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Article

Progress in the Design of V-Shaped Ligand-Regulated Copper-Based Coordination Polymers for Urease Inhibition

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Abstract: Urease inhibitors play a critical role in enhancing nitrogen use efficiency in agriculture by reducing nitrogen loss through ammonia volatilization. Copper-based coordination polymers (Cu-CPs) have emerged as promising urease inhibitors due to their tunable structures and functional versatility. Among various ligand designs, V-shaped auxiliary ligands uniquely direct the formation of two-dimensional Cu-CP architectures with enhanced exposure of active copper sites, leading to superior inhibitory performance. This review summarizes recent advances in the synthesis, structural characteristics, and urease inhibition mechanisms of V-shaped ligand-regulated Cu-CPs. Key synthetic strategies, including solvothermal and hydrothermal methods, are discussed alongside comprehensive characterization techniques. The synergistic role of stabilizers in prolonging inhibitory effects and minimizing environmental impacts is also examined. Finally, challenges and future perspectives for the development and application of Cu-CPs in sustainable agriculture are outlined, emphasizing the potential of ligand engineering to optimize functional properties.

Keywords: copper-based coordination polymers; urease inhibition; V-shaped auxiliary ligands; nitrogen use efficiency; sustainable agriculture

1. Introduction

Urease is a nickel-dependent metalloenzyme that catalyzes the hydrolysis of urea into ammonia and carbon dioxide. This reaction significantly contributes to nitrogen loss in agricultural soils through ammonia volatilization and nitrate leaching, leading to reduced fertilizer use efficiency and environmental pollution. Consequently, urease inhibitors have attracted considerable attention as effective agents to slow down urea hydrolysis, improve nitrogen utilization, and promote sustainable agriculture [1].

Among various inhibitors, copper-based coordination polymers (Cu-CPs) have emerged as promising candidates due to their unique combination of tunable structure, bioactivity, and stability. The ability to design Cu-CPs with specific geometries and functional groups enables targeted interaction with urease enzymes, enhancing inhibitory efficiency.

In recent years, the introduction of V-shaped auxiliary ligands into Cu-CP frameworks has provided new opportunities for structural control and performance optimization [2]. These ligands influence the dimensionality and porosity of the resulting polymers, promoting the formation of two-dimensional networks that facilitate better enzyme interaction and stability.

This review aims to summarize recent progress in the design and synthesis of V-shaped ligand-regulated Cu-CPs for urease inhibition. Key aspects covered include the

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structural features of Cu-CPs influenced by V-shaped ligands, synthetic approaches, urease inhibition mechanisms, and potential applications in soil and plant systems [3]. By providing a comprehensive overview, this article seeks to guide future research towards the development of efficient and environmentally friendly urease inhibitors based on copper coordination chemistry.

2. Copper-Based Coordination Polymers for Urease Inhibition

2.1. Structural Features and Functional Advantages of Cu-CPs

Copper-based coordination polymers (Cu-CPs) are a class of crystalline materials constructed from the coordination bonds between copper ions (Cu^{2+}) and organic ligands. These materials exhibit a broad range of architectures, spanning from one-dimensional chains and two-dimensional layers to three-dimensional frameworks, depending on the ligand type and synthesis conditions [4]. The intrinsic redox properties of copper combined with the versatile coordination chemistry provide Cu-CPs with unique structural and functional characteristics.

The coordination geometry around Cu^{2+} ions can vary, commonly adopting square planar, tetrahedral, or octahedral arrangements. Such diversity is influenced by the electronic configuration of copper and the steric and electronic properties of the ligands. This variability enables researchers to tailor pore size, shape, and connectivity within the polymer network, thereby tuning surface area and the accessibility of catalytic or active sites [5,6]. These features are essential for interaction with target biomolecules, such as urease enzymes.

Additionally, Cu-CPs can act as reservoirs for copper ions, allowing their controlled release into the environment. This sustained copper ion availability can maintain prolonged inhibitory activity against urease, overcoming limitations of simple copper salts that often leach quickly or degrade. Moreover, the structural robustness of Cu-CPs often ensures stability under various environmental conditions, which is crucial for their practical application in agriculture.

2.2. Traditional and Emerging Copper-Based Urease Inhibitors

Historically, urease inhibition using copper compounds involved the application of simple copper salts or low-molecular-weight copper complexes. While these agents demonstrate some inhibitory activity, they are often hampered by rapid degradation, poor selectivity, and environmental toxicity concerns. Their non-specific action can negatively affect soil microbiota and crop health.

In recent years, the design of copper-based coordination polymers has emerged as a more advanced strategy, leveraging the ability to engineer ligand environments and polymeric structures to improve performance. Cu-CPs provide enhanced stability, tunable release profiles, and specific interactions with urease, which lead to more effective and longer-lasting inhibition.

