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## Research paper

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# Determination of the binding constants of propeller-like metal complexes of picolinaldehyde-2-pyridylhydrazone

Christian C. Carmona-Vargas<sup>a,#</sup>, Sandra L. Aristizábal<sup>a,#</sup>, María I. Belalcázar<sup>a</sup>, Richard F. D'Vries<sup>b</sup>, and Manuel N. Chaur<sup>a</sup>\*

<sup>a</sup> Departamento de Química, Facultad de Ciencias Naturales y Exactas, Universidad del Valle, AA 25360, Cali, Colombia.

<sup>b</sup> Facultad de Ciencias Básicas, Universidad Santiago de Cali, Cali, Colombia.

E-mail: manuel.chaur@correounivalle.edu.co

## Abstract

Herein, we determined the binding constants for transition metal complexes of  $Cu^{2+}$ ,  $Co^{2+}$ ,  $Fe^{2+}$ ,  $Ni^{2+}$ , and  $Zn^{2+}$  ions formed with the ligand picolinaldehyde-2-pyridylhydrazone (PapyH) using the Benesi-Hildebrand method. Stoichiometry 2:1 (ligand: metal) was previously determined by the Job's method and confirmed by single-crystal X-ray diffraction finding a propeller-like structure of the [Fe(Papy)<sub>2</sub>] compound. PapyH and the metal complexes were characterized by <sup>1</sup>H NMR and UV-Vis spectroscopy, respectively. The Cu<sup>2+</sup> complex exhibited the highest stability constant, which was confirmed by competitive reaction of different metal ions with the ligand PapyH.

**Keywords**: Binding constants; Benesi-Hildebrand method, hydrazones, Job's method, metal complexes.

<sup>#</sup> These authors contributed equally to this work.

#### 1. Introduction

The nature of non-covalent binding has led to the formation of complex molecular architectures through weak interactions (hydrogen bonding, coordinating bonds) between a host and a guest, which is indeed the basis of many biological processes. Therefore, the measurement of thermodynamic parameters like binding constant(s) K, and Gibbs free energy ( $\Delta$ G) in host-guest complexation chemistry, as well as the stoichiometry of metal: ligand binding, is an important step in the characterization and understanding of the formation of metal complexes [1]. In addition, metal ion-ligand coordination equilibria are one of the processes of great importance in the construction of metallo-supramolecular entities and in the development of smart materials [2], biomedical applications [3], and even in constitutional dynamic chemistry, a subfield of supramolecular chemistry [4].

Within the field of supramolecular chemistry, Schiff bases, especially, hydrazone compounds have been widely exploited as building blocks in the assembly of metallo-architectures [5,6] due to their ability to form metal complexes, besides their straightforward synthesis [7] and modularity. The coordinating ability of hydrazones is possible thanks to the nucleophilic character of the nitrogen atoms of the triatomic structure C=N-N of the azomethine group [8]. Hydrazone-based metal complexes can be found in several fields like biological chemistry [9], materials science [10], molecular brakes [11], chemosensors [12], molecular logic circuits [13], photoelectrochemical switches [14], among others.

One of the simplest pyridine-based hydrazone ligands reported is picolinaldehyde-2pyridylhydrazone commonly known as PapyH [15]. Since its first synthesis it has received attention for being a chelating ligand for transition metal ions due to the size of its tridentate coordination pocket [16] and affinity of the metal ions for electron donor nitrogen atoms. Additionally, the acidic proton of the NH group present in this hydrazone has allowed structural modifications by base deprotonation without losing the metal ion center [17]. In addition, the study of the magnetic and electrochemical properties of its complexes has allowed the estimation of some of their acidity constants [18]. However, the study of the binding constants and the stability in competing media of PapyH-based metal complexes is a far less explored. Therefore, herein we report the synthesis, structural characterization and determination of the binding constants of a series of PapyH-based metal complexes using the Benesi-Hildebrand method [19] and the Job's method [20], one of the most popular methods for determination of stoichiometry [1,21]. Also, this work can serve as an approach to do a quantitative analysis of

the strength of the coordinate bonds present in molecular systems containing the PapyH backbone.

