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Copper- and Zinc-Based Coordination Polymers toward the Development of More Efficient Agrochemicals

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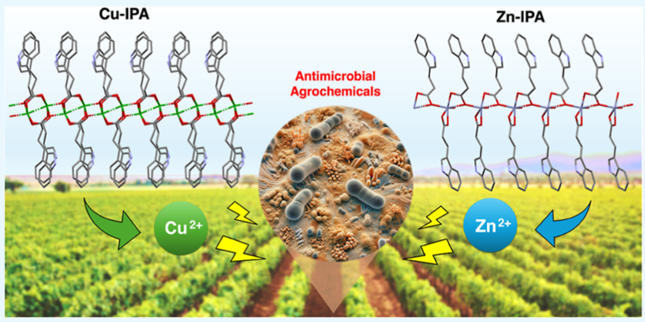
ABSTRACT: Inorganic agrochemicals have been used by the food industry for thousands of years to maximize production and quality, with copper(II) sulfate being one of the main used pesticides. Given the increasing global population (expected to reach 9.6 billion by 2050) and the challenges facing agricultural production, there is a pressing need to address the impact of intensified agrochemical use (e.g., soil and water contamination, human health risk, pesticide resistance, etc.). Coordination polymers (CPs) as agrochemicals offer several significant advantages compared to traditional agrochemicals, such as the controlled release of the active ingredients in the target zone and reduced toxic doses released to environment. In this work, the plant growth regulator 3-indolepropanoic acid (IPA), which stimulates root initiation and elongation, is used as a chelating agent of Cu^{2+} and Zn^{2+} metal ions, both known for their antibacterial and antifungal properties, to obtain two crystalline CPs, named Cu-IPA $[Cu(H_{10}C_{11}NO_2)_2]_n$ and Zn-IPA $[Zn(H_{10}C_{11}NO_2)_2(H_2O)]_n$. Their role as potential antibacterial agents was evaluated. First, the stability of these materials was studied, showing a fast release of both cations (100% after 8 and 3 h for Cu-IPA and Zn-IPA, respectively) in aqueous solution. The antibacterial test against *Escherichia coli*, a bacterium involved in many farm animal infections, evidenced a notable growth inhibition, with values of inhibition of the colony forming unit (CFU) for Cu-IPA of 10.2 and 26.2% and for Zn-IPA of 2.1 and 5.3% at 500 and 1500 ppm, respectively. This study highlights the potential of CPs for enhancing efficiency and sustainability of inorganic agrochemicals in agriculture.



■ INTRODUCTION

Agrochemicals have been used for centuries to improve harvest quality and quantity. According to the Food and Agriculture Organization (FAO) of the United Nation, the total used pesticides in 2020 reached 2.7 million tons of active ingredients (AIs), with a worldwide application of 1.8 kg per ha of pesticides.[1] The first recorded use of agrochemicals is about 4500 years ago by Sumerians, who used sulfur compounds to control insects and mites.[2] Particularly, one of the earliest inorganic pesticide to be developed was "Bordeaux mixture" (also known as Bordo Mix), based on $CuSO_4$ and CaO, which is used to control fungal infections on grape vines.[3] From this pioneer compound, many inorganic pesticides were developed containing metals,[4] and some of them are actually used in modern agriculture. Particularly, Cu-based plant-protection products are widely used in conventional agriculture. One of the main advantages of their use is their wide spectrum of activity against bacteria oomycetes, ascomycetes, and basidiomycetes, including diseases of worldwide importance (i.e., downy mildew of grape).[5] Furthermore, Cu is an essential mineral nutrient for the proper growth and development of crops. In plants, copper plays an essential role in mitochondrial respiration, in the electron transport chain, photosynthesis, cell wall metabolism, and lignin synthesis and has a pivotal function in oxidative stress response and hormone signaling. On the other hand, Zn is a further essential micronutrient for plants. The functions of Zn in plants are multiple: it has a prominent role in the synthesis of carbohydrates and in the transformation of sugars, regulates levels of certain auxins, is related with processes of maturation and seed production, improves the formation, viability, and fertility of pollen, and influences in the elongation of shoots and leaf development, among others.[6]

In our fields, Cu and Zn are administered as sulfates, oxides, and chelates, with an optimal supply range of Cu and Zn of 0.01−0.02 and 0.03−0.1 $mg \cdot g^{-1}$ dry weight measured as plant content, depending on the crop, respectively.[6,7] However,

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repeated foliar applications of high concentrations of Cu- and Zn-based products lead to their accumulation in soil, with the subsequent negative impacts on fertility.[8−10] For example, an excess of Cu imparts effects on germination, growth, photosynthesis, and antioxidant response in agricultural crops. Ideally, pesticides should release their AIs in a controlled manner, with no harmful effect to the environment. Therefore, there is an urgent need to find a new generation of environmentally benign Cu- and Zn-based agrochemicals with improved capabilities.

