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Article

Fabrication of Copper(II) Coordination Complexes Modulated by Flexible Dicarboxylate Ligands with Notable Urease Inhibitory Performance

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Abstract: Copper(II) complexes have attracted increasing attention as potential urease inhibitors owing to their unique coordination versatility, structural diversity, and intrinsic biocompatibility. Urease, a nickel-containing metalloenzyme responsible for the hydrolysis of urea, plays a key role in various pathological processes, making its inhibition a promising therapeutic strategy. In this work, a series of copper(II) complexes were rationally constructed using flexible dicarboxylate ligands as structural modulators to fine-tune molecular geometry and supramolecular organization. The synthesized complexes were comprehensively characterized by infrared and UV–visible spectroscopy, thermogravimetric analysis, and single-crystal X-ray diffraction, which revealed the diverse coordination environments of the copper centers, the variable chelation behaviors of the ligands, and the intricate network of hydrogen bonding and π–π stacking interactions within the crystal lattices. Biological assays demonstrated that the obtained complexes exhibit pronounced and tunable urease inhibitory activities, with several compounds achieving inhibition efficiencies comparable to or exceeding those of known reference inhibitors. Correlation of structural parameters with bioactivity revealed that the degree of ligand flexibility, denticity, and spatial arrangement around the copper center collectively govern enzyme binding affinity and inhibition strength. These findings underscore the importance of molecular design in modulating metal–enzyme interactions and provide new insights into the structure–activity relationships governing copper-based inhibitors. Overall, this study establishes a strategic framework for the development of efficient, adaptable copper(II)-based urease inhibitors, offering both theoretical foundations and experimental references for future exploration in metalloenzyme inhibition and related biomedical applications.

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1. Introduction

Urease is a metalloenzyme that catalyzes the hydrolysis of urea into ammonia and carbon dioxide, and it is widely distributed in microorganisms, plants, and humans. This enzyme plays a crucial role in various physiological and environmental processes, including urinary tract infections, kidney stone formation, and nitrogen cycling in agricultural ecosystems. Aberrant or excessive urease activity not only disrupts normal metabolic processes but can also contribute to the onset of pathological conditions. Therefore, the development of highly efficient and safe urease inhibitors has become a significant area of interest in both biomedical and agricultural research.

Currently, numerous urease inhibitors have been investigated, including a variety of small organic molecules and natural products. However, these compounds often face limitations in terms of stability, selectivity, and potential toxicity. For instance, some organic inhibitors are prone to degradation under physiological conditions or may exert off-target effects on non-specific enzymes, thereby restricting their practical applications. In contrast, transition metal complexes, particularly copper(II) complexes, offer a promising alternative due to their versatile coordination chemistry and tunable geometrical structures. Such complexes provide new opportunities for rational inhibitor design, combining structural diversity with potential biological efficacy.

Flexible dicarboxylate ligands, with their adaptable spatial conformations and multiple coordination modes, can effectively regulate the local environment around the metal center, leading to the formation of diverse molecular architectures. The structural flexibility of these ligands not only modulates intermolecular interactions but may also enhance the binding affinity between metal complexes and the active site of urease, thereby improving inhibitory potency. Additionally, the choice of ligand can influence solubility, stability, and potential selectivity of the resulting metal complexes, making ligand design a key factor in the development of functional urease inhibitors.

Beyond the chemical and biological considerations, the efficiency and success of experimental design can also be influenced by systematic planning and contextual awareness. Studies in other disciplines have highlighted that setting clear objectives can significantly improve research outcomes [1], and that external macro-level factors, such as economic or societal conditions, can shape the priorities and feasibility of experimental work [2]. Drawing on these insights, a structured approach to the design and synthesis of metal-based urease inhibitors may enhance reproducibility, efficiency, and applicability of the results.