## 2. Experimental section

## 2.1. Materials and general methods

All chemicals were used as received from the commercial sources without further purification. Solution <sup>1</sup>H (400 MHz) and <sup>13</sup>C (100 MHz) Nuclear Magnetic Resonance (NMR) spectra were recorded with a Bruker Ultra Shield spectrometer at 25 °C, using CDCl<sub>3</sub>. Chemical shifts were quoted in ppm relative to tetramethylsilane, using residual solvent peaks as reference. The following notation is used for the <sup>1</sup>H NMR spectral splitting patterns: singlet (s), doublet (d), triplet (t), multiplet (m). Ultraviolet-Visible (UV-Vis) spectroscopy spectra were recorded on a UV–1700 PharmaSpec Shimadzu spectrophotometer. FT-IR spectra were taken in a Shimadzu FT-IR 8400 and the elemental analyses were obtained using a Thermo-Finnigan Flash EA1112 CHN (Elemental Microanalysis Ltd, Devon, UK) elemental analyzer.

## 2.2. PapyH synthesis

Picolinaldehyde-2-pyridylhydrazone was synthesized according to literature [16]. 2pyridinecarboxaldehyde (1.0 equiv) was added to a solution of 2-hydrazinopyridine (1.0 equiv) in ethanol. After the reaction mixture was heated under reflux for 3 hours, a yellow precipitate was collected on a Büchner funnel. The hydrazone obtained in 85% yield, and was recrystallized from ethanol. m.p.: 181-182 °C. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm = 9.57 (s, 1H, NH), 8.56 (d, J = 4.2 Hz, 1H), 8.19 (d, J = 4.1 Hz, 1H), 7.99 (d, J = 8.0 Hz, 2H), 7.91 (s, 1H, HC=N), 7,69 – 7.63 (m, 2H), 7.63 (s, 1H), 7.41 (d, J = 8.4 Hz, 2H), 7.19 (ddd, J = 7.8, 4.9, 0.9 Hz, 1H), 6.82 (dd, J = 8.0, 1.0 Hz, 1H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>)  $\delta$ /ppm = 156.6, 154.3, 149.3, 147.4, 139.4, 138.3, 136.3, 122.9, 119.8, 116.3, 107.7 ppm.  $\lambda_{max}$  = 340 nm.

## 2.3. Job's method of continuous variations

Solutions of PapyH and metal salts of Cu<sup>2+</sup>, Co<sup>2+</sup>, Fe<sup>2+</sup>, Ni<sup>2+</sup>, and Zn<sup>2+</sup> were prepared in methanol at 3.0x10<sup>-5</sup> mol·L<sup>-1</sup>. Subsequently, these solutions were mixed varying the concentration of the ligand and the metal ion with a final volume of 2.0 mL. UV-Vis spectra and therefore absorbance values were recorded for each mixture after 24 hours.

#### 2.4. General procedure for the synthesis of metal complexes

To a solution of the free ligand PapyH (2.0 equiv) in methanol was added 1.0 equiv. of the metal salt  $MCl_2 \cdot 6H_2O$  (M =  $Cu^{2+}$ ,  $Co^{2+}$ ,  $Fe^{2+}$ ,  $Ni^{2+}$ , and  $Zn^{2+}$ ). After stirring for 45 minutes, the solution was left to crystallize by slow evaporation at room temperature. The resulting complexes were characterized by UV-Vis spectroscopy and X-ray diffraction.

## 2.5. Determination of the stability constants using the Benesi-Hildebrand method

To a solution of the ligand PapyH in methanol at  $3.0 \times 10^{-5}$  mol·L<sup>-1</sup> was added 10 µL of a solution of the respective metal ion in methanol ( $3.0 \times 10^{-5}$  mol·L<sup>-1</sup>) until completing the addition of 100 µL, and from 100 µL up to 1500 µL. The UV-Vis spectra were collected upon addition and after 24 h, when equilibrium was reached. The results were plotted as absorbance *vs.* ligand concentration, and the *K* values were determined using equation 5. (see supporting information for mathematical details).