A controlled released of the AIs in the target zone can be achieved by the coordination of organic agrochemicals to bioactive metals, reducing the toxic doses usually released to the environment.[11,12] If we look at nature, we can notice that plants are able to defend against metals' toxicity. Particularly, roots secrete exudates into the soil in a way to chelate metals and prevent their uptake. Other aspects to be considered in agroindustry applications are the need to use low-cost and long-lifetime materials and non-toxic and abundant safe precursors together with simple synthetic routes with a high space time yield (STY; kilogram of material produced per cubic meter of reaction per day). The production of large-scale materials is one of the major bottlenecks of agroindustry.[13,14] In our way to prepare less toxic but active pesticides, we have selected 3-indolepropanoic acid (IPA), a natural compound found in plants and animals, as a chelating agent for the controlled delivery of Cu and Zn. Further, IPA has demonstrated its role in agriculture as a plant growth regulator.[15] IPA is an auxin-like compound, which means it functions similarly to natural plant hormones that regulate various growth processes. Thus, IPA can influence multiple physiological activities in plants, including cell division and root development.[16] Thus, this article reports the synthesis of a novel coordination compound (namely, Cu-IPA) and the synthesis optimization of a previously reported Zn-IPA,[17] both based on IPA and Cu^{2+} and Zn^{2+}, respectively. After the syntheses were scaled up, their thermal and chemical stability in water was studied, and their potential as antibacterial agents was investigated.

■ RESULTS AND DISCUSSION

Synthesis, Scale-Up, and Characterization. Two IPA 1D coordination polymers (CPs) based on Cu^{2+} (Cu-IPA) and Zn^{2+} (Zn-IPA) were prepared by reacting IPA with $M(CO_2CH_3)_2$ (M = Cu^{2+} and Zn^{2+}) in a 1:1 molar ratio in an aqueous/ethanolic solution at room temperature (see details in Experimental Section in the Supporting Information, S1). After 24 h, high-purity crystals of Cu-IPA, or $[Cu(H_{10}C_{11}NO_2)_2]_n$, were obtained suitable for single-crystal X-ray diffraction (SCXRD) (see details in Experimental Section S2.1 Supporting Information). Cu-IPA crystallizes in the monoclinic crystal system in the $C2/c$ space group. The subunit is formed by two molecules of IPA connected to a copper atom by a coordination bond through the IPA carboxylic oxygen. The copper centers present a square-base pyramidal geometry connected to five oxygen atoms from five IPA molecules (Figure 1A). IPA molecules are arranged parallel to each other, and the whole structure results in a polymeric chain that extends parallel to the crystallographic *b* axis. Along this polymeric chain, the IPA molecules are oriented perpendicularly to the chain, and the structure seems stabilized by N−H⋯π interactions established between the indole NH group and the closest adjacent indole aromatic plane, with an average distance of 2.4 Å (Figure S2, Supporting Information). On the other hand, and in contrast to the previously reported synthesis, Zn-IPA, or $[Zn(H_{10}C_{11}NO_2)_2(H_2O)]_n$, was here synthesized using environmentally friendly conditions (at room temperature). Powder X-ray diffraction (PXRD) patterns confirm the phase purity of Zn-IPA (Figure 2B).

