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Short communication

Ascorbic acid-based quinoxaline derivative as a chromogenic chemosensor for Cu^{2+}

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ABSTRACT

Detection of cationic species represents an important field due to its importance in biological and environmental processes. This communication shows the synthesis and application of an ascorbic acid-based quinoxaline derivative (**1**) in the colorimetric detection of Cu^{2+} against several other cationic species, including Sr^{2+}, Fe^{2+}, Pb^{2+}, Mn^{2+}, Mg^{2+}, Ni^{2+}, Zn^{2+}, Sn^{2+}, Hg^{2+}, Ca^{2+}, Ba^{2+}, Co^{2+}, Cr^{3+}, Al^{3+}, and Fe^{3+}. Based on experimental and theoretical results, a 1:2 binding model involving **1** and Cu^{2+} is proposed.

The development of molecular and supramolecular strategies for the recognition and detection of cationic species represents a field of increasing importance in recent years [1]. In this context, the study of chromogenic chemosensors for these analytes is attractive due to the fact that the analysis procedures are simple and require low cost, with naked-eye detection also being possible [2–4]. Copper (II) ions are one of the main target analytes with relevance to be detected, since the referred metal is highly abundant in nature and essential to many biological processes; on the other hand, its abnormal levels may lead to several pathologies [5–8].

A wide range of quinoxaline derivatives has been reported in the literature due to their relevant biological activity [9] and applications in technological fields [10]. In addition, quinoxalines are found as interesting nitrogenated ligands for coordination chemistry [11,12]. Traditionally, the synthesis of 2,3-disubstituted quinoxalines proceeds through Brønsted or Lewis acid-catalyzed condensation of aromatic *o*-diamines and *α*-diketones [13]. Based on this synthetic strategy, there are several investigations reported in the literature concerned with reactions of dehydro-L-ascorbic acid and *o*-phenylenediamine, and an interesting aspect in these processes is related with the possibility of different products mainly depending on the ratio of the reactant and of the experimental conditions [14–21]. For instance, *one pot* procedure involving mixing an equimolar amount of L-ascorbic acid and 1,4-benzoquinone, followed by the addition of two equivalents of *o*-phenylenediamine, leads to the formation of *N*-(2-aminophenyl)-3-[(1*S*,2*S*)-1,2,3-trihydroxy-propyl]quinoxaline-2-carboxamide (**1**), as presented in Scheme 1 [14,15].

Although quinoxaline derivative **1** has been known since 1964 [16], this compound is surprisingly marginally reported in literature. A quick look at the molecular structure of compound **1** reveals the presence of eight Lewis basic sites from primary aniline, amide, quinoxaline and hydroxyl groups, suggesting an attractive design to be applied in coordination chemistry. In this context, we report herein the use of ascorbic acid-based quinoxaline **1** as a cationic chromogenic chemosensor. More specifically, we demonstrate that compound **1** in methanol is very selective for naked-eye and quantitative detection of Cu^{2+} between several utilized cations.

Compound **1** was easily obtained according to the literature (Scheme 1) [14,15], from low cost reactants starting from L-ascorbic acid in 72% yield, and spectroscopic data were in full agreement to the proposed structure [22]. NMR characterization of compound **1** was reported only in 2014, but not properly detailed [15], such as for data obtained from bidimensional analysis, which is found to be very relevant due to the complexity of the structural nature of the referred ligand, including chirality aspects. All NMR spectra related to compound **1** are presented here in the Supplementary Material (Figs. S1–S4). Fig. S4 (Supplementary Material) shows the experimental $^{1}J_{H,C}$–HSQC spectrum of compound **1**. Quinoxaline hydrogens are downfield in relation to a substituted phenyl ring. This is a consequence of the combination of the electron deficient nature of the heterocyclic unit, which is even increased due to its direct connectivity to the carbonyl group, with the

