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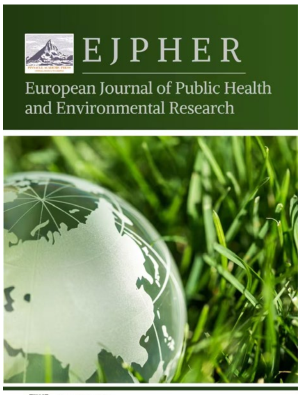
Advances in Copper Coordination Polymers and Chemical Stabilizers for Enhanced Urease Inhibition in Agricultural Soils

Xuan Liu [1,*], Yi Xu [1] and Nurul Aisyah Binti Ahmad [2]

[1] Shanxi University, Taiyuan, China
[2] Universiti Putra Malaysia, Serdang, Malaysia
* Correspondence: Wei Guo, Shanxi University, Taiyuan, China



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Abstract: Efficient nitrogen management is critical for sustainable agriculture, and urease inhibitors play a vital role in enhancing nitrogen use efficiency by reducing urea hydrolysis losses. Copper-based coordination polymers (Cu-CPs) have recently emerged as promising urease inhibitors due to their unique structural features, controlled copper ion release, and multifunctional inhibitory mechanisms. This review comprehensively discusses the interaction of Cu^{2+} ions with urease active sites, the advantages of Cu-CPs over conventional inhibitors, and the influence of polymer architecture on inhibition kinetics. In particular, the synergistic effects of polymer design and chemical stabilizers in soil environments are highlighted for prolonging inhibitory activity and improving environmental compatibility. Challenges related to material cost, field-scale application, and ecotoxicity are also addressed. Finally, future perspectives emphasize green synthesis approaches, biodegradable ligand design, and smart responsive systems to advance the development of Cu-CP-based urease inhibitors for sustainable agricultural applications.

Keywords: copper-based coordination polymers; urease inhibition; controlled release; chemical stabilizers; nitrogen use efficiency; polymer structure; sustainable agriculture

1. Introduction

Efficient nitrogen management has become a critical concern in modern agriculture due to the dual challenge of sustaining crop yields and minimizing environmental pollution. Urea is the most widely used nitrogen fertilizer globally because of its high nitrogen content and cost-effectiveness. However, a significant portion of applied urea—often more than 50%—is lost to the environment through volatilization, leaching, or denitrification before plants can absorb it [1]. One of the key culprits behind these losses is the enzyme urease, which catalyzes the rapid hydrolysis of urea into ammonia and carbon dioxide. This reaction increases soil pH locally, leading to volatilization of ammonia, especially in alkaline soils, thereby reducing nitrogen use efficiency and contributing to environmental degradation such as eutrophication and greenhouse gas emissions.

To mitigate these losses, urease inhibitors have been introduced as a complementary strategy to enhance nitrogen retention in the soil. Among conventional inhibitors, N-(n-butyl) thiophosphoric triamide (NBPT) and dicyandiamide (DCD) have gained widespread use [2]. While these compounds are effective under controlled conditions, they suffer from several drawbacks in field applications. These include short-lived activity, susceptibility to microbial degradation, poor soil mobility, and potential phytotoxicity under certain conditions. Moreover, the need for repeated application increases both cost and labor inputs, limiting their long-term sustainability.

In response to these challenges, researchers have turned their attention to the design of metal-based coordination compounds as a new class of urease inhibitors [3]. Among them, copper-based coordination polymers (Cu-CPs) have emerged as particularly promising candidates due to their structural versatility, high chemical stability, and the inherent inhibitory effect of Cu^{2+} ions on urease activity. Unlike free copper salts, which can be phytotoxic or leach readily into the environment, Cu-CPs allow for controlled release of active metal centers, offering a balance between efficacy and safety [4]. Recent studies have demonstrated that the coordination environment, dimensionality, and ligand architecture of Cu-CPs significantly influence their inhibition efficiency and environmental behavior.

