}SO_3sal_4bz)^{2-}$ at 498, 467, 334, and 262 nm, the chances of the synthesized cobalt complexes being same as the Kirker's cobalt complex is relatively low.

Because of differences in solubility of the three cobalt complexes, the concentration of the product used to measure absorbance for each of the cobalt complexes was different. For Trial 1a cobalt complex, the solute did not dissolve completely in the water; therefore, an accurate measurement of the concentration is hindered. If the solute dissolved completely, the solution should have a concentration of 9.5×10^{-4} g/mL. The Trial 1b and Trial 2 cobalt complexes dissolved completely and had a red to orange color, depending on the concentration. The UV-Vis spectra of Figure 4, Trial 1b and Trial 2 had concentrations of 1.45×10^{-4} g/mL and 9.7×10^{-5} g/mL, respectively.
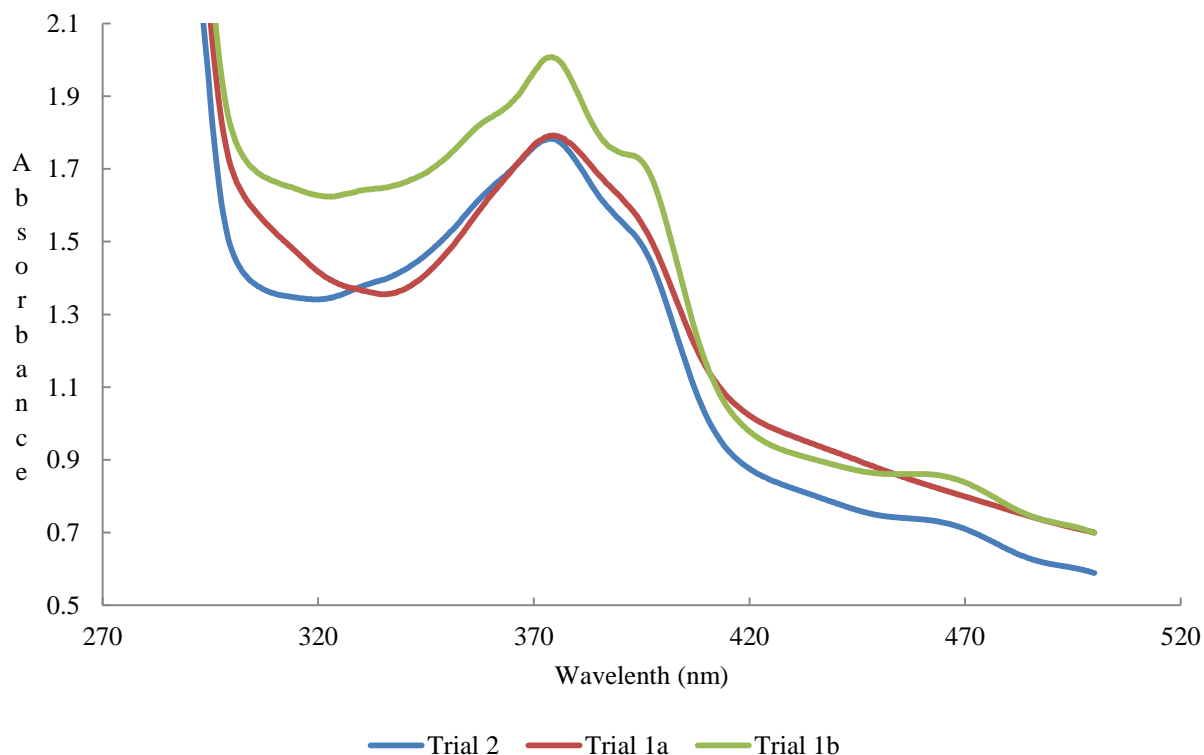

Figure 5. Spectral differences between cobalt complexes.

Conclusion

Based on the observed IR spectroscopy and melting point, one can assume that the experiment was successful in producing a cobalt complex of the sulfonated bis-salphen ligand. The minor differences between the previous research and this research are probably due to technology and human errors. Even without running a reaction under nitrogen or heating the product *in vacuo*, the analysis indicates the presence of the desired functional groups in the structure and high solubility in water. Thus, one can conclude that producing the cobalt complex of the sulfonated bis-salphen ligand with a good percent yield is possible in the presence of air, avoiding the necessity of N_2 atmosphere and *in vacuo* heating restrictions. However, a better method for removing impurities may be necessary. Moreover, unique differences in textures and solubilities of the cobalt complexes from the trials need further research in order to be explained.

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