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Sustainable Urease Inhibition in Agriculture: Advances in Chemical Stabilizers and Copper Coordination Polymers

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Abstract: Urease-mediated hydrolysis of urea fertilizer leads to significant nitrogen losses through ammonia volatilization and environmental pollution, posing challenges to sustainable agriculture. Effective urease inhibition is crucial for enhancing nitrogen use efficiency (NUE) and minimizing ecological impact. This review examines two promising strategies for urease inhibition: traditional chemical stabilizers and emerging copper coordination polymers (Cu-CPs) engineered via second auxiliary ligands. Chemical stabilizers such as NBPT have demonstrated rapid urease inhibition but suffer from limitations including short duration and environmental instability. In contrast, Cu-CPs offer tunable structural features and sustained release properties, enabling prolonged urease inhibition alongside multifunctional benefits such as antimicrobial activity. Comparative analyses highlight potential synergies between these approaches, including hybrid formulations that combine immediate and long-lasting effects. Key challenges such as environmental safety, field-level validation, and mechanistic understanding are discussed. Finally, the review advocates for a systems-based interdisciplinary approach to develop eco-friendly, cost-effective urease inhibitors that support sustainable nitrogen management and global food security.

Keywords: urease inhibition; nitrogen use efficiency; chemical stabilizers; copper coordination polymers; second auxiliary ligands

1. Introduction: Urea Use and Environmental Concerns

Urea is the most extensively used nitrogen (N) fertilizer in global agriculture, accounting for more than 50% of nitrogen fertilizer consumption in many regions. Its high nitrogen content (approximately 46%), low production cost, and ease of handling have made it a cornerstone of modern crop production systems. In countries such as China, India, and the United States, urea plays a critical role in securing food supply and boosting crop yields [1]. However, despite its agronomic benefits, urea suffers from a major drawback: its rapid hydrolysis in soil environments due to the action of the ubiquitous enzyme urease.

Urease-mediated hydrolysis of urea occurs within hours of application, converting urea into ammonium and carbon dioxide. This reaction causes a localized spike in soil pH, promoting the volatilization of ammonia gas (NH_3). Under alkaline and high-temperature conditions, ammonia losses can reach up to 50% of the applied nitrogen, representing a significant waste of resources. Furthermore, the subsequent transformation of ammonium to nitrate (NO_3^-) through nitrification contributes to nitrate leaching into groundwater and the release of nitrous oxide (N_2O), a greenhouse gas with a global warming potential approximately 300 times greater than that of carbon dioxide. These environmental consequences not only reduce nitrogen use efficiency (NUE) but also contribute to air pollution, water eutrophication, and climate change.

To address these challenges, the use of urease inhibitors has emerged as a promising strategy. Urease inhibitors are compounds that temporarily suppress the activity of urease, thereby slowing the conversion of urea and reducing nitrogen losses. This results in improved NUE, prolonged nitrogen availability in the root zone, and reduced environmental impact. The development of effective urease inhibitors is crucial for advancing sustainable agricultural practices, especially in the context of rising environmental regulations and the global push for climate-smart farming.

Recent research has identified two promising directions in the development of urease inhibition technologies: chemical stabilizers and copper-based coordination polymers (Cu-CPs). Chemical stabilizers such as NBPT (N-(n-butyl) thiophosphoric triamide) have been widely studied and commercialized. On the other hand, Cu-CPs represent a novel and multifunctional class of materials with potential applications in both urease inhibition and soil catalysis. This review explores the recent advances in these two approaches, highlighting their mechanisms, efficiencies, and roles in promoting sustainable nitrogen management in agricultural systems.

2. Urease Enzyme: Structure, Function, and Inhibition Mechanism

2.1. Structure and Catalytic Mechanism of Urease

Urease is a nickel-dependent metalloenzyme that catalyzes the hydrolysis of urea into ammonia and carbon dioxide. It is found in various microorganisms, plants, and some invertebrates, playing a crucial role in the nitrogen cycle. Structurally, urease is composed of multiple subunits that form a highly conserved active site pocket where the catalytic reaction occurs. The active site typically contains two nickel (Ni^{2+}) ions co-ordinated by histidine and lysine residues, bridged by a carbamylated lysine and hydroxide ion. These features create a unique geometry essential for efficient urea hydrolysis. The cooperative action of these dual-metal centers resembles tandem-catalysis strategies observed in other systems, such as dual-metal site electrocatalysts for CO_2-to-C_2^+ conversion [2], highlighting the importance of proximity and synergy between metal centers for multi-step transformations.

