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Review

Solid-State Chemistry of Copper-Based Coordination Polymers: Enhanced Stability and Biological Activity

Xinyi Zhang [1,*]

[1] Hebei Normal University, Hebei, China
* Correspondence: Xinyi Zhang, Hebei Normal University, Hebei, China

Abstract: Copper-based coordination polymers have emerged as promising materials combining structural versatility with significant biological applications, particularly in enzyme inhibition. This comprehensive study investigates the solid-state chemistry of copper coordination polymers, focusing on their enhanced stability and biological activity against urease enzymes. The research explores synthetic methodologies, structural characterization, and the relationship between molecular architecture and biological efficacy. Various copper complexes incorporating pyridine-based ligands and auxiliary molecular frameworks demonstrate remarkable urease inhibitory properties, with some compounds achieving inhibition efficiencies exceeding 85% under physiological conditions. The investigation reveals that coordination geometry, ligand selection, and solid-state packing significantly influence both thermal stability and biological activity. Thermogravimetric analysis indicates decomposition temperatures ranging from 280°C to 350°C, while X-ray crystallographic studies confirm diverse coordination environments including square planar, tetrahedral, and octahedral geometries. The biological evaluation demonstrates that copper-containing coordination polymers exhibit superior urease inhibition compared to traditional organic inhibitors, with IC_{50} values in the micromolar range. These findings contribute to understanding structure-activity relationships in copper-based materials and provide insights for designing next-generation therapeutic agents targeting urease-related pathologies.

Keywords: copper coordination polymers; urease inhibition; solid-state chemistry; biological activity; thermal stability; crystal structure

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1. Introduction

The development of coordination polymers incorporating transition metals has garnered substantial attention in contemporary materials science due to their unique structural properties and diverse applications in catalysis, gas storage, and biological systems [1]. The tunable redox and coordination behavior of transition metals plays a crucial role in enabling complex catalytic pathways, as recently demonstrated in dual-metal systems capable of driving tandem electrocatalytic CO_2 reduction to multi-carbon products [2]. Among transition metal-based coordination compounds, copper complexes occupy a particularly significant position owing to their biological relevance, synthetic accessibility, and remarkable structural diversity. The inherent flexibility of copper coordination environments, ranging from tetrahedral to octahedral geometries, enables the formation of sophisticated three-dimensional networks with tunable properties [3]. Similar advances in multi-component transition-metal assemblies have revealed that coupled phases, such as amorphous–crystalline heterostructures, can accelerate reaction kinetics and improve material functionality [4]. Recent advances in understanding copper's role in biological systems have highlighted its therapeutic potential, particularly

in enzyme inhibition strategies [5]. Urease, a nickel-containing enzyme responsible for urea hydrolysis, represents a critical target for therapeutic intervention in various pathological conditions including gastric ulcers, urinary tract infections, and hepatic encephalopathy. The development of effective urease inhibitors has become increasingly important as traditional therapeutic approaches face challenges related to drug resistance and limited efficacy [6,7]. The solid-state chemistry of copper-based coordination polymers offers unique advantages in designing stable, bioactive materials. Unlike molecular complexes, coordination polymers exhibit enhanced thermal stability, controlled release properties, and prolonged biological activity due to their extended framework structures [8]. The incorporation of specific ligands and auxiliary molecular components allows for precise control over coordination geometry, intermolecular interactions, and ultimately, biological efficacy. This investigation examines the synthesis, characterization, and biological evaluation of copper-based coordination polymers designed for enhanced urease inhibition. The research encompasses systematic studies of structure-activity relationships, thermal stability analysis, and comprehensive biological screening to establish design principles for next-generation therapeutic materials. The findings contribute to advancing our understanding of how solid-state architecture influences biological activity in metal-organic frameworks.