Notably, the syntheses of Cu-IPA and Zn-IPA were successfully scaled-up 100 times (from 0.053 to 5.3 mmol)

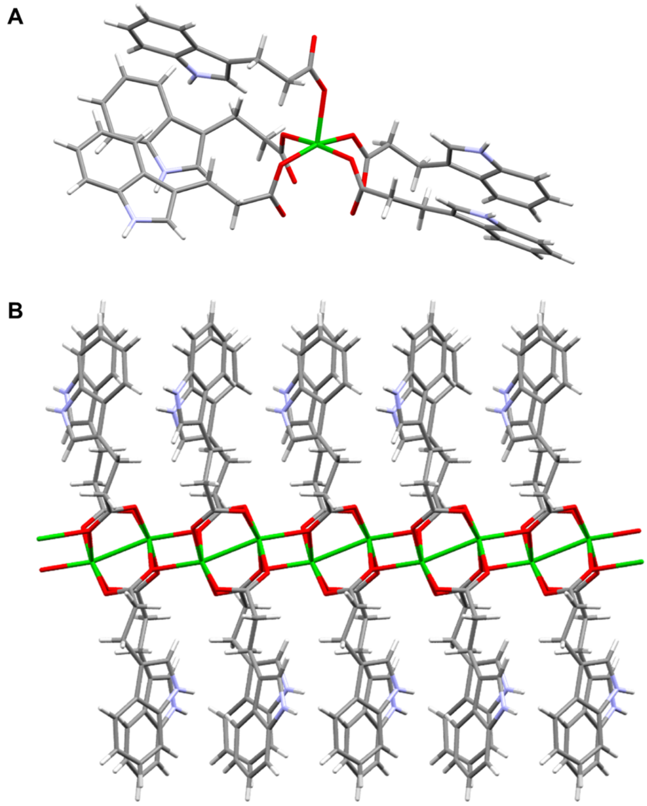

Figure 1. Copper coordination geometry (A) and polymeric chains along the *b* axis (B). Copper, oxygen, nitrogen, carbon, and hydrogen are represented in green, red, violet, gray, and white, respectively.

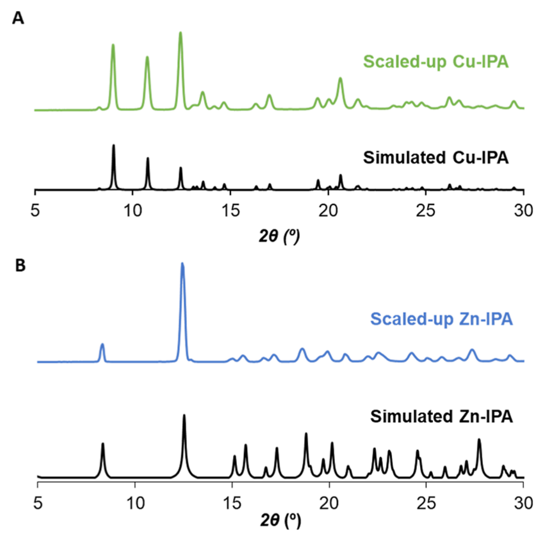

Figure 2. PXRD patterns of scaled synthesis compared with a theoretical (black) diffractogram obtained from SCXRD data of Cu-IPA (A, green) and Zn-IPA (B, blue).

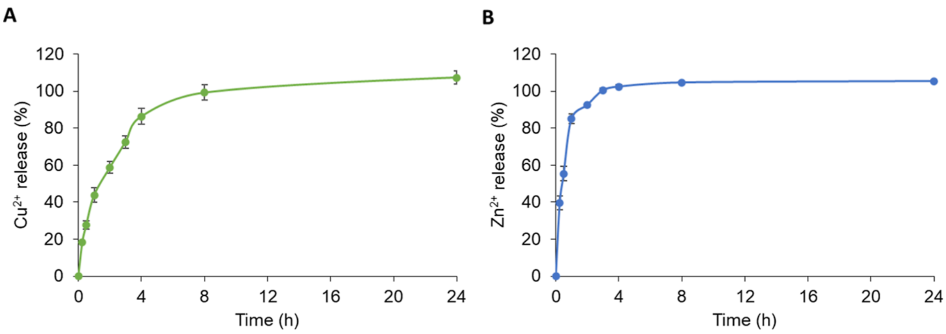

Figure 3. Metal leaching from Cu-IPA (A) and Zn-IPA (B) over time when suspended in water at room temperature.

