

Synthesis and Characterization of a New Compound of Cobalt II with Isonicotinamide and Evaluation of the Bactericidal Potential

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Abstract

In this work, the isonicotinamide was coordinated to the Cobalt ion in oxidation state +2. The relevance of this work is the investigation of the *in vitro* bactericidal potential of the synthesized complex when tested in Gram-positive and negative bacteria strains. This study is motivated by the need to obtain new materials that have antibiotic properties and that, in the future, may become an effective drug against resistant bacteria. A new coordination compound of Cobalt and isonicotinamide, $[\text{Co}(\text{H}_2\text{O})(\text{isn})_3](\text{BF}_4)_2$, was synthesized and described. The compound was characterized by thermoanalytical techniques TG-DTG and TG-DSC, where it was possible to propose the mechanism of thermal decomposition. Through the spectroscopy in the region of the medium infrared (FTIR), it is possible to infer the site of connection between isonicotinamide and metal. The bactericidal activity of $[\text{Co}(\text{H}_2\text{O})(\text{isn})_3](\text{BF}_4)_2$, CoCl_2 and free Isonicotinamide were tested for the bacteria *Streptococcus mutans* (Gram+) and *Escherichia coli* (Gram-) and the synthesized compound showed to be sensitive for both bacteria.

Keywords

Cobalt, Isonicotinamide, Spectroscopy Infrared, TG/DTG and TG/DTA, Bactericidal Activity

1. Introduction

Bacteria have been present on Earth for billions of years, and to survive the environment, they have developed adaptive mechanisms that have allowed them to resist natural medicines for all that time [1]. The discovery of active antimicrobial principles, later used as antibiotics, has been an important tool for in-

creasing longevity and quality of human life [2].

The discovery of penicillin in mid-1928 [1] boosted the search for new drugs and large numbers of antibiotics were described and reported until 1939 and in subsequent decades [2]. Man's constant struggle with the microbial environment has increased over the years, in the same way as has the use of antibiotics in an indiscriminate and incorrect way [3]. The ease in acquiring this type of substance, either naturally or through the pharmaceutical industry has caused the bacteria to develop mechanisms of resistance to these drugs [4]. The seriousness of this problem is worldwide and in May 2015 the World Health Organization approved a set of measures called the Global Plan of Action on Microbial Resistance [4], which sets out five general objectives: 1) Improve awareness and understanding of antimicrobial resistance through communication, education and effective training; 2) Strengthen the knowledge base and evidence through surveillance and research; 3) Reduce the incidence of infection through effective sanitation, hygiene and infection prevention measures; 4) Optimize the use of antimicrobial drugs in human and animal health; 5) Develop the economic argument for sustainable investment that considers the needs of all countries, and increases investment in new medicines, diagnostic tools, vaccines and other interventions [4].

Analyzing topic five of the Global Plan of Action on Microbial Resistance, there is a need for investments in new drugs, given that current antibiotics have a declining clinical life as soon as they are put on the market [3] [4]. Numerous studies, involving organic molecules with natural or synthetic biological activities coordinated to metals to intensify their properties, showed that the use of coordination compounds may be an alternative to the use of the drug in its free form as a medicine [5]-[13].

Studies such as by Asegbeloyin *et al.* [12] showed that compounds of cobalt (II) and other transition metals had higher bactericidal activity than imines in their free state. Tawfik *et al.* [13] Studied the biological activity of compounds containing Co^{2+} , Zn^{2+} and Sn^{2+} and showed that the coordination to the metallic centers resulted in an increase in the antimicrobial activity: $\text{Co}^{2+} > \text{Zn}^{2+} > \text{Sn}^{2+}$.

Studies that focus on the use of ligands coordinated to metals for use as bactericides consider that this type of interaction (metal-ligand) can present distinct toxicological and pharmacological characteristics, which may favor the reduction of side effects [14].

This study aimed to develop and characterize a new complex formed by the coordination of cobalt (II) isonicotinamide, and to perform a qualitative study of the potential bactericidal activity of the synthesized complex, tested *in vitro* on *Streptococcus mutans* (*S. mutans*) Gram (+) and *Escherichia coli* (*E. coli*) Gram (-).