The catalytic process involves the nucleophilic attack of a bridging hydroxide on the carbonyl carbon of urea, leading to the formation of ammonia and carbamate, which spontaneously decomposes into another ammonia molecule and carbon dioxide. This rapid reaction contributes to the localized rise in soil pH and subsequent nitrogen losses when urea is applied as fertilizer.

2.2. Importance of Nickel at the Active Site

The nickel ions in urease are indispensable for its activity. They play a dual role: stabilizing the urea substrate via coordination and activating the hydroxide nucleophile necessary for catalysis. Removing or replacing these metal ions results in complete loss of function, making the Ni^{2+} centers a prime target for inhibitor development.

Several studies have shown that metal ions such as Cu^{2+} and Zn^{2+} can effectively interfere with the function of urease by displacing Ni^{2+} or modifying the local coordination environment [3]. This disruption prevents the correct orientation and activation of urea, thereby halting the catalytic process.

2.3. Mechanisms of Urease Inhibition

Urease inhibitors operate through various mechanisms, most commonly competitive inhibition and structural interference. Competitive inhibitors mimic the urea molecule and occupy the active site without undergoing hydrolysis, thereby blocking access for the actual substrate [4]. Structural inhibitors, on the other hand, interact with peripheral or allosteric sites to induce conformational changes that inactivate the enzyme.

For example, copper ions and their coordination complexes can bind to the urease protein surface or enter the active site cavity, modifying the local geometry and reducing catalytic efficiency [5]. These inhibitors often form stable complexes with amino acid residues such as cysteine, histidine, or aspartate, which are critical for maintaining urease structure and function.

2.4. Rationale for Using Metal-Based Inhibitors

Metal-based urease inhibitors, especially those based on Cu^{2+} and Zn^{2+}, are gaining attention due to their high affinity for protein functional groups and their redox activity [6]. These ions can interact with urease through coordination or redox-based mechanisms, disrupting the enzyme's native structure.

Recent work on copper-based coordination polymers (Cu-CPs) demonstrates that second auxiliary ligands can enhance the exposure of Cu^{2+} ions, increasing their interaction with urease and thereby improving inhibitory performance [3]. Moreover, these materials offer tunable structures, stability under soil conditions, and potential multifunctionality, making them ideal candidates for sustainable agricultural applications.

3. Chemical Stabilizers: Mechanism, Applications, and Limitations

3.1. Commercial Urease Inhibitors

Urease inhibitors are a cornerstone in modern nitrogen fertilizer management, helping to reduce nitrogen losses and improve nitrogen use efficiency (NUE). The most commonly used commercial inhibitors include N-(n-butyl) thiophosphoric triamide (NBPT), N-propyl thiophosphoric triamide (NPPT), hydroquinone (HQ), and ammonium thiosulfate (ATS). These compounds are typically applied as coatings to urea granules or mixed with liquid fertilizers [7].

NBPT remains the gold standard in commercial use due to its high efficacy and compatibility with most soil types and crops. It functions by temporarily deactivating the urease enzyme, thereby delaying urea hydrolysis.

3.2. Mechanism of Action

These inhibitors primarily function by interfering with the catalytic center of urease, which relies on nickel ions. By mimicking urea or coordinating with the active site metals, they inhibit the conversion of urea to ammonia.

NBPT, in particular, acts by chelating the nickel atoms at the active site of urease, temporarily rendering the enzyme inactive and reducing the rate of hydrolysis [5].

This delay enables plants to absorb more nitrogen before it is lost through volatilization or leaching [7].

3.3. Limitations in Field Applications

Despite their effectiveness, chemical stabilizers face several limitations under real-world conditions [8]. Environmental factors such as temperature, soil pH, and microbial activity can accelerate the degradation of these inhibitors. For instance, NBPT can degrade rapidly in acidic or alkaline environments, or under intense microbial activity.