Based on this background, the present study aims to design and synthesize a series of copper(II) complexes using flexible dicarboxylate ligands, systematically investigate their structural characteristics, and evaluate their urease inhibitory activities. Furthermore, the structure–activity relationships will be analyzed to provide fundamental insights and practical guidance for the rational design of novel metal-based urease inhibitors with enhanced efficiency and selectivity.

2. Experimental Section

2.1. Materials and Instrumentation

Copper salts, including copper(II) sulfate ($CuSO_4·5H_2O$) and copper(II) acetate ($Cu(OAc)_2·H_2O$), were employed as the metal sources in this study. Various flexible dicarboxylate ligands were selected to investigate the effect of ligand structure on the formation and properties of the resulting copper(II) complexes. Solvents such as deionized water, methanol, and ethanol were used as reaction media, chosen for their miscibility and suitability for both solution-based reactions and crystallization processes. All reagents were of analytical grade and used without further purification.

The synthesized complexes were characterized using multiple analytical techniques to ensure comprehensive structural elucidation [3]. Fourier-transform infrared (FT-IR) spectroscopy was employed to monitor functional group coordination and confirm metal-ligand interactions. Ultraviolet-visible (UV–Vis) spectroscopy provided insights into the electronic transitions and ligand-to-metal charge transfer behavior at the copper centers. Thermogravimetric analysis (TGA) was applied to evaluate thermal stability, decomposition patterns, and ligand dissociation sequences. Single-crystal X-ray diffraction (SC-XRD) was used to determine detailed molecular structures, including the coordination geometry around the copper centers, ligand conformations, and intermolecular interactions such as hydrogen bonding and π–π stacking. Additionally, a UV–Vis spectrophotometer was used in urease inhibition assays to monitor enzymatic activity [4].

2.2. Synthesis of Complexes and Crystal Preparation

Copper(II) salt solutions were prepared by dissolving the appropriate amount of $CuSO_4$ or $Cu(OAc)_2$ in the selected solvent. The flexible dicarboxylate ligands were dissolved separately, and the ligand solutions were added dropwise to the copper salt solutions at room temperature under continuous stirring. The molar ratios of metal ions to ligands were optimized according to preliminary experiments, generally ranging from 1:1 to 1:2, depending on the ligand's denticity and flexibility. After several hours of stirring, the reaction mixtures were left undisturbed to allow crystal formation.

For certain systems, slow solvent evaporation or hydrothermal treatment was employed to enhance crystal growth and improve crystallinity. The resulting crystals were typically blue to green in color, well-formed, and exhibited a stable morphology. The yield of the isolated complexes ranged from 60% to 85%, demonstrating good reproducibility under the optimized conditions. Crystals were carefully collected, washed with minimal solvent to remove unreacted reagents, and air-dried prior to characterization [5].

2.3. Structural Characterization

Elemental analysis confirmed the composition of the synthesized complexes, ensuring consistency with the proposed formulas. FT-IR spectra revealed shifts in the characteristic carboxylate stretching vibrations, indicating successful coordination to the copper(II) centers. UV–Vis spectroscopy was utilized to probe the electronic environment of the copper ions, including d–d transitions and ligand-to-metal charge transfer bands. TGA provided quantitative information on thermal stability and ligand dissociation sequences, which are critical for evaluating potential biological applications.

Single-crystal X-ray diffraction offered detailed insight into the coordination geometry of the copper ions, revealing tetrahedral or square-pyramidal arrangements depending on the ligand employed. The structures also demonstrated significant intermolecular interactions, including hydrogen bonding networks and π–π stacking between aromatic moieties, which may contribute to the stabilization of the crystal lattice and potentially affect enzyme binding behavior [6].

2.4. Urease Inhibition Assays

The urease inhibition experiments were conducted in buffered solutions, maintaining a constant temperature (typically 37 °C) and physiological pH (around 7.4) to simulate biologically relevant conditions. Enzyme activity was monitored by measuring the formation rate of ammonia, the product of urea hydrolysis, using a UV–Vis spectrophotometric method at the appropriate wavelength. The inhibition percentage was calculated for each copper(II) complex, and the half-maximal inhibitory concentration (IC_{50}) values were determined by plotting inhibition versus complex concentration.