2. Experimental

2.1. Materials

Cobalt(II) chloride, p.a., anhydrous, $\geq 98.0\%$ (Sigma-Aldrich);

Isonicotinamide, p.a, 99% (Sigma-Aldrich);
Zinc, granular, 30 - 100 mesh, 99% (Sigma-Aldrich);
Sodium Tetrafluoroborate, 99% (Sigma-Aldrich);
MUELLER-HILTON AGAR (OXOID).

2.2. Synthesis of Compound

0.4804 g (0.0037 mol) of CoCl_2 were solubilized in 5 ml of distilled water, then immediately 1.3556 g of isonicotinamide (0.0111 mol) were dissolved in 10 mL of the same solvent and added to the beaker containing the cobalt(II) chloride solution. To this mixture, zinc amalgam [15] was added and placed under constant stirring for 1.5 h. Thereafter, the resulting solution was filtered and to the supernatant was added 0.8125 g of NaBF_4 (0.0074 mol), dissolved in 1 ml of distilled water. Finally, the mixture was refrigerated in an ice bath, and after 4 days the precipitate was filtered and put in a desiccator. Average yield: 70%.

2.3. Characterization

The determination of the stoichiometry of the compound was performed through minimal calculation formula from the thermogravimetric curve, as well as by studying the thermal behavior. The complex salt was also characterized by spectroscopy in the medium-infrared region, and by solubility tests and other qualitative tests. **Thermoanalytical Techniques:** The TG/DTG and TG-DSC curves were obtained on Mettler Toledo TGA/DSC 1 equipment. The system was calibrated following the specifications provided by the manufacturer. The analyses were obtained in $\alpha\text{-Al}_2\text{O}_3$ crucible (70 μL), with a sample mass of approximately 5 mg, a heating rate of $20^\circ\text{C}\cdot\text{min}^{-1}$, in dry air at $60\text{ mL}\cdot\text{min}^{-1}$ flow and range temperature of $30^\circ\text{C} - 1000^\circ\text{C}$. **Medium FT-IR Infrared Spectroscopy:** The spectra in the infrared region were acquired in a Perkin Elmer Model 100 Fourier transform spectrometer, with a resolution of 4 cm^{-1} in the region $4000\text{ cm}^{-1} - 600\text{ cm}^{-1}$ using the reflectance accessory for attenuated total reflection technique (ATR) with germanium crystal (Ge).

2.4. Microorganisms and Controls

The microorganisms used in the assays were enteropathogenic, *E. coli* and *S. mutans*, both provided by the ATCC (American Type Culture Collection). The antibiotic used as a positive control was gentamicin $10\text{ }\mu\text{g}/(\text{G5427})$ manufactured in July 2016, provided by Sensifar.

2.5. Lineage and Culture of *S. mutans*

S. mutans (ATCC®25175™) was used and stored at -70°C . The stock culture was maintained in semi-solid agar in the absence of light. From this stock culture 24 hours before the test, subcultures were performed in tubes containing 8 ml TSB (Tryptic Soy Broth-DIFCO) and incubated in an incubator at 37°C for 24 h.

2.6. Lineage and Culture of *E. coli*.

E. coli (EPEC) serotype O111: H–Al–, eae+, eaf+, bfp+ was used, conserved at 70°C. The stock culture was maintained in semi-solid agar in the absence of light. From this stock culture 24 h before the test, subcultures were performed in tubes containing 8 ml TSB (Trypic Soy Broth - DIFCO) and incubated in an incubator at 37°C for 24 h.