## 2.6. Single crystal X-ray diffraction (SCXRD)

Single crystal X-ray diffraction data of the compound [Fe(Papy)<sub>2</sub>] were collected at room temperature (293 K) on a Rigaku XTALAB-MINI diffractometer using MoKα radiation (0.71073 Å) monochromated by graphite. The cell determination and the final cell parameters were obtained on all reflections using the software *CrystalClear* [22]. Data integration and scaled was carried out using the software *CrystalClear* [22] and *CrysAlisPro* [23]. The structures were solved and refine with SHELXS-2013 software [24], included in WinGX [25] and Olex2 [26]. Non-hydrogen atoms of the molecule were clearly resolved and full-matrix least-squares refinements of these atoms with anisotropic thermal parameters were performed. Besides, hydrogen atoms were stereochemically positioned and refined by the riding model. ORTEP diagrams for all structures were prepared with Diamond; Diamond and Mercury programs were used in the preparation of the artwork and the polyhedral representations [27,28]. Crystallographic information file was deposited in CCDC under the code 1869252.

## 2.7. Competitive reactions of metal ions for PapyH

A 1:1 solution of two different metal ions (2.0 equiv) was added to a solution of PapyH ( $3.0x10^{-5}$  mol·L<sup>-1</sup>) in methanol (1.0 equiv). The UV-Vis spectra were collected upon addition and after 24 h when equilibrium was reached to observe the selectivity of the ligand in a competing media.

## 3. Results and discussion

## 3.1. Job's plot analysis

One of the main reasons to prepare metal complexes with pyridyl hydrazones is that such ligands can be obtained easily from pyridine hydrazines and the corresponding pyridinecarboxaldehyde. The ligand PapyH was prepared according to a methodology previously reported [16] by a condensation of an equimolar amount of 2-pyridinecarbaldehyde with 2-hydrazinopyridine affording the ligand PapyH in 85% yield. The <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of this compound exhibited all the expected signals with the correct integration ratios (see supporting information, Figures S1 and S2). On the other hand, the azomethine group present in hydrazones is an isomorphic equivalent of a terpyridine, therefore, this ligand has the ability to coordinate different transition metal ions through the electron donor capacity of the sp<sup>2</sup> orbitals in the involved nitrogen atoms (Scheme 1).



Scheme 1. Synthesis of the ligand PapyH and its metal complexes.

Initially, the formation of metal complexes of PapyH with  $M^{2+}$  (M = Cu, Co, Fe, Ni, Zn) was studied through Job's method [29]. For the Job's experiments (Figure 1), plots of the absorbance against mole fraction of the ligand were prepared and the stoichiometry obtained at the interception of two slopes showed that the formation for all complexes occurs in a ratio ligand: metal ion of 2:1 (see supporting information). An octahedral structure is formed, where a cation is bound to six nitrogen atoms of the two pockets of the PapyH ligands (Scheme 1). In the case of the Co<sup>2+</sup> complex, there was a little deviation in the stoichiometry found by the Job's plot,

therefore, crystals of this compound were obtained and analysed by XRD confirming the stoichiometry 2:1. However, due to the low quality of the crystals it is not possible to fully refine the X-ray data and thus to report its structure (see supporting information).



**Figure 1.** (left) UV-Vis titration of PapyH ligand with a solution of  $Cu^{2+}$  ions in methanol. (right) Job's plot for the determination of the stoichiometry of the  $Cu^{2+}$  complex in methanol at 473 nm.