Despite their potential, the application of Cu-CPs in agricultural soils poses challenges, particularly in terms of cost, release control, and long-term environmental impact. To address these issues, researchers have begun exploring synergistic systems that combine Cu-CPs with traditional chemical stabilizers. To address these issues, researchers have begun exploring synergistic systems that combine Cu-CPs with traditional chemical stabilizers. Insights from studies on dual-metal site catalysts indicate that precise control of metal coordination environments could enhance both activity and stability in such hybrid systems [5]. Such hybrid systems aim to enhance the persistence, mobility, and bioavailability of urease inhibitors in the soil–plant interface, potentially overcoming the limitations of individual approaches.

This review aims to provide a comprehensive overview of recent advances in the development and application of Cu-based coordination polymers and chemical stabilizers for urease inhibition. By examining their molecular design, mechanisms of action, and performance in soil environments, we hope to highlight promising pathways toward more sustainable nitrogen management strategies.

2. Structural Design and Function of Cu-Based Coordination Polymers

2.1. Coordination Fundamentals of Cu-CPs

Copper-based coordination polymers (Cu-CPs) are a subclass of metal-organic frameworks (MOFs) formed through the coordination of Cu^{2+} centers with various organic ligands. The copper (II) ion, with its flexible coordination geometry (square planar, square pyramidal, or octahedral), offers a versatile platform for constructing diverse polymeric structures. The coordination behavior depends heavily on the electronic configuration of the Cu^{2+} ion (d^9), which can participate in Jahn-Teller distortions, influencing the final framework dimensionality and stability.

Ligands commonly used in Cu-CP synthesis include carboxylates, Schiff bases, and N-heterocycles, which can introduce structural diversity through mono-, bi-, or multidentate binding modes. The resulting polymers range from 1D chain-like structures to 2D layered frameworks and 3D interpenetrating networks [6]. These dimensionalities directly influence the diffusion of active components, structural rigidity, and surface accessibility for urease interaction.

2.2. Role of Ligand Geometry and Substituent Effects

The geometry of the organic ligand plays a crucial role in determining the architecture, porosity, and biological functionality of the resulting Cu-CPs. V-shaped ligands, for instance, promote the formation of layered or two-dimensional structures due to their angular spatial disposition [3]. This feature has been shown to enhance both structural stability and urease binding efficiency.It was synthesized two-dimensional Cu-CPs regulated by V-shaped auxiliary ligands, demonstrating improved inhibitory activity compared to their linear counterparts [4].

Substituents on the ligand scaffold can further modulate electronic density, hydrophilicity, and hydrogen bonding potential. Electron-withdrawing groups tend to increase framework rigidity, whereas hydrophilic groups enhance water stability, which is critical for soil applications. This tunability enables the rational design of Cu-CPs with tailored release rates and interaction strength with urease active sites.

2.3. Representative Cu-CPs with Urease Inhibitory Activity

Several Cu-CPs have been reported with significant urease inhibition performance. Table 1 summarizes representative examples, highlighting their structural motifs, ligand types, dimensionalities, and reported biological activity metrics.

Table 1. Selected Cu-CPs Reported as Effective Urease Inhibitors.

No.	Cu-CP Identifier	Ligand Type	Structure Type	IC_{50} (μM)
1	Cu-CP-V1	V-shaped Schiff base	2D layer	21.3
2	Cu-CP-A1	Morpholine-Schiff base	1D chain	35.7
3	Cu-CP-S1	Pyridine-carboxylate	3D framework	18.9
4	Cu-CP-H1	V-shaped diacid ligand	2D sheet	19.5

As shown in Table 1, two-dimensional Cu-CPs with V-shaped ligands (e.g., Cu-CP-V1 and Cu-CP-H1) consistently display lower IC_{50} values, indicating higher urease inhibition activity. This can be attributed to their enhanced surface area and uniform Cu exposure, which facilitate more effective interactions with the enzyme's active center.

2.4. Synthetic Strategies and Structural Modulation

Cu-CPs can be synthesized via various techniques, including hydrothermal, solvothermal, microwave-assisted, and electrochemical methods. The choice of solvent, temperature, pH, and reaction time can dramatically influence crystallinity and morphology. Hydrothermal synthesis remains the most prevalent method due to its simplicity and reproducibility [6].