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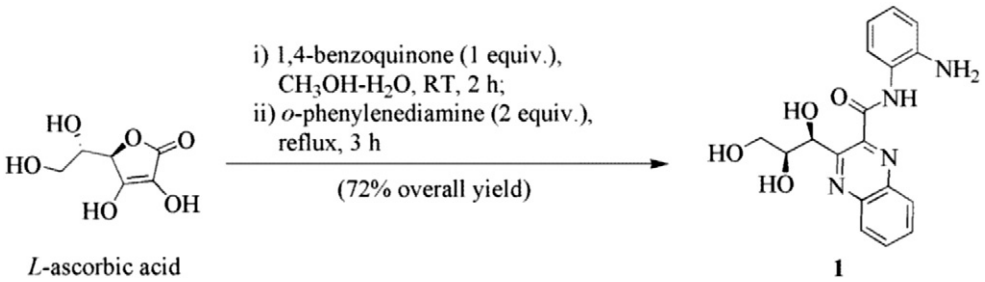

Scheme 1. *One pot* synthesis of compound **1**.

electron donation ability of both nitrogen atoms of the amine and amide groups attached to the phenyl ring. In the aliphatic moiety of the molecular structure, the diastereotopic hydrogens of the methylene group appear as two multiplets at the higher field region of the spectrum, as a consequence of the two stereogenic centers in the ligand.

Quinoxaline **1** (1×10^{-4} mol L^{-1}) was added to solutions containing 5 equivalents of several cationic species (Cu^{2+}, Sr^{2+}, Fe^{2+}, Pb^{2+}, Mn^{2+}, Mg^{2+}, Ni^{2+}, Zn^{2+}, Sn^{2+}, Hg^{2+}, Ca^{2+}, Ba^{2+}, Co^{2+}, Cr^{3+}, Al^{3+}, and Fe^{3+}) in methanol. Only the solution containing Cu^{2+} changes its color immediately after the addition of **1** (Fig. 1a), and this behavior is consistent with the results obtained from UV–vis analysis (Fig. 1b–c). All data in Fig. 1 were acquired 5 min after the mixture of the reagents. A new band emerges in the visible region with maximum absorbance at 416 nm, suggesting a formation of a coordination complex between **1** and Cu^{2+} (Fig. 1b–c).