of IPA from 26 to 100 mL vials in mild conditions, obtaining around 0.6–0.9 g of solid (26.6 and 36.0% yield, respectively) in a single reaction. The characteristic crystalline phase of all compounds was identified in the scaled-up bulk samples by comparing the location and intensity of the main Bragg reflections with those of the crystalline structure obtained from SCXRD (Figure 2). To check the phase purity, the Le Bail fitting was carried out using the unit cell parameters of Cu-IPA and Zn-IPA (Figure S3, Supporting Information). Fourier transform infrared (FTIR) spectra confirm the presence of coordinated IPA by a shift of the characteristic band corresponding to νCOO^- from 1689 to 1578 and 1533 cm^{-1} for Cu-IPA and Zn-IPA, respectively (Figure S4, Supporting Information).[17] Further, the Cu–O and Zn–O stretching vibrations appear at 498 and 499 cm^{-1}, for Cu-IPA and Zn-IPA, respectively. Interestingly, a strong band at 3393 cm^{-1} is observed in both CPs, corresponding to the NH···π interaction between the indole NH group and the closest adjacent indole aromatic plane, as mentioned above.

In both compounds, thermogravimetric analysis (TGA) curves show an initial weight loss (from RT to 200 °C) attributed to the physiosorbed water molecules and a second weight loss (at 220 and 300 °C for Cu-IPA and Zn-IPA, respectively), corresponding to the decomposition of the compounds by the oxidation and departure of the linker. Further, the chemical composition was compared with the % of thermal degradation residue: theoretical CuO (Cu-IPA) 18.12% and found 17.74%, and theoretical ZnO (Zn-IPA) 17.36% and found 18.08% (Figure S5, Supporting Information). Scanning electron microscopy (SEM) images showed well-faceted block crystals with a tabular shape and a size of ca. 30–300 μm (Figure S6, Supporting Information) being more elongated and slightly smaller in the case of Cu-IPA.

Cu-IPA and Zn-IPA: Stability Studies. Agrochemicals are commonly distributed mainly as a water-based solution or suspension in fields (e.g., the pesticides glyphosate or $CuSO_4$) targeting different parts of plants or the ground. A solid application in the form of powder or granulated formulation is also common, where the AI release can be driven by humidity or rain.[18] In the case of a metal-based agrochemical, their activity is related to the metal ion released under moisture conditions.[19] In view of their potential application as agrochemicals, a chemical stability study of Cu-IPA and Zn-IPA was performed in aqueous conditions. The chemical robustness in solution was investigated by inductively coupled plasma optical emision spectroscopy (ICP-OES) by means of the release of the active metal cations for 24 h (Figure 3). Note here that according to the Pourbaix diagram of Cu and Zn, at the studied pH (6.5), the potentially released metals are found in solution as Cu^{2+} and Zn^{2+} cations.[20] The results demonstrated that both materials showed a similar degradation profile, with a fast release of the metals within the first hours (ca. 100% of metal release after 8 and 3 h for Cu-IPA and Zn-IPA, respectively) when suspended in water.

At this point, in our way to gain understanding and to make these materials more efficient for practical uses, the release kinetics of metal ions were studied. Note that the kinetics studies were performed under continuous stirring to exclude the external diffusion process around the particles. In particular, the release kinetics were successfully fitted to Higuchi and a pseudo-second-order kinetic model for Cu-IPA and Zn-IPA, respectively. Both metals release fits to these models with a regression factor (R^2) > 0.99 (Figures S7 and S8, Supporting Information). Thus, the Cu^{2+} release could be explained by the equation $q(t) = K\sqrt{t}$, where q is the release capacity (mg·g^{-1}) at a determined time (t) and K is the release constant (g·mg^{-1}·h$^{-1/2}$), and the Zn^{2+} release by the equation $\frac{t}{q_t} = \frac{1}{K_2 \cdot (q_e)^2} + \frac{t}{q_e}$, where K_2 is the pseudo-second-order kinetic (g·mg^{-1}·h^{-1}). It should be noted here that according to the final application (controlled release of agrochemicals in fields), achieving a slow release of the AIs is imperative. However, it is not easy to compare the metal release rate from both materials since they follow different kinetics models. It is also important to consider that while we attempted to study the release of the AIs here, the release kinetics in the field will depend on factors such as application method (suspension, powder, and particle size), plant or soil humidity, rain, and irrigation, which could significantly affect the release process.

