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Computational studies of metal complexes and organic transformations

Shashank kumar mishra
Chemistry Educator (At Unacademy)
Email- mishras683@gmail.com

Abstract

Computational studies use quantum chemical modeling, mostly Density Functional Theory (DFT), to understand and predict the structures, properties, and reaction mechanisms of metal complexes and organic reactions. These studies help explain experimental results, guide the development of new catalysts, and support the creation of more environmentally friendly chemical processes. DFT is a type of computational method that helps understand chemical systems at the level of individual atoms. It is a quantum chemical approach that is used to calculate the electronic structure of a system. These calculations have been widely used in many studies to support and expand experimental understanding. DFT is used to back up experimental findings, clarify ambiguous results, or reveal details that are not easily observed through experiments. Metal-ligand cooperative (MLC) binding is when a metal and a ligand work together to activate small molecules that are attached to a metal complex. The first group of complexes studied included a triaryl tetradentate ligand made from o-phenylenediamine. This ligand is called N4 because it connects to metals through four nitrogen atoms. Overall, the study showed that the distance between iron atoms is greatly affected by the groups attached to them, which could lead to better ways of controlling metal-metal interactions and related magnetic properties in bimetallic complexes. DFT calculations were used to find out the origin of conjugation in polythiazyl derived polymers (polyNAS). Polythiazyl is one of the first known polymers made of sulfur and nitrogen with properties similar to metals. These properties include electrical conductivity. Geometry optimizations were carried out for oligomers and periodic systems of polythiazyl and polyNAS polymers to examine their shapes and optical properties.

Keywords:- Biomedical Applications; Catalysis; Electronic Structure; Metal complexes; Synthetic Methods;

Introduction

Understanding how reactions work, figuring out why some reactions happen more than others, and predicting new ways to use catalysts are big challenges in synthetic organic chemistry. To understand reactions at a molecular level and how catalysts work, scientists use computational studies[1]. These methods are especially useful in reactions with complex paths, reactive middle steps, strong solvent effects, and transition metal complexes that have unpaired electrons. In these cases, experimental techniques are not as effective. Transition metal complexes have properties that can be adjusted by choosing the right ligands and metals. This allows control over things like spin, oxidation state, and electronic or optical behavior[1]. By carefully tuning these properties, scientists have made big progress in catalysts and materials that have special functions, like being magnetic. Computational chemistry, especially quantum modeling, has always played an important role in understanding how structure relates to properties and in designing these types of inorganic molecules.More recently, faster computers, bigger data sets from both theory and experiments, and machine learning have helped speed up the discovery and design of transition metal complexes[1-2].

Advances in artificial intelligence are rapidly changing all areas of chemistry, and the complexity of metal-organic bonding at open-shell transition metals makes this area especially good for using data-driven and faster methods. Catalytic reactions in organic and bioorganic chemistry are powerful tools in making functional organic compounds used in biomedical and pharmaceutical research. Even though a lot has been achieved in developing synthetic methods, there are still challenges in designing better catalysts[1]. One major issue is understanding the factors that control regio- and stereoselectivity in reactions involving transition metal and enzyme catalysts. This is important in many reactions, such as glycosylation in carbohydrate chemistry and reactions that modify C-H and alkene bonds. The usual way to study reaction mechanisms and selectivity is by using density functional theory (DFT) to calculate reaction paths and energy profiles[3].

These profiles help identify the best reaction path, the steps that determine the rate and selectivity, and how ligands and substrates affect reactivity and selectivity. However, this standard approach has limits in situations where (a) solvent effects are very strong and hard to model with usual methods, (b) selectivity is influenced by a mix of factors from the substrate and the catalyst, and (c) in enzyme catalysis due to the flexibility and size of the enzyme[1-3].

My research is focused on solving these challenges, like understanding how reactions work and what factors control the selectivity in glycosylation reactions, figuring out why certain sites are chosen in silver-catalyzed C-H amination reactions,

and identifying what determines the enantioselectivity in P450-catalyzed bioorganic reactions. My work uses different computational methods, such as ab initio molecular dynamics (AIMD) to study glycosylation reactions with reactive oxocarbenium intermediates in a real solvent environment, DFT calculations to explore the mechanisms of silver-catalyzed C-H amination reactions, and coupled-cluster and multireference methods to examine the electronic structures of silver complexes[1]. I also used classical molecular dynamics (MD), hybrid quantum mechanics/molecular mechanics (QM/MM) calculations, and metadynamics simulations to study the mechanism and reasons behind the enantioselectivity in engineered P450 atom transfer radical cyclases. Earlier studies helped clarify the shape and stability of oxocarbenium intermediates in solution and the transition states in glycosylation reactions. However, there is still no general computational method that can reliably predict the mechanism of any given glycosylation reaction[4].

Applications in Metal Complexes

Computational methods help us better understand the complex behavior of metal complexes:

- **Structure and Geometry:** These methods calculate the best shapes of molecules, like octahedral, square planar, or tetrahedral, along with bond lengths and angles. These results match well with data from experiments like X-ray crystallography[4].
- **Electronic Properties:** They help analyze the electronic structure, oxidation states, and spin states of metal complexes.This is important for understanding how these complexes behave and function.
- **Spectroscopy:** Using methods like time-dependent DFT, computational studies can predict data from techniques such as UV-Vis, IR, and NMR.This allows scientists to compare and interpret experimental results more accurately[1].
- **Stability and Thermodynamics:** These studies help determine how strong metal-ligand bonds are and how stable metal complexes are. They also provide information about thermodynamic properties that influence complex formation[4].