2.7. Disk and Well Technique: Müller-Hinton Agar Medium

The preparation of the Müller-Hinton agar medium was made according to the Clinical and Laboratory Standards Institute (CLSI) [16] and the disk and well technique was performed according to the same, with adaptations. In the antimicrobial assays, plaques were inoculated with the *S. mutans* and *E. coli* bacteria, wells were prepared for each active ingredient alone (CoCl₂, [Co(H₂O)(isn)₃](BF₄)₂ and isonicotinamide). A gentamicin disk was used as a positive control for both bacteria. In the Petri dishes, with the solid medium already inoculated with the microorganisms, wells were prepared to receive the material to be analyzed. The masses used in the analyses were 0.0210 g CoCl₂, 0.1000 g [Co(H₂O)(isn)₃](BF₄)₂ and 0.0593 g isonicotinamide, equivalent to the stoichiometric ratio of 1:1:3 mol. The readings were made after 48 h and the results of the analyses were expressed as a function of the diameter of the inhibition halos, in millimeters, with the aid of a ruler.

3. Results and Discussions

3.1. Thermoanalytical Techniques

In the curves referring to the TG-DTG and TG-DSC analyses of isonicotinamide in its free form, it can be observed in **Figure 1** that it presented a single mass-loss step (160°C - 290°C) with the probable maximum loss rate at 282°C. Three peaks can be seen in DSC, where the first refers to the polymorphic transition at about 120°C [17] [18] and the second and third peaks indicate fusion followed by evaporation.

The thermal decomposition steps of the compound [Co(H₂O)_x(isn)_y](BF₄)_z can be seen in **Table 1**. As can be seen, the synthesized compound exhibited thermal stability up to 118°C and showed five consecutive mass losses.

All thermal decomposition steps were followed by endothermic peaks of DSC which indicate that there was no oxidative degradation of the material.

In order to propose a thermal decomposition mechanism, the material was flame tested, where it was initially macerated and then placed in a test tube. With the aid of a mercury thermometer up to 300°C, it was possible to monitor the thermal behavior of the compound. The sprayed material was a pink/reddish color and after being heated to about 120°C the complex salt became violet; this first change is attributed to the loss of coordinated water.

At 170°C a gas was released, and the test tube was removed from the plate. The gas crystallized on the wall of the test tube; it was initially thought to be free

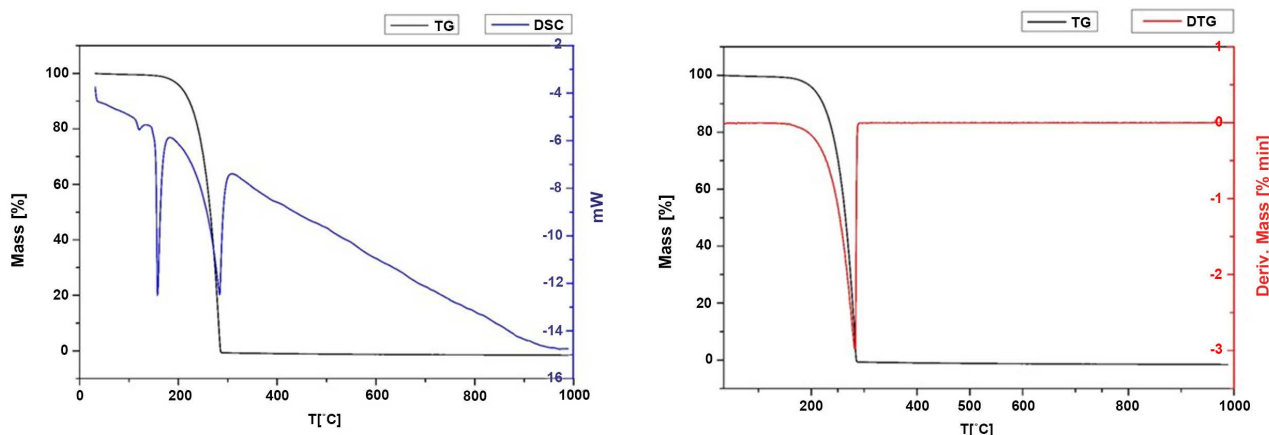


Figure 1. TG-DSC and TG-DTG of isonicotinamide.

Table 1. Thermal decomposition stages.