Antibacterial Tests. Cu- and Zn-based compounds present several advantages for their use as agrochemicals since they are known to exhibit antibacterial and antifungal activity,[21−23] and present low toxicity in animals and plants,[24,25] acting as micronutrients for plants at low concentrations.[26] Their antibacterial activity depends directly on the metallic ion release kinetics. In particular, Cu acts as antibacterial agents due to diverse mechanisms: (i) it can affect the integrity of the cell membrane through electrostatic interactions,[27] (ii) it can bind to cytoplasmic proteins affecting the metabolism of bacteria,[28] and (iii) it leads to an important oxidative stress and reactive oxygen species (ROS) production.[29,30]

Regarding the antibacterial mechanism of Zn, (i) it can interact with the positive charge bacteria surface, denaturing the structural protein of the cell membrane,[31] and (ii) it can be transformed into ZnO under UV, inducing oxidative stress and ROS production.[29] Therefore, and considering their potential as agrochemicals, the antibacterial activity of Cu-IPA and Zn-

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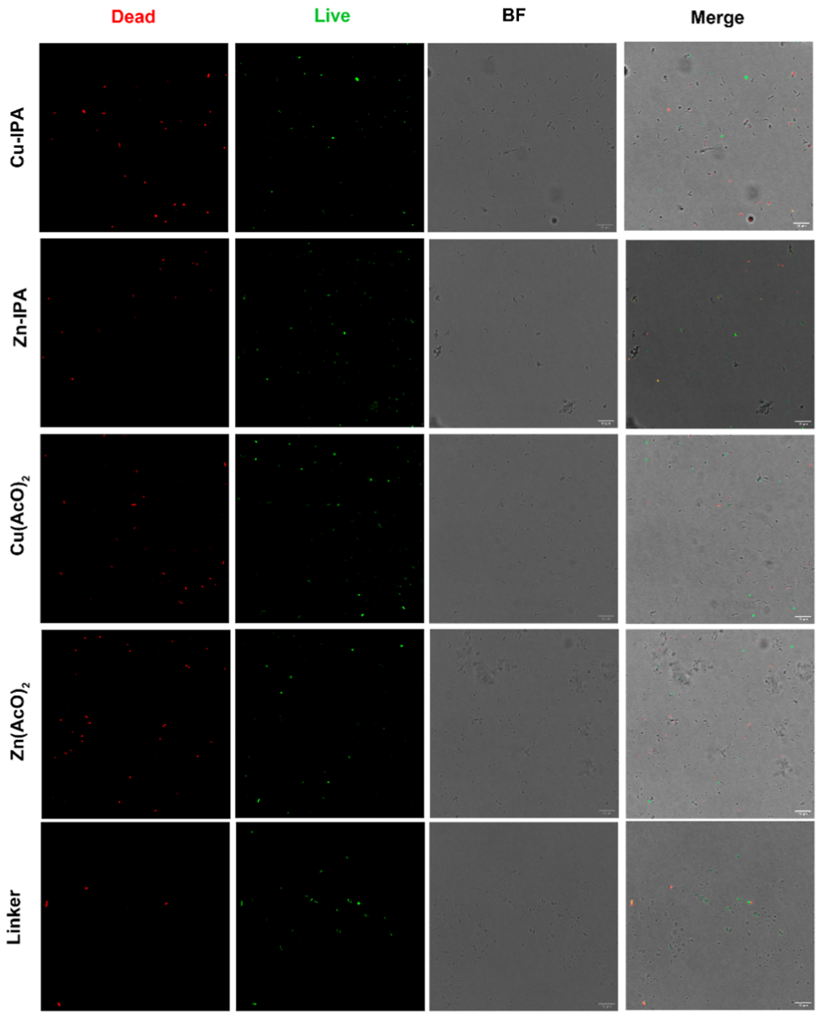

Figure 4. Confocal microscopy images showing the viability of *E. coli* treated with Cu-IPA, Zn-IPA, and their respective precursors. Dead (PI), live (FDA), and bright-field (BF) images and the corresponding merged images are shown to observe the distribution of live and dead cells.

IPA was evaluated. First, the inhibitory effect against *Escherichia coli* (*E. coli*) was determined by measuring the zone of inhibition around the disk of each material and their precursors for 14 days (further details in Section S4, Supporting Information). Agar diffusion assays indicated that Cu-IPA and Zn-IPA are active against *E. coli* (Cu-IPA: 17.40 ± 0.22 mm; Zn-IPA: 16.24 ± 0.34 mm, after 14 days). No significant differences in the inhibition zone were observed after different incubation times (1, 8, and 14 days). These results can be explained by an extremely fast release of the metals in the agar media.