Recent progress includes the successful synthesis of Cu-CPs incorporating secondary auxiliary ligands that regulate structural topology and enhance functional properties. For instance, Ding et al. fabricated two novel copper coordination polymers using V-shaped second auxiliary ligands, resulting in materials with significantly improved urease inhibitory activity compared to previous models [5]. These studies underscore the critical role of ligand design in modulating both structure and bioactivity.

Moreover, the multifunctionality of Cu-CPs extends beyond urease inhibition; they often possess antimicrobial properties that further contribute to soil health and plant protection [7,8]. Their environmental compatibility and potential biodegradability make them attractive candidates for sustainable agricultural practices.

The advancement of Cu-CPs as urease inhibitors represents a paradigm shift from simple copper salts to sophisticated, structure-directed materials. By integrating functional ligands with unique geometries, such as V-shaped motifs, researchers have opened new avenues for optimizing activity, stability, and environmental safety in crop nutrient management.

3. V-Shaped Auxiliary Ligands in Cu-CPs Design

3.1. Overview of Auxiliary Ligand Design in Coordination Polymers

Auxiliary ligands play a pivotal role in the construction and functional tuning of coordination polymers. They act as bridging units that connect metal centers and determine the overall geometry, dimensionality, and porosity of the resulting frameworks [9]. By modifying ligand shape, flexibility, and coordination sites, researchers can exert precise control over material properties such as stability, surface area, and chemical reactivity. This ligand-driven structural engineering is especially important for applications requiring specific interactions, such as enzyme inhibition, catalysis, and gas storage.

3.2. Structural Features of V-Shaped Auxiliary Ligands

V-shaped auxiliary ligands are characterized by two coordinating groups linked via a rigid or semi-rigid backbone forming a defined angle, typically between 90° and 120°. This angular configuration differs significantly from linear or flexible ligands, providing a distinct spatial orientation that favors the formation of layered, two-dimensional networks [10]. The rigidity of the backbone maintains the ligand's shape during coordination, preventing collapse or undesirable structural rearrangements.

This geometry allows for the spatial separation of metal nodes in a plane, creating open frameworks with accessible metal sites and potential channels. Such structural features enhance the interaction of Cu centers with target molecules, including enzymes, thereby improving catalytic or inhibitory performance.

3.3. Influence of V-Shaped Ligands on the Formation of Two-Dimensional Cu-CPs

The incorporation of V-shaped ligands into copper coordination polymers has been shown to effectively direct the assembly into two-dimensional layered structures, improving crystallinity and stability. Ding et al. successfully fabricated two Cu-CPs with V-shaped second auxiliary ligands, resulting in planar coordination networks that exhibited enhanced urease inhibition activity compared to their linear ligand counterparts [11].

The V-shaped ligands restrict polymer growth along certain crystallographic directions, favoring sheet-like morphologies. This anisotropic growth results in materials with larger surface-to-volume ratios and increased exposure of catalytically active Cu sites. Such 2D networks typically display better diffusion properties, facilitating substrate access and interaction with active centers.

Furthermore, the defined ligand angle improves packing efficiency and framework robustness, which contributes to higher thermal and chemical stability, crucial for practical applications in agricultural soil environments.

3.4. Mechanistic Insights into Ligand-Regulated Urease Inhibition

The enhanced inhibitory effects observed in V-shaped ligand-regulated Cu-CPs derive from the synergistic influence of their unique structural features [12]. The two-dimensional planar arrangement exposes more copper active sites to interact with the urease enzyme, potentially coordinating to the enzyme's nickel centers or interfering with substrate binding. Additionally, the rigidity of the ligand scaffold stabilizes the polymeric framework against decomposition, allowing sustained inhibitory action over longer periods. The precise spatial arrangement afforded by the V-shaped ligands may also facilitate stronger non-covalent interactions, such as hydrogen bonding or π–π stacking, with amino acid residues in the enzyme active site.

4. Synthesis and Characterization Methods

4.1. Solvothermal and Hydrothermal Synthesis of Cu-CPs

Solvothermal and hydrothermal methods are the most commonly employed techniques for the preparation of copper-based coordination polymers (Cu-CPs). These approaches involve reacting copper salts and organic ligands in sealed vessels under elevated temperatures and pressures, providing a controlled environment for nucleation and crystal growth [13]. The temperature typically ranges from 80 to 200 °C, and reaction times vary from several hours to days depending on the desired crystallinity and morphology.