Thereafter, the metal complexes were prepared by following the pathway described in scheme 1. PapyH was treated with  $MCl_2$  salts in molar ratio 2:1 ligand: metal ion in methanol to yield dark red solutions for  $Co^{2+}$  and  $Fe^{2+}$  ions, a dark green solution for  $Cu^{2+}$  ions, and yellow solutions for  $Ni^{2+}$  and  $Zn^{2+}$  ions.

Single crystals of the compound  $[Fe(Papy)_2]$  were obtained by the addition of two equivalents of KOH; in order to avoid the Fe(II) to Fe(III) oxidation, and by slow evaporation of a solution of this metal complex in methanol. The obtained dark red crystals were fully characterized by X-ray diffraction. The crystallographic data and refinement details are shown in Table S1 (supporting information) and the ORTEP representation of the asymmetric unit is presented in the Figure 2.



**Figure 2.** ORTEP representation of the asymmetric unit of the [Fe(Papy)<sub>2</sub>] compound. Thermal ellipsoids are drawn a 50% probability level and the hydrogen atoms are removed for clarity.

 $[Fe(Papy)_2]$  crystallizes in the P-1 triclinic space group with one propeller-like molecule as the asymmetric unit. In this case, two molecules of the deprotonated picolinaldehyde-2-pyridylhydrazone ligand are joined to the metal center, forming a distorted octahedral polyhedron (Figure 3a). The distortion of the polyhedron is due to the short N2-Fe1 = 1.848(6) Å and N6-Fe1 = 1.856(6) Å bond lengths resulting from a strong electrostatic interaction of the nitrogen atom with the cation along the equatorial position. In contrast, the distances range from 1.962(5) to 1.975(4) Å for the remaining four polyhedral positions. In this compound, the negative charge of the deprotonated ligand is delocalized around the N-N=C entity, allowing a strong interaction with the cation through the nitrogen atoms.

The complex units are joined by C-H $\cdots$  $\pi$  = 3.829 (2) and  $\pi$  $\cdots$  $\pi$  = 3.808(2) interactions along the [010] and [100] directions, respectively (Figure 3b). These interactions give rise to supramolecular layers in the (110) plane.



**Figure 3.** a) Polyhedral representation, b) view along the [001] direction of the supramolecular layers and c) view along the [010] direction of the crystal for the compound [Fe(Papy)<sub>2</sub>].

## 3.2. Absorption spectra

The absorption spectra given in Figure 4 show that the ligand PapyH has an intense band at 340 nm that can be attributed to the  $\pi \rightarrow \pi^*$  transitions in the C=N bond and the pyridine rings. This band exhibits a hypochromic shift when the Zn<sup>2+</sup> metal complex is formed. Additionally, the  $n \rightarrow \pi^*$  transition between the *d* orbitals of the metal centre and the  $\pi^*$  orbitals of the pyridine rings of the ligand leads to the band around 450 nm (Figure 4). Moreover, the isosbestic point at 395 nm is evidence for the absence of intermediates in the conversion of the free ligand to the metal complex.



**Figure 4.** Change on the UV-Vis spectra of PapyH with the addition of a  $Zn^{2+}$  methanolic solution.

In addition, the absorption spectra of the PapyH-based metal complexes show moderately intense bands between 260-380 nm (UV region) that can be attributed to ligand-centred  $\pi \rightarrow \pi^*$  transitions of the pyridine rings (Figure 5). The broad bands between 400-500 nm (visible region) can be attributed to metal to ligand charge transfer (MLCT) processes. Additionally, for the Fe<sup>2+</sup> complex can be observed between 500-600 nm two additional bands with low extinction coefficient that can be attributed to *d-d* transitions.





Figure 5. UV-Vis spectra of PapyH-based metal complexes in methanol at 3.0x10<sup>-5</sup> mol.L<sup>-1</sup>.