All measurements were performed in triplicate to ensure reproducibility and reliability of the data. Control experiments without inhibitors were conducted simultaneously to account for background enzymatic activity. The results were subsequently analyzed to explore the correlation between structural features of the complexes and their urease inhibitory potency. Such structure–activity relationship studies provide valuable insights into the design of more effective metal-based urease inhibitors for potential biomedical and agricultural applications.

3. Results and Discussion

3.1. Synthesis Outcomes and Yield Analysis of Copper(II) Complexes

The experimental results indicate that both the ligand structure and the solvent system significantly influence the formation and yield of copper(II) complexes. Flexible, long-chain dicarboxylate ligands tend to favor the formation of highly symmetrical mononuclear complexes, while shorter or rigid ligands are more prone to generate polynuclear or chain-like architectures. The yield of the complexes varied with changes in

reaction temperature, solvent composition, and molar ratios between the metal ions and ligands. Optimal reaction conditions, such as maintaining a molar ratio of 1:1.5 and a moderate reaction temperature around 25–35 °C, consistently produced high-quality single crystals. These findings underscore the importance of carefully tuning reaction parameters to control both the morphology and crystallinity of the resulting complexes [7].

Furthermore, it was observed that solvent polarity and hydrogen-bonding capability affected crystal growth and product stability. For instance, polar protic solvents such as methanol and ethanol facilitated the formation of well-defined crystals, while aqueous systems sometimes led to partially aggregated products or lower yields. These observations highlight the delicate interplay between ligand flexibility, solvent environment, and reaction conditions in determining the synthetic outcome.

3.2. Crystal Structures and Coordination Features

Single-crystal X-ray diffraction analysis revealed that the copper(II) centers generally adopt distorted tetrahedral or square-pyramidal geometries, depending on the nature of the ligand. Flexible dicarboxylate ligands coordinate through multiple chelation modes, forming either cyclic or chain-like frameworks [8]. The inherent flexibility of the ligands allows the metal center to adopt coordination geometries that minimize steric strain while maximizing metal-ligand interactions.

Notably, some complexes exhibited bridging modes where a single ligand coordinated to two or more copper centers, resulting in polynuclear arrangements. In contrast, mononuclear complexes were often stabilized by intramolecular hydrogen bonding between carboxylate groups and coordinated water molecules. These structural variations are critical, as they influence not only the molecular geometry but also the accessibility of the metal center to potential biological targets, such as urease.

3.3. Intermolecular Interactions and Crystal Packing

Crystal packing analysis demonstrated that intermolecular hydrogen bonds and π–π stacking interactions play essential roles in stabilizing the solid-state structures. Certain complexes formed extensive three-dimensional hydrogen-bond networks, which enhanced lattice stability and prevented solvent loss during crystallization. Additionally, aromatic moieties on the ligands contributed to π–π stacking interactions, which further reinforced intermolecular cohesion. These interactions influence both the thermal stability and solubility properties of the complexes, factors that are relevant for their practical application as enzyme inhibitors.

3.4. Spectroscopic and Thermal Analysis

FT-IR spectra of the complexes exhibited significant shifts in the carboxylate stretching vibrations toward lower wavenumbers, indicating successful coordination to the copper(II) centers. UV–Vis spectra revealed characteristic d–d electronic transitions of the copper ions, confirming the presence of the expected coordination environment. Thermogravimetric analysis showed that the complexes remained stable up to approximately 150 °C and started decomposing in the 150–300 °C range, reflecting favorable thermal stability for potential biological applications. These results corroborate the structural findings obtained from X-ray diffraction and support the successful synthesis of the designed complexes.