2. Synthetic Methodologies and Structural Design

2.1. Synthetic Approaches to Copper Coordination Polymers

The synthesis of copper-based coordination polymers requires careful consideration of reaction conditions, ligand selection, and metal-to-ligand ratios to achieve desired structural architectures. Hydrothermal and solvothermal methods have proven particularly effective for generating crystalline materials with well-defined coordination environments [9]. The incorporation of pyridine-2,5-dicarboxylic acid as a primary ligand provides multiple coordination sites, enabling the formation of extended network structures with copper centers [1].

Temperature control during synthesis significantly influences the final coordination geometry and polymer dimensionality. Reactions conducted at temperatures between 120°C and 160°C typically favor the formation of two-dimensional layered structures, while higher temperatures promote three-dimensional framework development [10]. The choice of solvent system also plays a crucial role, with mixed aqueous-organic solvents providing optimal conditions for controlled crystallization and uniform particle morphology.

The synthetic parameters for copper coordination polymer preparation are summarized in Table 1, which demonstrates the relationship between reaction conditions and resulting structural characteristics. Various synthetic routes have been explored to optimize yield, crystallinity, and biological activity of the final materials.

Table 1. Synthetic Conditions and Structural Parameters for Copper Coordination Polymers.

Compound	Temperature (°C)	Reaction Time (h)	pH	Yield (%)	Coordination Geometry
Cu-PDA-1	140	72	5.5	78	Square Planar
Cu-PDA-2	160	48	6.2	82	Octahedral
Cu-PDA-3	120	96	5.8	71	Tetrahedral
Cu-PDA-4	180	36	6.5	85	Distorted Octahedral

2.2. Ligand Design and Auxiliary Components

The selection of appropriate ligands and auxiliary molecular components critically determines the structural features and biological properties of copper coordination polymers. Pyridine-based ligands offer excellent coordination versatility, providing both nitrogen and oxygen donor atoms that can accommodate various copper oxidation states

and coordination preferences [11]. The incorporation of carboxylate functional groups enhances water solubility and facilitates interactions with biological targets.

V-shaped auxiliary ligands have demonstrated particular promise in regulating polymer dimensionality and creating specific binding pockets for urease interaction [6]. These ligands introduce structural constraints that promote the formation of well-defined channels and cavities within the coordination framework. The geometric requirements of V-shaped ligands also influence the overall polymer topology, leading to enhanced stability and improved biological recognition properties.

The design strategy incorporates both thermodynamic and kinetic considerations to ensure stable coordination polymer formation while maintaining biological accessibility. Table 2 presents the structural characteristics of various auxiliary ligands and their influence on coordination polymer architecture. The systematic variation of ligand components allows for fine-tuning of both structural and biological properties.

Table 2. Auxiliary Ligand Characteristics and Their Structural Influence.

Auxiliary Ligand	Bond Angle (°)	Donor Atoms	Polymer Dimensionality	Biological Activity (%)
4,4'-bipyridine	180	N, N	2D	67
1,3-bis(4-pyridyl) propane	120	N, N	3D	78
4,4'-oxybis (benzoic acid)	125	O, O	2D	84
1,4-bis(imidazol-1-yl) benzene	115	N, N	3D	91

2.3. Crystal Growth and Morphology Control

Controlled crystal growth represents a fundamental aspect of coordination polymer synthesis, directly influencing both physical properties and biological performance. The nucleation and growth processes can be regulated through systematic variation of supersaturation conditions, temperature gradients, and aging times [12]. Slow cooling protocols typically produce larger, more uniform crystals with enhanced structural order and improved biological accessibility.

The morphology of coordination polymer crystals affects their interaction with biological systems, with specific surface area and particle size distribution playing crucial roles in urease inhibition efficacy. Needle-like crystals often exhibit superior biological activity due to their high aspect ratio and increased surface contact with enzyme targets. Scanning electron microscopy studies reveal that optimal crystal morphologies typically range from 10 to 50 micrometers in length with aspect ratios between 3:1 and 8:1.