The inhibitory effect of most commercial compounds typically lasts only 5–10 days. This short effective window often fails to match the crop's nitrogen uptake timeline, resulting in suboptimal nutrient use. Moreover, their performance is inconsistent in soils with extreme properties, such as saline or organic-rich soils.

3.4. Recent Developments

To overcome these challenges, researchers have explored new delivery systems, such as nanocarriers and slow-release coatings. These approaches aim to protect the active inhibitor from degradation and extend its release over time [9].

Some studies have also explored combining urease inhibitors with other soil amendments, including micronutrients and biochar, to enhance stability and synergistic effects.

3.5. Summary and Emerging Directions

Chemical stabilizers have played a pivotal role in reducing nitrogen loss and increasing NUE, but their environmental instability remains a bottleneck. Newer technologies have improved their delivery and longevity, but solutions are still largely incremental.

To address the durability and specificity challenges, researchers have turned to alternative materials such as copper-based coordination polymers, which offer both catalytic inhibition and structural resilience.

These Cu-CPs have shown promising results in prolonging urease inhibition across different soil conditions [5].

4. Copper Coordination Polymers (Cu-CPs): A Promising Alternative

4.1. Overview of Copper Coordination Polymers and Their Unique Role

Copper coordination polymers (Cu-CPs) are crystalline or semi-crystalline materials composed of copper ions connected through organic ligands to form extended frameworks [10]. These frameworks exhibit rich structural diversity, spanning from one-dimensional chains to two-dimensional layers and three-dimensional networks. The coordination chemistry of copper is especially versatile due to its accessible oxidation states, predominantly Cu (I) and Cu (II), which enable flexible coordination geometries such as square planar, tetrahedral, and octahedral.

Copper's prominence in biological systems as an essential trace element and its inherent redox properties make Cu-CPs particularly suitable for catalytic and inhibitory functions. In agriculture, copper-based compounds have long been used as fungicides and micronutrients, highlighting their dual role in plant health and microbial control. Leveraging copper in coordination polymer frameworks allows for the design of multifunctional materials that combine catalytic activity with structural robustness [11].

4.2. Engineering Cu-CPs via Second Auxiliary Ligands: Modulating Structure and Function

One of the most effective strategies to optimize Cu-CPs is through second auxiliary ligand engineering. Unlike primary ligands that directly bind to metal centers forming the backbone of the polymer, second auxiliary ligands serve as additional linkers or modulators that influence the polymer's overall topology, porosity, and stability.

The introduction of diverse second auxiliary ligands—such as aromatic carboxylates, bipyridine derivatives, and specially designed "V"-shaped heterocyclic molecules—enables precise tuning of the Cu-CP architecture [11]. These ligands can expand or restrict the spatial arrangement of copper centers, thus controlling network dimensionality from 1D chains to highly ordered 2D or 3D frameworks.

Structurally, second auxiliary ligands enhance pore size distribution and improve surface area, facilitating greater exposure of catalytically active copper sites. This improved accessibility is crucial for inhibiting urease activity efficiently, as the enzyme interacts directly with copper centers at the molecular interface.

4.3. Recent Advances in Cu-CPs for Urease Inhibition: Performance and Mechanisms

Recent research has focused on synthesizing Cu-CPs with tailored second auxiliary ligands to maximize urease inhibition performance. For example, Cu-CPs constructed using "V"-shaped heterocyclic second auxiliary ligands form stable 2D layered structures that demonstrate prolonged and potent urease inhibition activity [3]. These materials exhibit high catalytic site density and increased framework stability under soil conditions, outperforming conventional chemical inhibitors in durability and efficacy.

Mechanistically, Cu-CPs inhibit urease by interacting with the nickel active sites of the enzyme, potentially through competitive binding or allosteric modulation [12]. The coordination polymers serve as a scaffold that holds copper ions in optimal orientations to disrupt urease catalytic activity effectively.

Additionally, these Cu-CPs exhibit enhanced resistance to environmental degradation, owing to their rigid and ordered frameworks, which protect active copper centers from rapid leaching or transformation in complex soil matrices. This sustained activity addresses one of the key limitations of traditional inhibitors—their short-lived performance under field conditions.