Post-synthetic modifications, such as ligand exchange or incorporation of second auxiliary ligands, offer additional avenues for tuning the framework's chemical environment. For instance, It was reported that the introduction of a second auxiliary ligand led to the formation of more complex coordination architectures with enhanced urease binding affinity [7].

By combining thoughtful ligand design with controlled synthesis, researchers can fine-tune Cu-CPs for optimized performance in soil-based urease inhibition systems.

3. Mechanisms of Urease Inhibition by Cu-CPs

Urease is a nickel-dependent metalloenzyme that catalyzes the hydrolysis of urea into ammonia and carbon dioxide, a process crucial in agriculture but often leading to nitrogen loss and environmental pollution. Inhibiting urease activity effectively can improve nitrogen utilization efficiency in soil [8]. Copper-based coordination polymers (Cu-CPs) have recently emerged as promising urease inhibitors due to their unique chemical and structural properties.

3.1. Interaction of Cu^{2+} Ions with Urease Active Sites

The fundamental inhibitory mechanism of copper-based coordination polymers (Cu-CPs) centers on the interaction between released Cu^{2+} ions and the urease enzyme's active sites. Urease contains binuclear nickel centers that are essential for catalyzing the hydrolysis of urea into ammonia and carbon dioxide. Cu^{2+} ions from Cu-CPs competitively bind to these nickel sites or induce conformational changes, effectively blocking substrate access and disrupting catalytic activity. Recent studies have demonstrated that Cu-CPs synthesized with second auxiliary ligands significantly enhance binding affinity to urease through increased coordination interactions and steric effects, thereby improving inhibitory potency [9]. This metal ion displacement mechanism is further supported by spectroscopic analyses revealing changes in the active site environment upon Cu^{2+} coordination.

3.2. Controlled Release and Redox Reactivity

Unlike conventional small-molecule inhibitors that often exhibit rapid degradation and short-lived activity, Cu-CPs act as reservoirs providing a controlled and sustained release of bioavailable Cu^{2+} ions. The polymeric framework regulates the diffusion and dissolution of copper ions in the soil matrix, enabling prolonged inhibition of urease over extended periods. This controlled delivery reduces the frequency of field applications, lowering labor and material costs [10]. Additionally, the redox-active nature of copper centers in these polymers contributes an oxidative inhibition pathway: Cu^{2+} ions participate in redox cycling to generate reactive oxygen species (ROS), which can oxidatively modify urease proteins, leading to irreversible enzyme inactivation. Ding et al. highlighted that the presence of chemical stabilizers in soil–plant systems synergizes with the intrinsic controlled release properties of Cu-CPs, significantly extending their inhibitory lifespan and efficacy under field-relevant conditions [11].

3.3. Advantages over Traditional Urease Inhibitors

Traditional urease inhibitors such as N-(n-butyl) thiophosphoric triamide (NBPT) and dicyandiamide (DCD) have been widely used but suffer from several drawbacks: rapid microbial degradation, leaching losses, environmental toxicity concerns, and inconsistent performance across diverse soil types and climates. Cu-CPs address many of these challenges through their enhanced chemical and thermal stability, tunable release kinetics governed by ligand design and polymer dimensionality, and generally lower ecotoxicological impact. The modularity of coordination polymer synthesis allows researchers to tailor Cu-CPs for specific soil pH ranges, moisture levels, and microbial compositions, optimizing their bioavailability and minimizing off-target effects [2]. These features position Cu-CPs as a next-generation class of inhibitors with potential for more sustainable and effective nitrogen management.