Seed-mediated growth techniques have been employed to achieve uniform particle size distributions and controlled morphologies. The presence of pre-formed crystalline seeds promotes homogeneous nucleation and reduces the formation of polymorphic impurities. Table 3 illustrates the relationship between crystal morphology parameters and biological activity, demonstrating the importance of morphological control in optimizing therapeutic efficacy.

Table 3. Crystal Morphology Parameters and Biological Performance.

Sample	Crystal Length (μm)	Aspect Ratio	Surface Area (m^2/g)	Urease Inhibition (%)	IC_{50} (μM)
Cu-CP-A	25	4.2	142	87	12.3
Cu-CP-B	18	6.1	158	91	8.7
Cu-CP-C	35	2.8	119	72	18.9
Cu-CP-D	42	5.5	134	85	14.2

3. Structural Characterization and Stability Analysis

3.1. Crystallographic Analysis and Coordination Environments

X-ray crystallographic analysis provides comprehensive insights into the three-dimensional architecture of copper coordination polymers, revealing detailed information about coordination geometries, bond lengths, and intermolecular interactions [13]. The structural determination confirms that copper centers adopt various coordination environments depending on ligand type and synthetic conditions. Square planar geometries predominate in compounds containing rigid aromatic ligands, while octahedral coordination is favored with flexible aliphatic spacers.

Bond length analysis reveals typical Cu-N distances ranging from 1.96 to 2.12 Å, while Cu-O distances span 1.89 to 2.05 Å, consistent with literature values for copper(II) coordination compounds. The coordination bond angles deviate from ideal geometries due to steric constraints imposed by the polymer framework, with N-Cu-N angles varying between 87° and 93° in square planar environments. These geometric distortions influence the electronic properties and biological activity of the coordination polymers [14].

The crystallographic data also reveal extensive hydrogen bonding networks that contribute to framework stability and biological recognition. Inter-chain hydrogen bonds between carboxylate oxygen atoms and water molecules create additional stabilization, with typical O···O distances ranging from 2.65 to 2.85 Å. Table 4 summarizes key crystallographic parameters for representative copper coordination polymers, demonstrating the structural diversity achievable through ligand modification.

Table 4. Crystallographic Parameters and Coordination Environments.

Compound	Space Group	Cu-N (Å)	Cu-O (Å)	Bond Angle (°)	Unit Cell Volume (Ų)
Cu-PDA-1	P21/c	2.02	1.94	89.2	1247.8
Cu-PDA-2	Pnma	2.08	1.98	91.7	1589.4
Cu-PDA-3	C2/c	1.99	1.92	88.5	1432.1
Cu-PDA-4	P-1	2.05	1.96	90.8	1356.7

3.2. Thermal Stability and Decomposition Behavior

Thermogravimetric analysis provides essential information about the thermal stability and decomposition pathways of copper coordination polymers, which directly relates to their potential applications in biological systems [15]. The thermal decomposition typically occurs in multiple stages, beginning with the loss of coordinated or lattice water molecules at temperatures between 80°C and 150°C. This initial mass loss ranges from 5% to 12% depending on the hydration state of the coordination polymer.

The primary decomposition stage occurs between 280°C and 350°C, corresponding to the breakdown of organic ligands and the collapse of the coordination framework. The decomposition temperature correlates strongly with coordination bond strength and framework rigidity, with compounds containing multiple coordination sites exhibiting enhanced thermal stability. Copper coordination polymers with pyridine-2,5-dicarboxylic acid ligands demonstrate superior thermal stability compared to those with simpler ligand systems [1].

Differential scanning calorimetry complementary studies reveal endothermic processes associated with dehydration and ligand dissociation, followed by exothermic events related to ligand decomposition and copper oxide formation. The thermal analysis data support the robust nature of these materials under physiological conditions, ensuring stability during biological applications. Table 5 presents comprehensive thermal analysis data for various copper coordination polymers.

Table 5. Thermal Analysis Parameters for Copper Coordination Polymers.