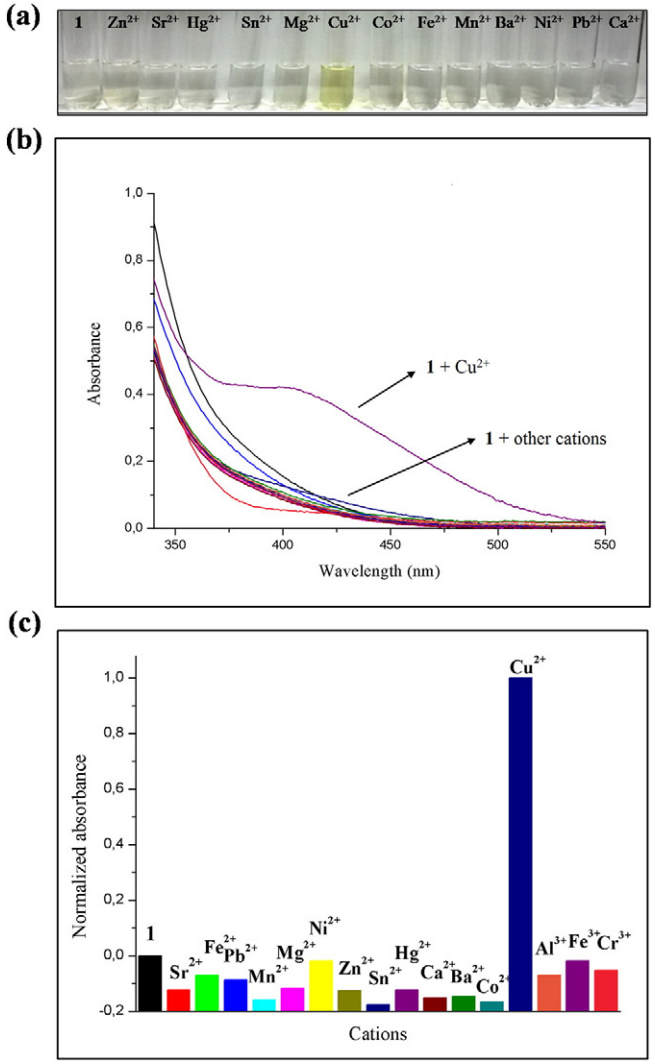

Fig. 1. Methanolic solutions of compound **1** (1.0×10^{-4} mol L^{-1}) in absence and in presence of Cu^{2+}, Sr^{2+}, Fe^{2+}, Pb^{2+}, Mn^{2+}, Mg^{2+}, Ni^{2+}, Zn^{2+}, Sn^{2+}, Hg^{2+}, Ca^{2+}, Ba^{2+}, Co^{2+}, Fe^{3+}, Cr^{3+} and Al^{3+} (5.0×10^{-4} mol L^{-1}): (a) naked-eye detection of Cu^{2+}; (b) UV–vis spectra of resulting solutions; (c) changes in the absorbances at 416 nm. All spectra were obtained 5 min after the addition of the reagents.

Spectrophotometric titration was performed in order to investigate the stoichiometry of this interaction and it was found that absorbance of the complex between ligand **1** (1×10^{-4} mol L^{-1}) and Cu^{2+} was enhanced as the concentration of Cu^{2+} ion increased until saturation at approximately 2×10^{-4} mol L^{-1}, suggesting a 1:2 **1**:Cu^{2+} stoichiometry (Fig. 2). In attempt to verify sensibility aspects, another experiment using 0.5 μmol L^{-1} of chemosensor **1** toward 10 equivalents of each metal was performed and Cu^{2+} selectivity could be demonstrated by UV–vis spectroscopy, through with an increase in the absorbance at 416 nm. The selectivity of compound **1** for Cu^{2+} in the presence of different metal ions was investigated using UV–vis analysis of solutions containing compound **1** together with one equivalent of Cu^{2+} and an equimolecular amount of another cation (Fig. 3). A small increase in the absorbance at 416 nm was found when Mg^{2+} and Pb^{2+} compete with Cu^{2+}. On the other hand, Al^{3+} and Sn^{2+} lead to a substantial decrease in the absorbance at 416 nm. This is not an unexpected result since there are several electronic donor sites in compound **1** able to complex cationic species. Data suggest that those metal ions are complexing with **1** in a different binding site than the site responsible for the complexation of Cu^{2+}. Those metal ions would be responsible for reinforcing or weakening the interaction of Cu^{2+} with **1**, leading to the observed results.

The infrared spectra of compound **1** and its coordination complex were compared in an attempt to understand the chemical nature of

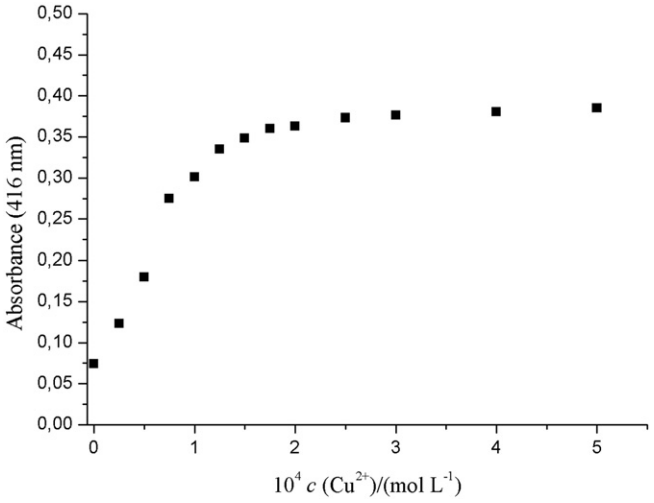

Fig. 2. Corresponding titration curve based on addition of Cu^{2+} (0 to 5 equivalents) to solutions of compound **1** (1.0×10^{-4} mol L^{-1}). All spectra were obtained 5 min after the addition of the reagents.