Subsequently, the antibacterial potential of Cu-IPA and Zn-IPA was confirmed by a live/dead BacLight bacterial test via staining using fluorescein diacetate (FDA) for live bacteria and propidium iodide (PI) markers for dead bacteria and imaging under a fluorescence microscope (Figure 4). The results showed the abundance of red cell population in cells treated with Cu-IPA and Zn-IPA (1500 ppm) compared to the precursor IPA, suggesting that the antibacterial activity is attributed to the chelated metals.

After these initial tests, the bactericide effect was evaluated by counting the colony forming unit (CFU) using two different compounds concentrations (C_1 = 500 ppm and C_2 = 1500 ppm) and the corresponding precursor amounts. Note that the concentrations here selected are between the range of the Cu concentration recommended to be applied in fields by agrochemicals suppliers (from 1200 to 10,000 ppm).[32,33] The results demonstrated that both materials have antibacterial activity. The highest CFU reduction was observed using Cu-IPA at both concentrations (10.2 ± 3.2 and 26.2 ± 4.2% for C_1 and C_2, respectively) compared to Zn-IPA (2.1 ± 0.33 and 5.3 ± 1.05 for C_1 and C_2, respectively) (Figure 5). Interestingly, Zn-IPA is significantly ($p < 0.01$) more active than its precursor $Zn(AcO)_2$, improving its antibacterial activity. However, Cu-IPA reached a statistically similar (C_2) or lower (C_1) antibacterial activity than its precursor $Cu(AcO)_2$ or the well-known $Cu(SO_4)$ (100% inhibition at 1000 ppm).[34] On the other hand, although some inhibition effect of IPA was demonstrated in the inhibition halo experiments (16.9 ± 1.5 mm), IPA did not show any CFU reduction against *E. coli*, which is in agreement with the previously reported results.[35] We can argue that the antibacterial activity of both CPs should be explained by the collapse of the polymer structure and the subsequent release of the metal.[36] Here, we should point out that although the rate of CFU reduction of Cu-IPA is similar to the one obtained using their precursors, the coordination of Cu and Zn with IPA together with the slower release may reduce the potential metal toxicity in crops, leaching a smaller amount over time, in contrast to concentration peaks of Cu^{2+} and Zn^{2+} normally detected in our fields. The antibacterial activity in

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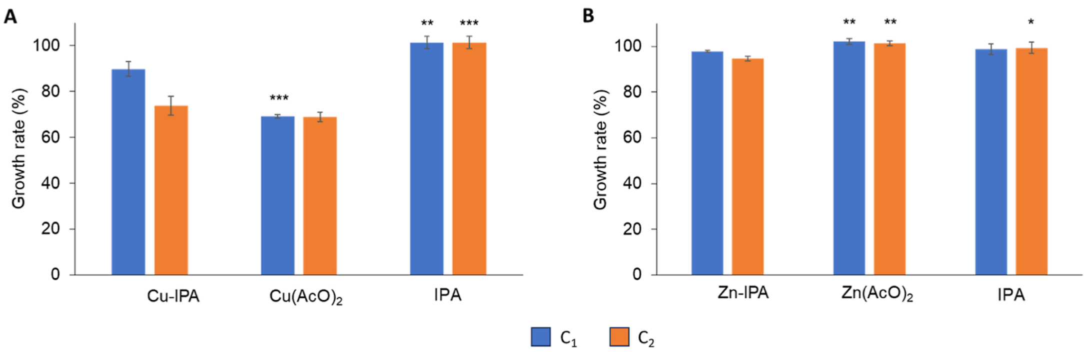

Sample	Concentration (ppm)	Log_{10} (CFU mL^{-1})	CFU reduction (%)
Control	0	8.45	0.0
Cu-IPA	500	7.50	10.2
Cu-IPA	1500	6.24	26.2
Cu(AcO)$_2$	72	5.80	30.8
Cu(AcO)$_2$	216	5.80	31.0
IPA	428	8.24	0.0
IPA	1284	8.37	0.0