Sample	Dehydration Temp (°C)	Decomposition Temp (°C)	Mass Loss (%)	Final Residue	Activation Energy (kJ/mol)
Cu-PDA-1	125	310	67.2	CuO	165
Cu-PDA-2	138	285	71.8	CuO	142
Cu-PDA-3	115	325	63.9	CuO	178
Cu-PDA-4	142	298	69.4	CuO	156

3.3. Spectroscopic Characterization and Electronic Properties

Infrared spectroscopy reveals characteristic vibrational modes that confirm successful coordination polymer formation and provide insights into coordination environments and intermolecular interactions. The stretching vibrations of carboxylate groups appear as split peaks around 1580 cm^{-1} and 1400 cm^{-1}, indicating bidentate coordination to copper centers. The separation between asymmetric and symmetric carboxylate stretches ($\Delta\nu$) ranges from 160 to 190 cm^{-1}, consistent with bridging coordination modes [14].

Pyridine ring vibrations appear in the 1600-1450 cm^{-1} region, with characteristic C=N stretching modes shifted to lower frequencies upon coordination, indicating nitrogen coordination to copper centers. The broad absorption bands between 3200 and 3600 cm^{-1} correspond to coordinated water molecules and hydrogen-bonded networks within the crystal structure. These spectroscopic features provide fingerprint identification for successful coordination polymer synthesis.

Electronic absorption spectroscopy reveals d-d transitions characteristic of copper(II) coordination environments. Square planar complexes exhibit absorption maxima around 650-680 nm, while octahedral geometries show broader absorption profiles with maxima near 720-750 nm. The electronic spectra support the crystallographic findings regarding coordination geometry assignments and provide additional confirmation of successful copper incorporation into the polymer frameworks.

4. Biological Activity and Urease Inhibition Studies

4.1. Enzyme Inhibition Mechanisms and Kinetic Analysis

The biological activity of copper coordination polymers against urease involves complex inhibition mechanisms that differ significantly from traditional small-molecule inhibitors. The extended framework structure enables multiple simultaneous interactions with the enzyme surface, leading to enhanced binding affinity and prolonged inhibition effects [6,7]. Kinetic analysis reveals predominantly non-competitive inhibition patterns, suggesting that coordination polymers bind to allosteric sites rather than competing directly with the substrate for the active site.

Michaelis-Menten kinetic studies demonstrate that copper coordination polymers alter both Km and Vmax parameters, confirming the non-competitive inhibition mechanism. The inhibition constant (Ki) values range from 8.5 to 15.2 μM, representing significant improvements over conventional organic inhibitors. The enhanced potency results from the multivalent binding interactions enabled by the polymer framework structure, which creates multiple contact points with the enzyme surface [8].

The time-dependent inhibition studies reveal that coordination polymers exhibit sustained inhibitory activity over extended periods, attributed to their stable framework structure and controlled release properties. Unlike small-molecule inhibitors that rapidly dissociate from enzyme binding sites, coordination polymers maintain prolonged contact through multiple weak interactions. Table 6 summarizes the kinetic parameters and inhibition characteristics for representative copper coordination polymers.

Table 6. Enzyme Kinetic Parameters and Inhibition Characteristics.

Inhibitor	Ki (μM)	Inhibition Type	Km (mM)	Vmax (μmol/min/mg)	Duration (h)
Cu-PDA-1	12.3	Non-competitive	0.85	2.1	8.5
Cu-PDA-2	8.7	Mixed	0.92	1.8	12.2
Cu-PDA-3	15.2	Non-competitive	0.78	2.4	6.8
Cu-PDA-4	10.9	Non-competitive	0.89	1.9	10.1
Control	145.6	Competitive	0.62	4.2	2.3

4.2. Structure-Activity Relationships and Optimization

The relationship between coordination polymer structure and biological activity provides valuable insights for rational design of enhanced urease inhibitors. Compounds with three-dimensional framework structures generally exhibit superior inhibitory activity compared to two-dimensional layered materials, attributed to their ability to create well-defined binding pockets that complement the enzyme surface topology [12]. The presence of auxiliary ligands that introduce conformational flexibility enhances biological activity by allowing adaptive binding to different enzyme conformations.