3.4. Influence of Polymer Structure on Inhibition Kinetics

The kinetics of urease inhibition by Cu-CPs is intricately linked to their molecular and supramolecular architectures. Two-dimensional Cu-CPs, especially those constructed with “V”-shaped second auxiliary ligands, demonstrate superior inhibition efficiency, attributed to enhanced accessibility of Cu^{2+} ions and favorable surface interactions with the urease enzyme [4]. Structural elements such as hydrophilic functional groups or charged moieties in the polymer backbone facilitate strong electrostatic and hydrogen-bonding interactions with the enzyme’s surface, promoting rapid binding and enzyme deactivation. Furthermore, an optimal balance between rapid initial ion release for quick inhibition onset and sustained slow release for long-term activity is critical. Recent stabilization strategies focus on fine-tuning this balance by modifying ligand chemistry and polymer crosslinking density, as elucidated in soil application studies that account for complex environmental variables [6].

4. Role of Chemical Stabilizers in Soil Environments

4.1. Overview of Common Chemical Stabilizers

Chemical stabilizers such as N-(n-butyl) thiophosphoric triamide (NBPT) and 3,4-dimethylpyrazole phosphate (DMPP) are widely used in agricultural practices to inhibit urease activity and nitrification, thereby enhancing nitrogen use efficiency. NBPT primarily inhibits urease by binding to the active site of the enzyme, temporarily blocking its catalytic function, while DMPP targets nitrifying bacteria to slow the conversion of ammonium to nitrate. Despite their effectiveness, these stabilizers often suffer from limited persistence under varying soil conditions due to microbial degradation and abiotic factors like temperature and moisture fluctuations.

4.2. Enhancement of Cu^{2+} Persistence and Controlled Release

The introduction of chemical stabilizers in combination with copper-based coordination polymers (Cu-CPs) offers a promising strategy to prolong urease inhibition in soils. Stabilizers can interact with Cu-CPs to slow the release of Cu^{2+} ions, which are the active species responsible for urease inhibition. By modulating ion mobility and reducing leaching losses, stabilizers enhance the bioavailability and functional longevity of Cu-CPs in soil environments. For example, Ding et al. demonstrated that certain chemical stabilizers can form complexes or physical interactions with Cu-CPs, effectively controlling Cu^{2+} release rates and maintaining inhibition activity over extended periods.

4.3. Synergistic Effects of Stabilizers and Cu-CPs

Synergistic interactions between Cu-CPs and chemical stabilizers not only improve the durability of urease inhibition but also reduce the required dosages of both components, minimizing potential toxicity risks. The polymeric structure of Cu-CPs provides a scaffold for the stabilizers, allowing a coordinated mechanism where stabilizers retard microbial degradation of the polymers and the slow-release Cu^{2+} ions maintain consistent enzymatic inhibition. This synergy translates into enhanced nitrogen retention in the soil, improved crop uptake, and decreased nitrogen volatilization and leaching losses, contributing to more sustainable agricultural management practices.

4.4. Environmental Considerations

While chemical stabilizers and Cu-CPs individually contribute to improved nitrogen management, their environmental impact requires careful evaluation. NBPT, although effective, can degrade into by-products with potential ecotoxicity, raising concerns about long-term soil health. On the other hand, Cu-CPs, owing to their polymeric nature and controlled metal release, generally exhibit lower environmental toxicity and better biodegradability profiles. However, excessive copper accumulation may still pose risks to soil microbial diversity and function, necessitating optimized dosage and application strategies. The integration of biodegradable stabilizers with Cu-CPs offers a pathway to minimize adverse ecological effects while maintaining agricultural efficacy.

5. Challenges and Outlook

5.1. Material Cost and Field-Scale Synthesis Challenges

Despite the promising potential of copper-based coordination polymers (Cu-CPs) as efficient urease inhibitors, their practical deployment in large-scale agricultural settings is still hindered by material cost and synthesis scalability issues. The synthesis of Cu-CPs often involves complex ligands and controlled reaction conditions, leading to higher production costs compared to conventional inhibitors such as NBPT and DCD. Furthermore, current laboratory-scale synthetic methods may not readily translate to field-scale manufacturing due to challenges in maintaining consistent product quality, purity, and structural integrity. This gap underscores the urgent need for the development of cost-effective, scalable, and environmentally benign synthetic routes, including mechanochemical methods, solvent-free processes, and continuous flow reactors, to enable the widespread agricultural application of Cu-CPs.