$[\text{Co}(\text{H}_2\text{O})_x(\text{isn})_y](\text{BF}_4)_z$	Stages				
T °C	118 - 155	170 - 260	270 - 330	330 - 380	830 - 930
$\Delta m\%$	4.4460	32.2399	30.2311	9.7562	10.7721
Peaks	141°C/endo.	248°C/endo.	306°C/endo.	370°C/endo.	917°C/endo.

isonicotinamide because it was a white crystalline solid. This solid was removed from the whole assay and the material studied by infrared spectroscopy. The infrared spectrum of the free isonicotinamide (A) and the test tube residue (B) can be seen in Figure 2.

In the interval 270°C - 280°C there was the appearance of a yellowish gas that was probably the formation of $\text{NO}_{2(g)}$; however, it is not possible to say whether this gas came from the $-\text{NH}_2$ of the amide group or from the nitrogen of the pyridine ring. Soon thereafter, the material melted to an azure blue hue (gas formation and melting occurred almost simultaneously).

At higher temperatures, it was not possible to keep up with the thermometer. Soon after the melting, the material kept the blue tone, and it was no longer possible to observe changes. After the material cooled, a solution of silver nitrate was added to the test tube, and a whitish solid appeared, which is attributed to cobalt tetrafluoroborate.

Analyzing Figure 2, it can be stated that the FTIR spectra of isonicotinamide in its free state (A) and of the crystallized white solid in the wall of the whole test are different. With this, it can be inferred that the isn has been degraded. Isonicotinamide is a primary amide exhibiting two strong bands in the region corresponding to the 3361 cm^{-1} asymmetric, and 3179 cm^{-1} symmetric stretch of the ν (N-H) amide group. In addition, the material that crystallized was characteristic of a secondary amide with only one band in the region of 3322 cm^{-1} referring to ν (N-H) [19].

The band refers to the angular deformation of isonicotinamide δ (N-H) appears at 1621 cm^{-1} ; this band is superimposed by the stretches of the amide ν

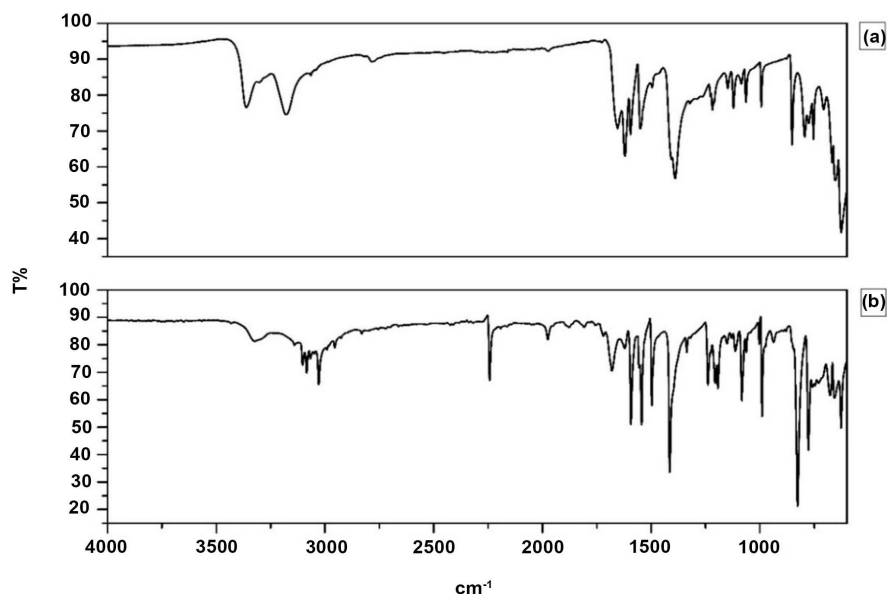


Figure 2. (a) Isonicotinamide; (b) Residue of the flame test.