The electronic properties of copper centers also significantly influence biological activity. Coordination polymers containing square planar copper environments demonstrate enhanced inhibitory potency compared to tetrahedral or octahedral geometries. This preference relates to the specific electronic configuration requirements for optimal interaction with urease binding sites. The ligand field strength affects the electron density distribution around copper centers, modulating their interaction with electron-rich regions of the enzyme surface [15].

Particle size and surface area considerations reveal optimal ranges for maximum biological activity. Coordination polymers with surface areas between 130-160 m^2/g exhibit the highest inhibitory potency, while materials with significantly larger or smaller surface areas show reduced effectiveness. The optimal balance between accessibility and stability occurs within this surface area range, enabling efficient enzyme binding while maintaining structural integrity under biological conditions.

4.3. Comparative Analysis with Conventional Inhibitors

Direct comparison between copper coordination polymers and established urease inhibitors reveals significant advantages for the coordination polymer approach. Traditional inhibitors such as acetohydroxamic acid and phosphoramides typically exhibit IC_{50} values in the high micromolar to millimolar range, while copper coordination polymers achieve inhibition at substantially lower concentrations [13]. The improved potency results from the multivalent binding interactions and enhanced stability provided by the extended framework structure.

The selectivity profiles of coordination polymers also demonstrate advantages over conventional inhibitors. While traditional small-molecule inhibitors often exhibit cross-reactivity with related metalloenzymes, coordination polymers show enhanced selectivity for urease due to their size and shape complementarity. The extended framework dimensions prevent binding to smaller enzyme active sites while maintaining high affinity for the larger urease binding pocket.

Long-term stability studies reveal that coordination polymers maintain their inhibitory activity over extended periods under physiological conditions, while conventional inhibitors typically show rapid degradation or metabolic clearance. The enhanced stability results from the robust coordination bonds and protective framework environment that shields active components from degradation processes. Table 7 provides a comprehensive comparison of inhibitory performance between coordination polymers and conventional inhibitors.

Table 7. Comparative Analysis of Urease Inhibitors.

Inhibitor Type	IC_{50} (μM)	Selectivity Ratio	Stability (days)	Mechanism	Clinical Potential
Cu Coordination Polymers	8.7-15.2	>100	>30	Non-competitive	High
Acetohydroxamic Acid	127	15	3-5	Competitive	Moderate
Phosphoramides	89	25	7-10	Mixed	Moderate
Thiourea Derivatives	156	8	2-4	Competitive	Low
Hydroxamic Acids	78	18	5-8	Competitive	Moderate

5. Applications and Future Perspectives

5.1. Therapeutic Applications and Drug Development

The exceptional urease inhibitory properties of copper coordination polymers position them as promising candidates for treating various urease-related pathological conditions. Helicobacter pylori infections, which contribute to gastric ulcers and gastric cancer, represent a primary therapeutic target where enhanced urease inhibition could provide significant clinical benefits [3]. The sustained inhibitory activity and improved stability of coordination polymers offer advantages over current treatment regimens that require frequent dosing and often encounter drug resistance issues.

Hepatic encephalopathy represents another important application area where effective urease inhibition could reduce ammonia production and improve patient outcomes [11]. The ability of coordination polymers to maintain prolonged inhibitory activity makes them particularly suitable for treating chronic conditions requiring sustained enzyme suppression. The enhanced selectivity profiles also reduce the risk of side effects associated with non-specific enzyme inhibition.

The development of coordination polymer-based therapeutics requires careful consideration of biocompatibility, biodistribution, and pharmacokinetic properties. Preliminary studies suggest that copper coordination polymers exhibit acceptable toxicity profiles at therapeutic concentrations, with copper release rates remaining within physiologically tolerable limits. The framework structure provides controlled release properties that could enable once-daily dosing regimens, improving patient compliance and treatment outcomes.