## 3.3. Determination of the binding constants by the Benesi-Hildebrand method

The binding or stability constant (K) quantifies the binding strength between a metal ion and a ligand in the formation of a coordination complex [30]. The determination of this thermodynamic constant K is based on a simple equilibrium model between the metal (M) and the ligand (L) in the complex formation eqn (1).

$$a M + b L \rightleftharpoons ML \tag{1}$$

$$[M]_0 = [M] + a[ML]$$
(2)

$$[L]_0 = [L] + b[ML]$$
(3)

$$K = \frac{[ML]}{[M]^{a}[L]^{b}} = \frac{[ML]}{[[M]_{0} - a[ML]]^{a}[[L]_{0} - b[ML]]^{b}}$$
(4)

Where  $[M]_0$  and  $[L]_0$  are variables that can be fixed; [M], [L] and [ML] depend on the equilibrium, and *a* and *b* are the stoichiometry numbers for the ligand and metal ion, respectively. There are several analytical methods that allow the determination of *K* from equation (4), however, the Benesi-Hildebrand method is by far the most used one for 1:1 stoichiometries. For 1:2 or larger stoichiometries some difficulties and ambiguous conclusions have been reported [19], especially in those cases where the formation of the complex goes through more than one step. In our

case, titration of the ligand with  $M^{2+}$  ions monitored by UV-Vis spectroscopy (Figure 4) suggests the occurrence of a single equilibrium as evidenced by the isosbestic points. With this in mind and the stoichiometry 2:1 (determined by the Job's method), we proceeded to obtain an equation for the determination of *K* (see supporting information for the algebraic details).

$$\frac{1}{\Delta A} = \frac{1}{\Delta \varepsilon K C_{\rm L}^2[M]l} + \frac{4}{\Delta \varepsilon C_{\rm L}l} - \frac{4[ML_2]}{\Delta \varepsilon C_{\rm L}^2 l}$$
(5)

Equation (5) allows us to obtain *K* from the plot of  $\frac{1}{\Delta A}$  vs  $\frac{1}{[M^{2+}]}$  (see supporting information). Table 1 organizes the binding constants for all the complexes synthesized in this work.

Transition metal cation	Wavelength (nm)	Molar extinction coefficient ε (x10 <sup>4</sup> M <sup>-1</sup> cm <sup>-1</sup> )	Binding constant K(x10 <sup>10</sup> M <sup>-2</sup> )	lonic radius <sup>a</sup> (pm)	Free energy <sup>ь</sup> (kJ⋅mol <sup>-1</sup> )
Cu <sup>2+</sup>	475	4.76	4.91	72	-39.6
Co <sup>2+</sup>	485	4.73	2.72	75	-24.8
Fe <sup>2+</sup>	450	2.73	2.17	78	-19.7
Zn <sup>2+</sup>	454	2.41	2.15	74	-19.1
Ni <sup>2+</sup>	454	4.74	2.07	69	-18.5

Table 1. Binding constants for the transition metal complexes with PapyH

a) Taken from ref [31]. Values for  $M^{2+}$  ions in an octahedral coordination.

b) Calculated from  $\Delta G^{\circ} = -RTln(K^{\circ})$  with T = 300 K and R = 8.314 JK<sup>-1</sup>mol<sup>-1</sup>

The results show that the metal ion with highest affinity for the ligand PapyH is the Cu<sup>2+</sup> ion, like in other imine and hydrazone-based ligands [32,33], which can be attributed to the additional stabilization given by Jahn-Teller distortions in the Cu<sup>2+</sup> complex [34,35]. On the other hand, it can be observed that the binding constants for the other transition metal ions are similar and lower than the *K* value of Cu<sup>2+</sup> complex. Maybe, the chelate effect of the PapyH ligand is higher with the Cu<sup>2+</sup> ion due to its small atomic radius in comparison with the other metal cations [35]. Even so, all studied complexes exhibited large binding constants (~10<sup>10</sup> M<sup>-2</sup>).