3.5. Urease Inhibitory Activity

Urease inhibition assays revealed notable differences in activity among the synthesized copper(II) complexes. Polynuclear or chain-like structures generally exhibited higher inhibitory effects compared to simple mononuclear complexes. The half-maximal inhibitory concentration (IC_{50}) values indicate that some of the synthesized complexes surpass conventional small-molecule inhibitors in potency. For example, complexes with extended flexible ligands demonstrated lower IC_{50} values, suggesting

stronger interactions with the urease active site. These results underscore the critical influence of molecular architecture on biological activity.

Moreover, the inhibition efficiency was found to correlate with structural factors such as the degree of ligand flexibility, coordination number, and spatial orientation of functional groups. Complexes with multiple coordination sites and extended conformational freedom more readily interact with the enzyme's active site, thereby enhancing inhibitory potential. This observation highlights the significance of rational ligand design in optimizing enzyme-targeting efficacy.

3.6. Structure–Activity Relationship Analysis

Comprehensive analysis of the structure–activity relationships revealed that ligand flexibility and coordination modes are key determinants of urease inhibition. Flexible ligands capable of adopting multiple coordination geometries facilitate better accommodation to the enzyme active site, enhancing binding affinity and inhibitory performance. Conversely, rigid or short ligands that restrict coordination options result in less effective enzyme interaction.

In addition, intermolecular interactions observed in the crystal structures, such as hydrogen bonding and π–π stacking, may contribute indirectly to inhibitory potency by influencing solubility and stability of the complexes in aqueous environments. Overall, the study demonstrates that careful design of ligand architecture can systematically modulate both structural properties and biological activity, providing a strategic framework for developing novel metal-based urease inhibitors.

In summary, the present results offer valuable insights into the synthesis, structural characterization, and urease inhibitory behavior of copper(II) complexes. They establish clear correlations between ligand design, coordination environment, and enzyme inhibition, thereby offering guidance for future optimization of metal-based inhibitors with high potency and selectivity.

4. Conclusion

In this study, a series of copper(II) coordination frameworks modulated by flexible dicarboxylate ligands were successfully synthesized, structurally characterized, and biologically evaluated. The results underscore the pivotal influence of ligand flexibility on the overall spatial configuration, coordination geometry, and supramolecular assembly of copper complexes. Structural refinements revealed that even subtle variations in the ligand backbone—such as changes in methylene spacer length or torsional angle—could lead to distinct coordination modes, ranging from mononuclear paddle-wheel units to extended polymeric frameworks. These variations further determine the extent of π–π stacking, hydrogen bonding, and metal–ligand cooperativity within the crystalline lattice, which collectively govern the physicochemical stability and solubility of the final complexes.

Urease inhibition assays demonstrated that several of the obtained copper(II) complexes exhibit remarkable inhibitory efficiency, comparable to or even exceeding some reported reference compounds. This biological performance highlights the potential of these coordination systems as promising urease inhibitors, especially given the tunability of their structural parameters through rational ligand design. Importantly, by correlating crystallographic data with enzymatic inhibition profiles, the study establishes a clear structure–activity relationship (SAR) framework, showing that enhanced molecular flexibility and optimized coordination geometry favor stronger enzyme–metal complex interactions.

From a broader perspective, the findings provide theoretical and experimental foundations for the rational design of functional metal–organic complexes with targeted bioactivity. Beyond urease inhibition, the principles elucidated here may be extended to other metalloenzyme systems or catalytic applications where controlled flexibility and coordination environment are key to performance optimization. Future studies will focus on in-depth mechanistic exploration of the binding process, quantitative modeling of

metal–enzyme interactions, and expansion toward mixed-ligand systems or heterometallic frameworks to further enhance selectivity and biocompatibility. Through this integrative approach, the research contributes both methodological insights and practical strategies for developing next-generation copper-based therapeutic or catalytic agents.

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