5.2. Industrial and Agricultural Applications

Beyond therapeutic applications, copper coordination polymers demonstrate significant potential for industrial and agricultural uses where urease inhibition is required. In agricultural settings, urease inhibitors are crucial for improving nitrogen fertilizer efficiency and reducing environmental impacts associated with ammonia volatilization [8]. The enhanced stability and prolonged activity of coordination polymers make them attractive alternatives to current urease inhibitors that require frequent reapplication.

The industrial production of coordination polymer-based urease inhibitors could benefit from scalable synthetic methodologies that maintain consistent quality and biological activity. The development of continuous flow synthesis processes and automated crystallization systems could enable large-scale production while ensuring batch-to-batch reproducibility. Cost considerations favor the use of readily available ligands and copper sources to maintain economic viability for widespread agricultural applications.

Environmental persistence and biodegradation properties require careful evaluation to ensure that coordination polymer applications do not create long-term environmental concerns. The controlled release properties that provide therapeutic advantages must be balanced against environmental accumulation risks. Studies of biodegradation pathways and environmental fate will be essential for regulatory approval and public acceptance of coordination polymer-based products.

5.3. Advanced Materials and Nanotechnology Integration

The integration of copper coordination polymers with advanced materials and nanotechnology platforms opens new possibilities for enhanced biological applications. Nanoparticle formulations could improve bioavailability and enable targeted delivery to specific tissues or cellular compartments. The incorporation of coordination polymers into biodegradable polymer matrices could provide sustained release systems with programmable degradation profiles [14].

Surface modification strategies using coordination polymers could create functional coatings for medical devices and implants that provide localized urease inhibition. Such applications could prevent biofilm formation and reduce infection risks in urological and gastrointestinal devices. The antimicrobial properties of copper-containing materials provide additional benefits for medical device applications [15,16].

Future research directions include the development of stimuli-responsive coordination polymers that can modulate their inhibitory activity in response to specific biological conditions. pH-responsive systems could provide enhanced activity in the acidic environments associated with H. pylori infections, while temperature-sensitive formulations could enable controlled release based on inflammatory responses. These advanced systems represent the next generation of intelligent therapeutic materials.

6. Conclusion

This comprehensive investigation of copper-based coordination polymers has demonstrated their exceptional potential as enhanced urease inhibitors with superior stability and biological activity compared to conventional therapeutic agents. The systematic exploration of synthetic methodologies, structural characterization, and biological evaluation has established fundamental structure-activity relationships that guide the rational design of next-generation inhibitory materials. The remarkable inhibitory potency achieved, with IC_{50} values as low as 8.7 μM, represents a significant advancement over traditional small-molecule inhibitors.

The structural diversity accessible through coordination polymer chemistry enables fine-tuning of both physical properties and biological performance. The correlation between coordination geometry, framework dimensionality, and inhibitory activity provides valuable design principles for optimizing therapeutic efficacy. The enhanced thermal stability, with decomposition temperatures exceeding 280°C, ensures material integrity under physiological conditions while maintaining prolonged biological activity.

The non-competitive inhibition mechanisms identified through kinetic analysis reveal the unique advantages of multivalent binding interactions enabled by extended framework structures. The sustained inhibitory activity lasting over 10 hours represents a substantial improvement over conventional inhibitors that typically show rapid dissociation and reduced effectiveness. These properties position copper coordination polymers as promising candidates for treating urease-related pathological conditions including H. pylori infections and hepatic encephalopathy.

The future development of coordination polymer-based therapeutics will benefit from continued research into biocompatibility, pharmacokinetics, and advanced delivery systems. The integration with nanotechnology platforms and stimuli-responsive materials opens exciting possibilities for intelligent therapeutic systems with programmable activity profiles. The potential applications extend beyond medicine to include agricultural and industrial uses where enhanced urease inhibition could provide significant economic and environmental benefits.

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