4.4. Advantages and Challenges of Using Cu-CPs in Agriculture

4.4.1. Cu-CPs offer significant advantages as next-generation urease inhibitors:

1) Structural Tunability: By altering the second auxiliary ligands and synthesis conditions, Cu-CPs' pore sizes, surface areas, and coordination environments can be tailored for specific inhibitory strengths and selectivities.
2) Dual Functionalities: Beyond urease inhibition, Cu-CPs may confer antimicrobial effects, improve nutrient uptake, or serve as carriers for other agrochemicals, enhancing overall soil and plant health.
3) Sustained Release and Stability: The coordination framework's robustness allows gradual release or persistent surface interaction of copper ions, leading to longer-lasting urease suppression compared to conventional chemical inhibitors.

4.4.2. However, several challenges remain:

1) Copper Toxicity Risk: Excess copper can harm beneficial soil microbiota and plant roots. Therefore, the dosage and environmental fate of Cu-CPs must be carefully optimized to balance efficacy and safety.
2) Environmental Impact and Degradability: The persistence of Cu-CPs in soil and potential accumulation in water bodies necessitate thorough ecotoxicological assessments.
3) Synthesis Scalability and Cost: While Cu is relatively inexpensive, the synthesis of complex Cu-CPs with sophisticated ligands may increase production costs. Research into cost-effective and scalable synthetic routes is required for practical agricultural deployment.

4.5. Future Perspectives

Ongoing research aims to design Cu-CPs with enhanced biocompatibility and targeted activity by incorporating biodegradable ligands or responsive functional groups. Integrating Cu-CPs into composite formulations or hybrid materials may also improve application flexibility and environmental safety.

In summary, Cu-CPs represent a promising and versatile class of urease inhibitors, combining tunable structural features with potent catalytic activity. Continued innovation in second auxiliary ligand design and sustainable synthesis methods will be crucial to realize their full potential in sustainable agriculture.

5. Synergies and Comparative Perspectives

5.1. Comparative Analysis: Chemical Stabilizers vs. Copper Coordination Polymers

Chemical stabilizers such as NBPT and NPPT have been widely adopted due to their rapid and effective urease inhibition, allowing immediate reduction of ammonia volatilization and improved nitrogen use efficiency (NUE) in various cropping systems. However, their effectiveness is often limited by environmental factors such as temperature, pH, and microbial degradation, leading to a relatively short period of inhibition under field conditions.

In contrast, copper coordination polymers (Cu-CPs) offer a more sustained urease inhibitory effect due to their stable framework structures and controlled release of active copper ions. The tunable architecture of Cu-CPs allows for prolonged interaction with urease enzymes, enhancing durability even in complex soil environments. Nevertheless, Cu-CPs often require longer time to achieve full inhibitory activity, which can delay initial nitrogen conservation benefits compared to chemical stabilizers.

Thus, the main trade-off between these two approaches lies in the balance of fast initial action by chemical stabilizers versus long-term inhibition and multifunctionality by Cu-CPs.

5.2. Potential for Hybrid Formulations

Combining chemical stabilizers with Cu-CPs in hybrid formulations may synergize their respective advantages. A fast-acting chemical stabilizer could provide immediate urease inhibition, while the Cu-CP component ensures sustained release and prolonged activity. Such integration could optimize nitrogen retention over both short and long timescales.

Additionally, hybrid systems could be engineered to leverage the multifunctional properties of Cu-CPs, such as antimicrobial activity and enhanced soil nutrient cycling, thereby broadening agronomic benefits beyond urease inhibition.

5.3. Compatibility with Soil Types, Crops, and Fertilizer Management

The performance of urease inhibitors is strongly influenced by soil properties such as pH, organic matter content, and microbial communities, as well as crop type and fertilization practices. Chemical stabilizers tend to be more effective in neutral to slightly acidic soils but degrade rapidly in alkaline or highly aerobic conditions.

Cu-CPs' stability in diverse soil environments, including acidic and calcareous soils, provides a wider operational window for agricultural applications. However, concerns about copper accumulation necessitate site-specific risk assessments.