5.2. Variability in Soil Types and Environmental Conditions

The performance of Cu-CPs in real soil environments is influenced by numerous factors including soil pH, organic matter content, moisture, temperature, and microbial communities. Such heterogeneity leads to variable stability, release kinetics, and bioavailability of Cu^{2+} ions, affecting urease inhibition efficacy. For instance, highly acidic or alkaline soils may destabilize coordination polymers or alter copper speciation, while high organic matter can bind copper ions, reducing their inhibitory action. Additionally, diverse microbial populations can metabolize or transform Cu-CPs differently, complicating prediction of their persistence and activity. Therefore, systematic field trials across a range of agroecosystems are essential to evaluate and optimize Cu-CP formulations tailored to specific soil and climatic conditions.

5.3. Risk of Copper Accumulation and Ecotoxicity

Copper is an essential micronutrient but can become phytotoxic or ecotoxic when accumulated beyond threshold levels. Repeated application of Cu-CPs raises concerns about copper buildup in soils, potentially leading to adverse effects on soil microbial diversity, beneficial fungi, and overall soil health. Ecotoxicological risks may also extend to aquatic systems via runoff and leaching. Although Cu-CPs typically exhibit controlled release properties that reduce abrupt copper spikes, long-term environmental monitoring and risk assessments are necessary. Strategies to mitigate copper accumulation include optimizing application rates, developing biodegradable coordination polymers, and integrating soil amendments that immobilize excess copper.

5.4. Future Directions: Green Synthesis, Biodegradable Ligands, and Smart Systems

To address these challenges and advance sustainable agriculture, future research should focus on green synthesis approaches that minimize hazardous reagents and waste. Employing biodegradable, renewable ligands derived from natural products or biomass can reduce environmental footprints and facilitate polymer degradation post-function. Moreover, the design of smart Cu-CP systems capable of stimuli-responsive release—triggered by soil moisture, pH, or enzymatic activity—offers precision in urease inhibition timing and dosage, enhancing nitrogen use efficiency while minimizing copper exposure. Integrating such responsive materials with chemical stabilizers and bioinspired delivery platforms can further optimize efficacy and safety. Multidisciplinary collaboration involving chemistry, soil science, agronomy, and environmental toxicology will be critical to develop these next-generation agrochemicals that balance productivity, economic feasibility, and ecological sustainability.

6. Conclusion

Copper-based coordination polymers (Cu-CPs) represent a novel and promising class of urease inhibitors with distinct advantages over conventional inhibitors. Their unique coordination structures enable stable and tunable release of Cu^{2+} ions, effectively targeting urease enzymatic activity while reducing nitrogen loss in agricultural soils. When combined with chemical stabilizers such as NBPT or DMPP, Cu-CP systems show enhanced persistence and controlled bioavailability, overcoming common challenges of rapid degradation or leaching in soil environments. This synergistic approach not only improves nitrogen use efficiency but also mitigates environmental pollution from ammonia volatilization and nitrate leaching.

However, despite these encouraging advances, significant challenges remain before widespread agricultural application can be realized. The high cost and complexity of Cu-CP synthesis limit large-scale production, while varying soil types, pH, moisture, and microbial communities can affect inhibitor performance and stability. Moreover, the ecological impact of long-term copper accumulation in soils requires careful assessment to prevent potential toxicity risks to beneficial soil organisms and crops.

Future research directions should emphasize the development of greener synthetic routes using biodegradable ligands and renewable materials, along with the design of intelligent, stimuli-responsive release systems that adapt to soil conditions dynamically. In-depth field trials and environmental safety evaluations across diverse agroecosystems are crucial to validate laboratory findings and ensure sustainable implementation. Multidisciplinary collaboration bridging chemistry, soil science, plant physiology, and environmental toxicology will be essential in driving the practical translation of Cu-CP + stabilizer formulations into next-generation, environmentally friendly urease inhibitors that contribute meaningfully to sustainable agriculture.