In solvothermal synthesis, organic solvents such as dimethylformamide (DMF), ethanol, or their mixtures are often used to dissolve ligands and metal salts. Solvent polarity and coordination ability influence the solubility of precursors and the kinetics of coordination, thereby affecting the dimensionality and topology of the resulting Cu-CPs. The method offers flexibility to tune reaction parameters (temperature, time, concentration) for desired structural outcomes.

Hydrothermal synthesis, which uses water as the solvent, is considered more environmentally friendly and scalable. This method is particularly suitable for ligands with polar functional groups and enables the formation of highly crystalline Cu-CPs [14]. Control over pH and additives during hydrothermal reactions further allows fine-tuning of crystal size, morphology, and phase purity.

Both methods facilitate the incorporation of complex ligands, including V-shaped auxiliary ligands, which direct the assembly of two-dimensional layered structures. Precise control of reaction conditions is critical to achieve uniform morphology and high structural stability, which are essential for effective urease inhibition.

4.2. Microwave-Assisted and Mechanochemical Synthesis Approaches

To address the limitations of long reaction times in traditional solvothermal and hydrothermal methods, microwave-assisted synthesis has emerged as a powerful alternative. Microwave irradiation provides rapid and uniform heating, drastically reducing reaction durations from days to minutes [15]. The enhanced kinetics often lead to smaller, more uniform crystals with improved phase purity.

Microwave synthesis also allows fine control over nucleation and growth, resulting in Cu-CPs with tailored porosity and surface area, beneficial for catalytic and inhibitory applications. However, optimization of microwave power, solvent system, and reaction time is necessary to prevent decomposition or undesired phases.

Mechanochemical synthesis, involving grinding of solid reactants under solvent-free or minimal solvent conditions, offers a green, solvent-less route to Cu-CPs. This method reduces environmental impact and energy consumption but poses challenges in controlling crystal growth and achieving high crystallinity. Advances in ball milling and liquid-assisted grinding have improved product quality, but mechanochemical approaches still require further development for broad application in Cu-CP synthesis.

4.3. Influence of Ligand Design on Synthetic Strategies

The choice and design of auxiliary ligands critically influence the synthetic route and final structure of Cu-CPs. V-shaped ligands, characterized by their rigid angular geometry, demand specific reaction environments to facilitate the formation of two-dimensional networks [16]. Their steric hindrance and coordination mode necessitate controlled synthesis parameters, such as temperature and ligand-to-metal ratio, to promote layer formation instead of extended three-dimensional frameworks.

Tailoring the ligand backbone length, functional groups, and flexibility can modulate solubility and coordination behavior, which directly affects crystallization kinetics. Multistep synthetic protocols, including pre-synthesis of ligands or post-synthetic modification, have been employed to introduce functional moieties that enhance stability or biological activity.

Optimizing these variables allows precise control over pore size distribution, metal site exposure, and overall material robustness, which are key determinants for efficient urease inhibition.

4.4. Structural Characterization Techniques

X-ray diffraction (XRD) is the principal technique for determining the crystalline structure and phase purity of Cu-CPs. Single-crystal XRD provides detailed atomic-level insight into coordination environments, ligand orientation, and network topology, essential for correlating structure with function. Powder XRD complements this by confirming bulk sample uniformity and crystallinity.

Fourier-transform infrared spectroscopy (FTIR) identifies characteristic functional groups and confirms metal-ligand coordination through shifts in vibrational bands. Thermogravimetric analysis (TGA) assesses thermal stability, an important factor for materials exposed to varying environmental conditions in agricultural soils.

Additional techniques such as elemental analysis and inductively coupled plasma spectroscopy (ICP) verify chemical composition and metal content, ensuring reproducibility and reliability.

4.5. Morphological and Surface Area Analysis

The morphology and microstructure of Cu-CPs are typically investigated using scanning electron microscopy (SEM) and transmission electron microscopy (TEM). These techniques reveal particle size, shape, and surface texture, providing insights into the effects of ligand geometry and synthesis conditions.

Brunauer–Emmett–Teller (BET) nitrogen adsorption-desorption measurements determine specific surface area and porosity, which are critical parameters influencing enzyme accessibility and inhibitory efficiency. Higher surface areas generally correlate with increased exposure of active copper sites and improved interaction with urease enzymes.

Complementary techniques like energy-dispersive X-ray spectroscopy (EDS) provide elemental mapping to confirm the homogeneous distribution of copper and ligand elements throughout the material.

5. Mechanisms and Applications

5.1. Mechanisms of Urease Inhibition by Cu-CPs

Copper-based coordination polymers (Cu-CPs) inhibit urease activity through multiple interrelated mechanisms. Primarily, Cu^{2+} ions interact with the nickel centers in the urease enzyme's active site, which are crucial for catalytic hydrolysis of urea. The coordination of Cu^{2+} can disrupt the enzyme's metallo-center, leading to conformational changes that reduce its catalytic efficiency.