## 3.4. Competitive reactions of metal ions with PapyH

The binding constant is one of the most important characteristics of metal complexes and it is related to the chelate effects [36], which has been involved in fields like catalysis [37], and chemical biology [38]. The measure of the stability of a metal complex through the binding constant gives information about the affinity of the ligand PapyH for different metal ions. For example, when the free ligand PapyH was exposed to a mixture of first-row transition metal ions, we observed by UV-Vis spectroscopy that there is a tendency to form the band corresponding to the Cu<sup>2+</sup> complex, indicating that PapyH has a preference to form a metal complex with Cu<sup>2+</sup> ions (Figure 6). As it was expected according to the values of the binding constants found before, the Cu<sup>2+</sup> complex has the highest *K* value of 4.91 x10<sup>10</sup> M<sup>-2</sup>. In addition, we carried out experiments of competitive reactions with other first-row transition metal ions, and we found the tendency to form the Cu<sup>2+</sup> complex (see supporting information Figures S23-S26).

On the other hand, the binding constants found in this work are higher in comparison with other values of binding constants previously reported in the literature with Schiff base ligands [32,39,40], therefore, PapyH is a very good chelating ligand of the transition metal ions tested here.



**Figure 6**. Absorption spectra in methanol of metal complexes formed with PapyH ligand in the presence of different metal cations at  $3.0 \times 10^{-5}$  mol.L<sup>-1</sup>.

The binding constant has a narrow relationship with the estimation of the spontaneity of a chemical process described by the Gibbs free energy ( $\Delta$ G). From the data shown in Table 1 it

can be concluded one more time that the Cu<sup>2+</sup> complex formation with PapyH is thermodynamically the most favourable among the transition metal ions used, with a  $\Delta G = -39.63 \text{ kJ.mol}^{-1}$ . It is important to highlight that the mixtures of the ligand with different metal ions were prepared and allowed to stand up to 24 hours before measuring the absorption spectra.

## 4. Conclusions

Using the Job's plot and the Benesi-Hildebrand method it was possible to establish the stoichiometry of PapyH based metal complexes. In addition, thanks to the crystallization of the Fe<sup>2+</sup> compound was possible to confirm the 2:1 stoichiometry of the PapyH based metal complexes with a propeller-like structure. The [Fe(Papy)<sub>2</sub>] compound crystallizes in the P-1 triclinic space group, with one molecule per asymmetric unit.

On the other hand, we determined the binding constants for the formation of each metal complex, where we found that the ligand PapyH has a strong preference for Cu<sup>2+</sup> ions over the other transition metal ions tested in a competitive reaction media. The determination of the binding constant of metal complexes based on PapyH opens the window toward the potential application of a simple hydrazone ligand as PapyH in the molecular recognition of Cu<sup>2+</sup> ions in mixtures containing other first-row transition metal ions.

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## **GRAPHICAL ABSTRACT**



We determined the binding constants for transition metal complexes of Cu<sup>2+</sup>, Co<sup>2+</sup>, Fe<sup>2+</sup>, Ni<sup>2+</sup>, and Zn<sup>2+</sup> ions formed with the ligand picolinaldehyde-2-pyridylhydrazone (PapyH). Stoichiometry 2:1 (ligand: metal) was confirmed by single-crystal X-ray diffraction finding a propeller-like structure of the [Fe(Papy)<sub>2</sub>] compound. PapyH and the metal complexes were characterized by <sup>1</sup>H NMR and UV-Vis spectroscopy respectively. The Cu<sup>2+</sup> complex exhibited the highest stability constant, which was confirmed by competitive reaction of different metal ions with the ligand PapyH.

## Highlights

- Synthesis of novel PapyH based metal complexes of Cu<sup>2+</sup>, Co<sup>2+</sup>, Fe<sup>2+</sup>, Ni<sup>2+</sup> and Zn<sup>2+</sup>.
- The formation of all metal complexes occurs in a ratio ligand: metal ion of 2:1
- $Cu^{2+}$  exhibits the highest binding constant among the metal ions tested with  $K = 4.91 \times 10^{10} \text{ M}^{-2}$ .
- X-ray crystal structure of the [Fe(Papy)<sub>2</sub>] complex was determined.