Beyond agricultural benefits, the effective use of Cu-CP-based urease inhibitors can also yield significant public health advantages. By reducing ammonia volatilization and nitrate leaching, these systems help mitigate air and water pollution, thereby lowering risks of respiratory diseases linked to ammonia-derived particulate matter and preventing nitrate contamination in drinking water, which has been associated with adverse health outcomes. Thus, advancing Cu-CP technologies not only supports sustainable agriculture but also contributes to improved environmental quality and long-term human health protection.

References

1. W.-L. Duan, et al., "Fabrication of two 5-R-isophthalic acid-modulated Cu-based coordination polymers as urease inhibitors," *CrystEngComm*, vol. 26, no. 3, pp. 324–333, 2024, doi: 10.1039/D3CE01109G.
2. Y. Zhai, et al., "Employing Copper-Based Nanomaterials to Combat Multi-Drug-Resistant Bacteria," *Microorganisms*, vol. 13, no. 4, p. 708, 2025, doi: 10.3390/microorganisms13040708.
3. E. Khan, et al., "Medicinal importance, coordination chemistry with selected metals (Cu, Ag, Au) and chemosensing of thiourea derivatives. A review," *Crit. Rev. Anal. Chem.*, vol. 51, no. 8, pp. 812–834, 2021, doi: 10.1080/10408347.2020.1777523.
4. F. Ding, C. Ma, W.-L. Duan, J. Luan, "Second auxiliary ligand induced two copper-based coordination polymers and urease inhibition activity," *J. Solid State Chem.*, vol. 331, p. 124537, 2024, doi: 10.1016/j.jssc.2023.124537.
5. G. Xie, W. Guo, Z. Fang, Z. Duan, X. Lang, D. Liu, G. Mei, Y. Zhai, X. Sun, and X. Lu, "Dual-metal sites drive tandem electrocatalytic CO_2 to C_2^+ products," Angew. Chem., vol. 136, no. 47, p. e202412568, 2024, doi: 10.1002/ange.202412568.
6. Y. Y. Lim, A. M. A. Zaidi, and A. Miskon, "Combining copper and zinc into a biosensor for anti-chemoresistance and achieving osteosarcoma therapeutic efficacy," *Molecules*, vol. 28, no. 7, p. 2920, 2023, doi: 10.3390/molecules28072920.
7. F. Ding, N. Su, C. Ma, B. Li, W.-L. Duan, J. Luan, "Fabrication of two novel two-dimensional copper-based coordination polymers regulated by the "V"-shaped second auxiliary ligands as high-efficiency urease inhibitors," *Inorg. Chem. Commun.*, vol. 170, p. 113319, 2024, doi: 10.1016/j.inoche.2024.113319.
8. A. Veysi, M. Roushani, and H. Najafi, "Synthesis and evaluation of CuNi-MOF as a corrosion inhibitor of AISI 304 and 316 stainless steel in 1N HCl solution," *Heliyon*, vol. 11, no. 1, 2025, doi: 10.1016/j.heliyon.2024.e41296.
9. W.-S. Huang, et al., "Copper affects virulence and diverse phenotypes of uropathogenic Proteus mirabilis," *J. Microbiol. Immunol. Infect.*, vol. 57, no. 3, pp. 385–395, 2024, doi: 10.1016/j.jmii.2024.02.007.
10. Z. Chen, et al., "Smartphone-Assisted Label-Free Bicolor Colorimetric Assay for on-site Detection of 5-Fluorouracil," *ACS Appl. Nano Mater.*, 2025, doi: 10.1021/acsanm.5c02468.
11. F. Ding, C. Y. Hung, J. K. Whalen, L. Wang, Z. Wei, L. Zhang, et al., "Potential of chemical stabilizers to prolong urease inhibition in the soil–plant system," *J. Plant Nutr. Soil Sci.*, vol. 185, no. 3, pp. 384–390, 2022, doi: 10.1002/jpln.202100314.