In addition, the structural framework of Cu-CPs, especially those constructed with V-shaped auxiliary ligands, exposes abundant copper active sites in a two-dimensional layered arrangement. This enhanced exposure facilitates stronger and more sustained binding to urease molecules, blocking substrate access or directly interfering with the enzyme's active pocket.

Furthermore, Cu-CPs can generate reactive oxygen species (ROS) under certain environmental conditions, contributing to oxidative damage of urease or surrounding microbial communities that regulate nitrogen cycling. The polymer matrix also allows for controlled release of Cu^{2+} ions, prolonging inhibition duration and reducing rapid ion leaching compared to simple copper salts.

5.2. Applications in Soil–Plant Systems

The application of Cu-CPs as urease inhibitors in soil–plant systems has garnered increasing attention for their potential to enhance nitrogen use efficiency and reduce ammonia volatilization. By slowing urea hydrolysis, these materials mitigate nitrogen loss, promoting better fertilizer utilization and crop growth.

Field and greenhouse studies have demonstrated that Cu-CPs can be effectively integrated into fertilizer formulations or applied as soil amendments. Their structural stability ensures functional persistence under variable soil pH, moisture, and temperature conditions. Compared to traditional inhibitors, Cu-CPs show reduced toxicity and better environmental compatibility, aligning with sustainable agricultural practices.

Moreover, the modular design of Cu-CPs enables the tailoring of materials for specific crop or soil types by adjusting ligand composition and polymer morphology, optimizing inhibitory performance and minimizing adverse effects.

5.3. Synergistic Effects of Stabilizers and Environmental Impact

Stabilizers incorporated alongside Cu-CPs can significantly enhance urease inhibition efficacy and environmental safety. For instance, organic stabilizers or polymers may improve Cu-CPs dispersion in soil, protect active sites from premature degradation, and modulate copper ion release rates.

Ding et al. investigated the use of chemical stabilizers in conjunction with Cu-CPs and found that these additives prolonged urease inhibition effects in the soil–plant system, reducing nitrogen losses more effectively than Cu-CPs alone [14].

From an environmental perspective, the use of Cu-CPs with stabilizers reduces the total copper input needed, lowering risks of copper accumulation and toxicity to non-target organisms. The controlled release and biodegradability of polymeric matrices help mitigate long-term soil contamination.

6. Conclusions and Future Outlook

6.1. Summary of Major Progress

In recent years, significant advancements have been made in the design and synthesis of copper-based coordination polymers (Cu-CPs) for urease inhibition, particularly through the use of V-shaped auxiliary ligands. These ligands have demonstrated remarkable ability to direct the assembly of two-dimensional Cu-CPs with enhanced structural stability, higher surface areas, and improved exposure of catalytically active copper sites. Such structural features contribute to the superior urease inhibitory performance observed in these materials compared to traditional copper salts or linear ligand-based polymers.

Comprehensive characterization techniques have elucidated the relationship between ligand geometry, polymer structure, and functional activity, enabling rational design strategies. Moreover, the integration of stabilizers and tailored synthetic protocols have extended the practical applicability of Cu-CPs in soil–plant systems, promoting sustainable agricultural practices through reduced nitrogen loss and environmental impact.

6.2. Current Challenges

Despite these promising developments, several challenges remain. The precise mechanisms underlying urease inhibition at the molecular level require further elucidation to optimize material design. Additionally, large-scale, cost-effective synthesis methods with consistent product quality are yet to be fully established.

Environmental safety and long-term stability of Cu-CPs in diverse soil conditions also require in-depth study to prevent potential metal accumulation and toxicity. Furthermore, the complexity of soil microbiomes and their interactions with Cu-CPs and stabilizers poses challenges for predicting real-world efficacy.

6.3. Future Research Directions and Application Prospects

Future research should focus on multidisciplinary approaches combining advanced synthetic chemistry, materials characterization, and soil science to address these challenges. Designing multifunctional Cu-CPs with responsive or stimuli-triggered release capabilities could further enhance their efficiency and environmental compatibility.

Development of eco-friendly, biodegradable stabilizers and rigorous field trials across varied agroecological zones are essential to validate performance and safety. Exploration of synergistic effects between Cu-CPs and other nutrient management strategies may open new avenues for integrated fertilizer solutions.

In summary, with continued innovation and collaboration, copper-based coordination polymers regulated by V-shaped auxiliary ligands hold great promise for advancing sustainable agriculture by improving nitrogen utilization efficiency and minimizing environmental impact.

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