(C=O) carbonyl at 1655 cm^{-1} , which in the spectrum appears as doublet. For the flame test, this double-deck behavior is less evident, since the band corresponding to ν (C=O) moved to the region of higher energy, 1681 cm^{-1} , and the band referring to the angular deformation of δ (N-H) was maintained at 1621 cm^{-1} . Both bandwidths when compared to free isn, showed a decrease in intensity that must be attributed to the new structure of this compound. [19]

For the residue, a strong band in the region of 1543 cm^{-1} is characteristic of a secondary amide and is attributed to the set of stretching ν (C-N) combined with a band of the angular deformation of the δ (N-H). With the FTIR analysis of isonicotinamide and the residue, it is possible to conclude that the thermal degradation of isonicotinamide is followed by a hydrogen substitution reaction with the formation of a secondary amide.

It is inferred that the first step of mass loss is attributed to the loss of coordinated water ($118\text{ }^{\circ}\text{C} - 155\text{ }^{\circ}\text{C}$) [11] [20]. The following three stages commenced with the loss of isonicotinamide ($170\text{ }^{\circ}\text{C} - 260\text{ }^{\circ}\text{C}$; $270\text{ }^{\circ}\text{C} - 330\text{ }^{\circ}\text{C}$, $330\text{ }^{\circ}\text{C} - 380\text{ }^{\circ}\text{C}$) and the last step was the counter-ion output and the CoO_4 reduction to CoO ($830\text{ }^{\circ}\text{C} - 930\text{ }^{\circ}\text{C}$) [21] [22].

The **Figure 3** demonstrates that for the minimum formula calculations, the total $\Delta m\%$ was used because it was not possible to determine the stoichiometry of the material using the stepwise $\Delta m\%$; it is believed that the material loses mass concomitantly. The total empirical $\Delta m\%$ for the compound is 87.4453 and the calculated $\Delta m\%$, which matches the synthesized compound, is 87.8544 for stoichiometry $[\text{Co}(\text{H}_2\text{O})(\text{isn})_3](\text{BF}_4)_2$.

3.2. Medium FT-IR Infrared Spectroscopy

Isonicotinamide has three binding sites: the pyridine ring nitrogen, the amide group nitrogen and the carbonyl oxygen [23] [24]. **Figure 4** shows the FTIR

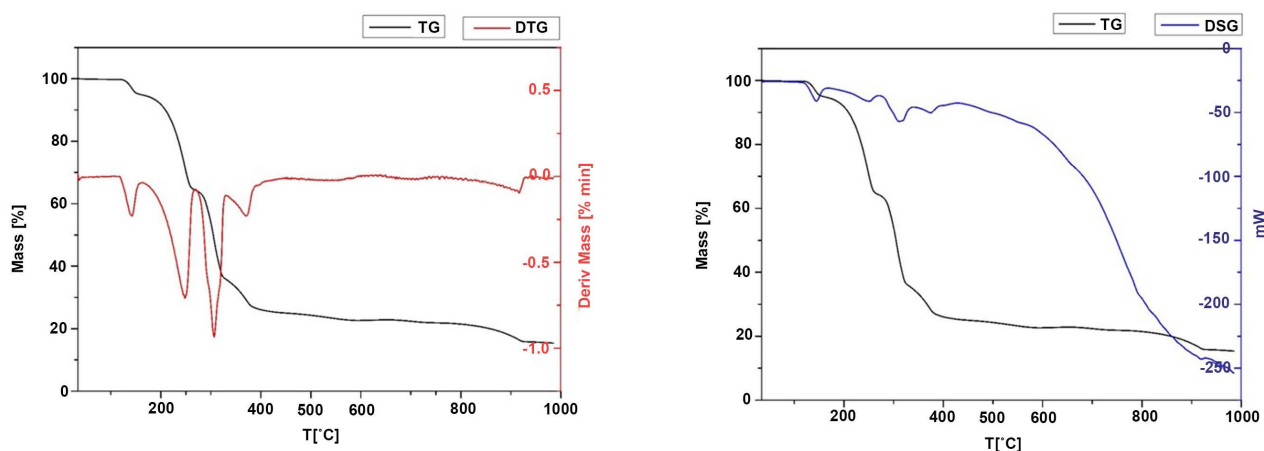


Figure 3. TG-DTG and TG-DSC of $[\text{Co}(\text{H}_2\text{O})_x(\text{isn})_y](\text{BF}_4)_2$.