Sample	Concentration (ppm)	Log_{10} (CFU mL^{-1})	CFU reduction (%)
Control	0	8.45	0.0
Zn-IPA	500	8.09	2.1
Zn-IPA	1500	7.90	5.3
Zn(AcO)$_2$	71	8.47	0.0
Zn(AcO)$_2$	213	8.44	0.0
IPA	409	8.20	1.2
IPA	1228	8.30	0.6

Figure 5. Bacterial growth rate (%) of *E. coli* in contact with two different concentrations of Cu-IPA (A), Zn-IPA (B), and their precursors after 24 h, represented as the logarithmic ratio of CFU·mL^{-1} of each sample with respect to the positive control (CFU_0). The average of three replicates and its standard deviation is represented. The statistical was performed using the ANOVA test, comparing each concentration of Cu-IPA or Zn-IPA with the respective concentration of precursors, where p values * <0.05, ** <0.01, and ***< 0.001. Log_{10}(CFU·mL^{-1}) is represented in Figure S11, Supporting Information.

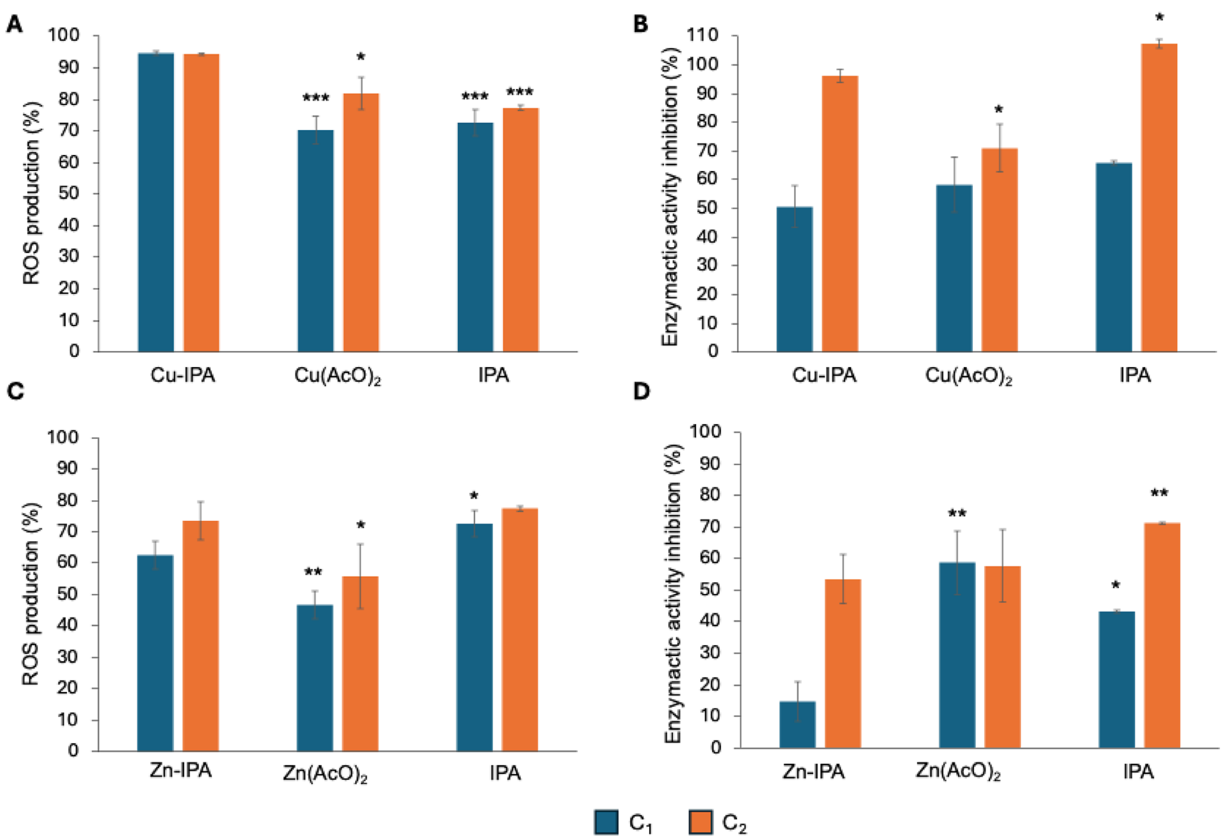

Figure 6. ROS production determined by 2,7-dichlorodihydrofluorescein (DCFH) fluorescence emission and enzymatic activity inhibition determined by FDA fluorescence emission of the compounds Cu-IPA (A,B) and Zn-IPA (C,D) at two different concentrations and their precursor at the respective concentration present in the above-mentioned compounds. The fluorescence signal raw data is shown in Figures S12 and S13, Supporting Information. Statistical analysis was performed using the ANOVA test comparing each concentration of Cu-IPA or Zn-IPA with the respective concentration of precursors, where *p* value * <0.05, ** <0.01, and *** <0.001.