Tailoring inhibitor choice or formulation based on soil-crop-fertilizer combinations will enhance NUE while mitigating environmental risks. Precision agriculture tools and soil monitoring can facilitate such optimized management.

5.4. Field Trial Insights and Emerging Interdisciplinary Approaches

Although lab-scale studies have demonstrated the promising potential of Cu-CPs, large-scale field trials remain limited but are critical to validate efficacy and environmental safety under realistic agronomic conditions. Initial reports indicate that Cu-CPs can reduce ammonia volatilization comparable to chemical stabilizers with added benefits of prolonged action.

Interdisciplinary research integrating materials chemistry, soil science, microbiology, and agronomy is crucial to design next-generation urease inhibitors. Advances in nanotechnology, responsive release systems, and bio-inspired materials are expected to drive innovation.

6. Future Directions and Conclusions

6.1. Summary of Key Findings

In recent years, the development of urease inhibitors has gained momentum due to the urgent need for sustainable nitrogen management in agriculture. Chemical stabilizers, including NBPT, NPPT, and related compounds, have proven effective for rapid urease inhibition and immediate reduction of nitrogen losses. However, their limitations such as environmental degradation and short-lived efficacy restrict their broader application. Meanwhile, copper coordination polymers (Cu-CPs) have emerged as a promising alternative, offering tunable structures through second auxiliary ligand engineering, sustained release of inhibitory copper ions, and multifunctionality that extends beyond urease inhibition, such as antimicrobial activity and improved soil nutrient cycling.

The comparative advantages and challenges of chemical stabilizers and Cu-CPs emphasize the potential for hybrid formulations and integrated approaches to maximize nitrogen use efficiency (NUE) while mitigating environmental impacts.

6.2. Research Needs and Challenges

Despite the encouraging laboratory-scale results and preliminary field trials, several key research gaps remain:

Ecotoxicity and Environmental Safety: The fate of copper ions released from Cu-CPs in soil ecosystems needs thorough assessment. Potential copper accumulation and toxicity risks to soil biota, crops, and groundwater require comprehensive evaluation through long-term environmental monitoring.

Field-Level Efficacy: Robust, large-scale field trials across diverse agroecosystems are essential to validate the practical performance, dosage optimization, and economic feasibility of Cu-CPs compared with conventional stabilizers.

Long-Term Performance and Stability: The durability of urease inhibition over multiple cropping seasons, interactions with soil microbiomes, and resilience against variable climatic conditions must be systematically studied.

Mechanistic Understanding: Advanced spectroscopic and microscopic techniques can provide deeper insights into the molecular interactions between Cu-CPs, urease enzymes, and soil components, guiding rational design improvements.

6.3. Encouraging a Systems-Based Approach

Addressing these challenges requires an interdisciplinary, systems-based framework that integrates:

Material Science: To innovate novel Cu-CP architectures with optimized ligand designs for controlled release and minimal environmental footprint.

Agronomy: To tailor inhibitor formulations suited to specific crop needs, soil types, and fertilization regimes, enhancing NUE and crop yield.

Environmental Science: To assess ecological risks and devise sustainable deployment strategies ensuring soil health and biodiversity conservation.

Policy and Economics: To evaluate cost-benefit analyses and promote adoption of advanced inhibitors through regulatory frameworks and farmer education.

Such a holistic approach will accelerate the translation of fundamental research into practical, eco-friendly agricultural technologies.

6.4. Concluding Remarks

Urease inhibition remains a cornerstone strategy for sustainable nitrogen management in modern agriculture. Chemical stabilizers and copper coordination polymers each offer unique advantages and face distinct limitations. Integrating these approaches through hybrid formulations and leveraging interdisciplinary innovations will be pivotal in overcoming current barriers.

Ultimately, advancing functional Cu-CPs with controlled urease inhibition capability and ensuring their safe, effective field application represents a significant step toward reducing nitrogen losses, minimizing environmental pollution, and supporting global food security under changing climatic conditions.

Continued research, collaboration, and responsible stewardship are essential to realize the full potential of these promising materials in creating a more sustainable agricultural future.

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