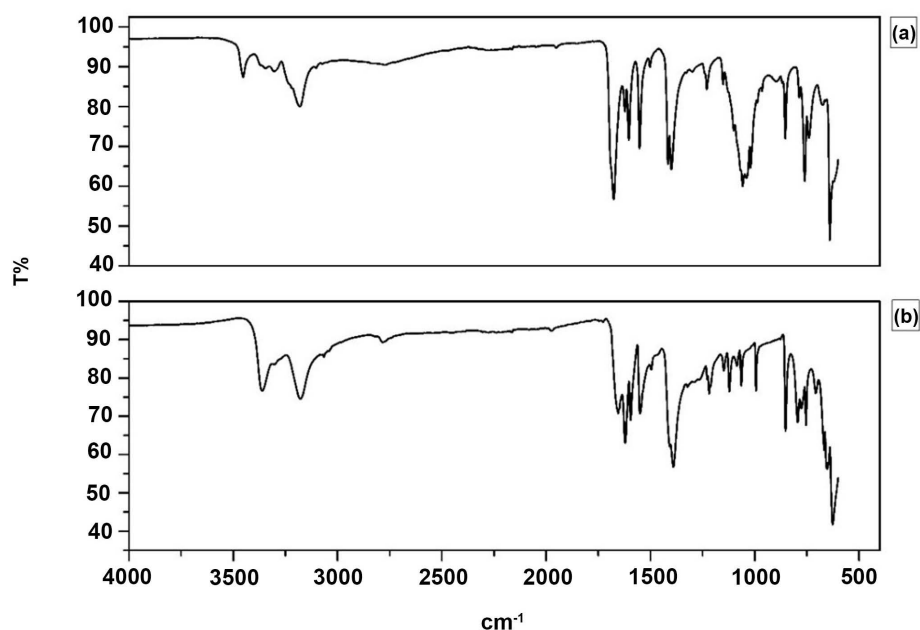


Figure 4. FTIR of (a) $[\text{Co}(\text{H}_2\text{O})(\text{isn})_3](\text{BF}_4)_2$ and (b) isn.

spectra of the free ligand (isonicotinamide) and the synthesized complex salt $[\text{Co}(\text{H}_2\text{O})(\text{isn})_3](\text{BF}_4)_2$.

The FTIR spectrum for free isonicotinamide shows bands at 3361, 3303 and 3179 cm^{-1} , which are related to the asymmetric and symmetric stretches of ν (N-H) of the amide group. Peaks in the region 3077 and 3065 cm^{-1} are attributed to the ν (C-H) stretches of the pyridine ring. Other bands characteristic of free isn are reported at 1621 cm^{-1} , attributed to the angular deformation of δ (N-H), and at 1655 cm^{-1} corresponding to the stretching of the carbonyl of the amide group ν (C=O). A band at 1390 cm^{-1} refers to the ν (C-N) of the amide and those at 1595 and 994 cm^{-1} to the stretching of the pyridine ring [23] [25] [26].

Table 2 shows the main vibrational modes in the infrared region for the compound $[\text{Co}(\text{H}_2\text{O})(\text{isn})_3](\text{BF}_4)_2$, where we can highlight bands in the regions

Table 2. Main bands observed in the infrared (synthesized compound and ligand).