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play here lies within the same range when further compared to previous antibacterial compounds against *E. coli* (Table S3, Supporting Information), such as RTCuZn800 (100 ppm based on Zn^{2+} with a CFU reduction of 0.6% after 24 h),[37] or much lower when compared with other materials, like nCuO/AC (43 ppm with a CF reduction of 95% after 4 h),[38] CuO–Co_3O_4@C NWs (CF reduction of 100%),[39] or ZnO–Al_2O_3 (CF reduction of 70% in 24 h).[40]

In a further step to understand the antibacterial mechanism of Cu-IPA and Zn-IPA, the toxicity to bacteria associated with the production of ROS and enzymatic activity inhibition capacity was studied. Cu-IPA showed a high ROS production (94.6 and 94.3% for C_1 and C_2, respectively), even statistically significantly higher in comparison with its precursor $Cu(AcO)_2$ (70.3 and 81.8% for C_1 and C_2, respectively) (Figure 6A). The same results are obtained for Zn-IPA, where the ROS production (62.6 and 73.5 for C_1 and C_2, respectively) is higher than that of its metallic precursor (46.8 and 55.7 for C_1 and C_2, respectively). This observation suggests that the antibacterial effect of both CPs could be associated with the generation of an important ROS production, among other effects. On the contrary, the enzymatic activity inhibition in the bacteria of Cu-IPA and Zn-IPA is lower than their metallic precursors, except for Cu-IPA (96.1 vs 71.0%) at higher concentration (C_2) (Figure 6B). Note here that free IPA is also active in ROS generation (72.6 ± 4.2 and 77.4 ± 0.8% for C_1 and C_2, respectively) and in the enzymatic activity inhibition (65.9 ± 0.8 and 100 ± 1.5% for C_1 and C_2, respectively) but does not present antibacterial activity as previously reported in the literature.[35] This phenomenon might be explained by a combination of different bactericidal mechanisms, depending on multiple factors. Considering all of the obtained results, the effectiveness of the use of CPs as agrochemicals is demonstrated. In the case of Zn-IPA, a synergetic enhancement of the antibacterial activity was observed when compared to both precursors. On the other hand, the Cu-IPA activity is a result of the bactericidal activity average from both precursors. These results supported the necessity of a deeper understanding of the IPA antibacterial activity as evidenced in the literature, where it is described as both an antibacterial and non-antibacterial molecule. Nevertheless, this work reports the potential use of CPs based on IPA with enhanced bactericidal activity and as a potential source of micronutrients.

■ CONCLUSIONS

The crystal structure of a novel CP based on IPA and Cu is here reported. Further, the synthesis of a CP based on Zn and IPA was optimized. Cu-IPA and Zn-IPA compounds exhibited a fast degradation profile with 100% metal release after 8 and 3 h for Cu-IPA and Zn-IPA, respectively. Furthermore, they displayed remarkable antibacterial activity against *E. coli*. The CFU test confirmed that Cu-IPA (from 10.2 to 26.2%) and Zn-IPA (from 2.1 to 5.3%) have bactericidal effects, and particularly for Zn-IPA, they are statistically greater compared with its precursor (0%). The bactericidal effect is probably related with their high ROS productivity (94.6 and 94.3% for Cu-IPA and 62.6 and 73.4 for Zn-IPA at C_1 and C_2, respectively), among others. Considering the ROS generation capacity and enzymatic inhibition activity of IPA, the improved Zn-IPA antibacterial activity may be a combination of IPA and Zn^{2+} in the same formulation. Overall, Zn-IPA exhibits a combined antibacterial property, in contrast with the isolated constituents, and can be considered as an interesting active agent for use in agriculture.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c10977.

Materials and methods, crystallographic studies, materials characterization (Le Bail, FTIR, TGA, and SEM), release kinetics analysis, and antibacterial activity (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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