Ligand (isn)	COMPLEX [Co (H ₂ O) (isn) ₃] (BF ₄) ₂	STRETCH STRATEGIES
3361 cm ⁻¹ (F)	3453 cm ⁻¹ (m)	ν_a (N-H)
3303 cm ⁻¹ (w)	3304 cm ⁻¹ (w)	ν (N-H)
3179 cm ⁻¹ (F)	3181 cm ⁻¹ (F)	ν_s (N-H)
3077 cm ⁻¹ (w)	3103 cm ⁻¹ (w)	ν (C-H)
3065 cm ⁻¹ (w)	3074 cm ⁻¹ (w)	ν_s (C-H)
1595 cm ⁻¹ (m)	1604 cm ⁻¹ (m)	ν_s of ring (CN) (py)
1550 cm ⁻¹ (m)	1552 cm ⁻¹ (m)	ν_s og ring (CC) (py)
1655 cm ⁻¹ (F)	1676 cm ⁻¹ (F)	ν (C=O)
1621 cm ⁻¹ (F)	1622 cm ⁻¹ (w)	δ (N-H)
1407 cm ⁻¹ (F)	1416 cm ⁻¹ (F)	ν_a CC (py)
1390 cm ⁻¹ (F)	1400 cm ⁻¹ (F)	ν (C-N)
994 cm ⁻¹ (m)	-	ring contraction (py)
-	965 a 1152 cm ⁻¹ (F)	ν BF ₄ ⁻

Stretching (ν); Asymmetrical Stretching (ν_a); Symmetrical Stretching (ν_s); Angular Deformation (δ); Strong (F); average (m); weak (w).

3453, 3304 and 3181 cm⁻¹, the positions and relative intensities of the bands are altered due to the formation of hydrogen bonds between NH, water molecules and counter ion. These interactions can shift the bands to greater or lesser wave numbers [26].

Coordination compounds having amide groups or carbonyl donors show a decrease in the wave number of these groups, indicating that they are coordinated to metals [24] [25]. For the complex, a strong band attributed to the stretches of the group ν (C=O), whereas the angular deformation of the δ (N-H) showed a weak band and did not exhibit a relevant variation in wave number. This change is influenced by the hydrogen-bonding dimer of the amide groups [26].

In the literature, compounds of cobalt with isonicotinamide have the nitrogen of the pyridine ring as the binding site, and in the infrared spectra of these compounds, the bands of the ring stretches, 1595 and 994 cm⁻¹, and move to higher energy regions. In the FTIR spectrum of the synthesized complex salt we noted a band in the region of 1604 cm⁻¹, which refers to the stretching of the pyridinium ring (free isn) observed at 994 cm⁻¹ cannot be observed in the compound. Therefore, the coordination of isonicotinamide in the complex must be happening through the ring nitrogen, thus shifting the wave number to a higher energy, and the band referring to the displacement at 993.63 cm⁻¹ is being covered up by a strong and intense band that is attributed to the set of vibrations of the counter-ion BF₄⁻, which moves from 965 to 1152 cm⁻¹ covering all other peaks in this area of the spectrum [25] [26] [27].

Thus, it is proposed that isonicotinamide is coordinated to the metal center through the ring nitrogen and that amide groups are free by hydrogen bonding with other amide groups in the system.

3.3. Evaluation of Bactericidal Activity

The results of the biological activity studies are represented in graphical (Figure 5). In this work, not only was there a concern to demonstrate that the binder is, when coordinated to the Co^{2+} metal ion, has a higher bactericidal potential, but also to show the toxicological potential of the metal in its free form.

The reason why these masses are different is that the mole ratio of the separated compounds in the case of CoCl_2 and isonicotinamide correspond to the proportions contained in the compound $[\text{Co}(\text{H}_2\text{O})(\text{isn})_3](\text{BF}_4)_2$, *i.e.*, 1 mol of complex contains 3 mol of isn and 1 mol of CoCl_2 .

For the *S. mutans* bacterium (Gram +), the ligand in its free form showed no inhibition halo. However, when the synthesized complex was analyzed, the inhibition diameter was identical to that of the control drug and 25% smaller than for CoCl_2 . It is then proposed that, in this case, the metal ion coordinated to isn decreases the permeability of the compound in the bacterium, so decreasing the toxicity of the synthesized compound. Isonicotinamide in its free state showed an inhibition halo 5% larger than the control material for *E. coli*. On the other hand, the synthesized compound and CoCl_2 presented equal diameters of inhibition, corresponding to twice the activity of gentamicin.

Thus; the active ingredients CoCl_2 , $[\text{Co}(\text{H}_2\text{O})(\text{isn})_3](\text{BF}_4)_2$ and isonicotinamide showed distinct results for the *S. mutans* and *E. coli* bacteria. Perhaps this is due to the difference in the chemical composition of the cell walls of these bacteria. Works by Asegbeloyin *et al.* [12] and Karekal *et al.* [28] explain the importance of the metal-binder interaction and how the chelation interferes by reducing the polarity of the central atom, which shares the positive charge with the donor electron-donor groups. This type of interaction increases the lipophilic nature of the metal ion, making it easier to penetrate the cell wall of the bacterium.

This type of interaction is common in many chelated systems where π electrons are delocalized on the chelating ring, decreasing the polarity of the metal ion, thereby increasing the lipophilicity of the complexes, preventing the free metal ion from binding to the enzymes contained in the cell wall of the bacteria [12].

Gentamicin is a broad-spectrum antibiotic, *i.e.*, it inhibits strains of Gram-positive and -negative bacteria. The interpretation pattern is given by the zone of inhibition in millimeters (mm) and can be classified as resistant (≤ 12 mm), intermediate (13 - 14 mm) or sensitive (≥ 15 mm). As shown in Figure 5, inhibition of bacterial growth was observed for all compounds. The only exception was observed for the bacterium *S. mutans*, which is not sensitive to the isonicotinamide ligand, all other compounds tested have been shown to be active.

4. Conclusion

Using the set of techniques TG-DTG and TG-DSC, the stoichiometry $[\text{Co}(\text{H}_2\text{O})(\text{isn})_3](\text{BF}_4)_2$ was proposed for the synthesized compound. Through the FTIR of the binder in its free and complexed form, the binding sites between

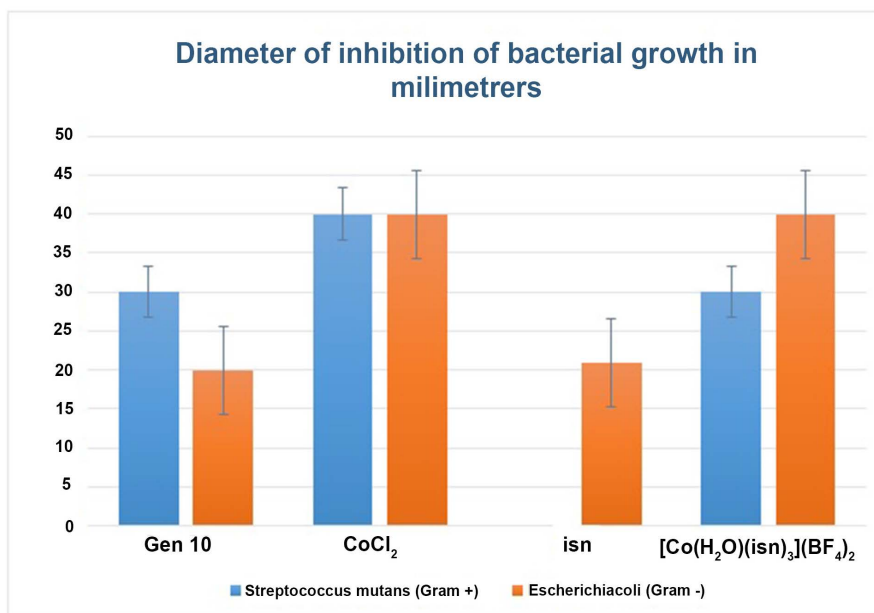


Figure 5. Graph of inhibition diameter of bacterial growth in millimeters.

the isn and the metal ion Co^{2+} were inferred. It was possible to determine the solubility of the material in hot water and the electrical nature of the synthesized chemical species was presented as a complex salt. The synthesized compound tested for both bacteria was shown to be active as bactericide and may present different action/toxicity depending on the type of bacterium tested.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Data Availability Statement

The diameters of the discs (antibiogram) and pasta used to obtain data used to support the findings of this study have been deposited in the figshare repository (DOI 10.6084/m9.figshare.7125065) and (DOI:10.6084/m9.figshare.7125125)

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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