Applications in Organic Transformations

Computational tools are very useful for studying the steps and efficiency of organic reactions, especially those involving metal catalysts:

- Mechanistic Elucidation: These methods give detailed views of reaction pathways, transition states, and intermediate steps, which are hard to see in experiments.This helps scientists improve reaction conditions.
- Catalyst Design: Computational modeling allows scientists to design new metal-based catalysts, such as those used in metal-organic frameworks (MOFs), that have specific properties like high efficiency and selectivity for reactions like oxidation, epoxidation, and coupling[4].
- High-Throughput Screening: Using machine learning and computer screening, scientists can explore a large number of potential catalysts, identifying promising candidates for real lab work.
- Green Chemistry: By understanding how reactions work, computational studies help create more sustainable and efficient synthetic methods, such as reactions that use less harmful chemicals and waste[4].

Key Computational Methods

- Density Functional Theory (DFT): This is the most commonly used method for studying the electronic structure of molecules. It is widely used to calculate energies, shapes, and properties of metal complexes.
- Wave Function Methods (e.g., Coupled Cluster): These are more advanced methods that are used to check and improve the accuracy of results for specific systems[4-5].
- QM/MM (Quantum Mechanics/Molecular Mechanics): These combined methods are used for large or complex systems, like enzymatic reactions or metal-organic frameworks, where a small part is studied using quantum mechanics and the rest is modeled with classical methods.

In summary, computational studies play a big role in modern chemistry. They speed up discovery and give important knowledge about how metal complexes and organic reactions work[4].

Scope of the Review

This review looks at situations where computational chemistry and machine learning are key in speeding up the discovery of inorganic complexes. To understand how they help, we look at how electronic structure theory, molecular modeling, cheminformatics, and machine learning have developed together[4]. We explain how large-scale automation helps explore the chemical space of transition metals by looking at both experimental and computational high-throughput screening methods. We also look at specific challenges when dealing with open-shell, first-row (like 3d) transition metals, especially in terms of how much data is available and how reliable it is, both from traditional computational models and from

experiments. We briefly mention heavier elements, like those with open 4d, 5d, or lanthanide 4f shells, but the discussion is more limited because there is less available experimental data[6].

This review highlights recent advancements in the past few years about machine learning models that can predict electronic structure properties quickly and cheaply, which is useful for high-throughput screening and faster discovery in transition-metal chemistry.

It also covers related work from the past 50 years in data mining, semiempirical modeling, and molecular mechanics. This background is important to show where machine learning models can replace these methods or learn from them. Other topics in this review include data-driven approaches for getting information from experimental literature and creating linear quantitative structure-property and scaling relationships from experimental and literature data[4-7].

The main focus of this review is on methods and software that help predict properties and speed up chemical discovery in metal-organic complexes and related materials, like porous metal-organic frameworks, at the edge of traditional electronic structure theory.

Other inorganic materials, such as most solid-state materials or biological systems (like metalloenzymes), are not included. This review also doesn't cover special considerations related to neural network potentials and how they are used in molecular dynamics. When we talk about catalytic applications, we focus on designing catalysts rather than discovering reaction mechanisms[4].

Computational Methods

Density Functional Theory (DFT) Calculations

DFT is a common method in computational chemistry that uses quantum mechanics to study how glycosylation reactions work. There are many different DFT methods that help with finding the best shape of molecules in their normal state and during reactions, as well as calculating other properties and energy levels. To get good results without spending too much time, I used the dispersion-corrected PBE functional. This method is known for being accurate enough for organic molecules while using less computer power, which helps in studying the steps of glycosylation reactions[7]. All the DFT calculations were done on supercomputers called Pitt CRC, TACC, and XSEDE. To compare the reaction path structures from calculations done in air and those done with a model for water, I used Gaussian 16 software. I studied the structures optimized in the gas phase using the PBE-D3/6-311+G(d,p) level, and also in a water-like environment using the SMD model with the same level[4]. The Gibbs free energy and enthalpy values I reported include corrections for temperature, which were calculated at 298 K and standard concentration of 1 mol/L using GoodVibes. The 3D images of the best shapes were made with CYLView[7].

AIMD Simulations

AIMD simulations were carried out using the QUICKSTEP module from the CP2K software. The structure of the liquid solution was represented by an orthorhombic box with dimensions 20.0 Å × 16.0 Å × 16.0 Å, which contained 49 acetonitrile (ACN) molecules. In the simulations involving dichloromethane (DCM) and methyl tert-butyl ether (MTBE) as solvents, the box contained 44 DCM molecules and 21 MTBE molecules, respectively. The size of the box was selected to match the density of pure ACN (0.786 g/cm³), DCM (1.327 g/cm³), and MTBE (0.740 g/cm³)[7]. The forces acting on atoms were calculated using DFT methods with the PBE exchange-correlation functional. The Kohn-Sham orbitals were described using a combination of Gaussian and plane-wave basis functions. For all atoms, DZVP basis sets and Goedecker-Teter-Hutter pseudopotentials were used. The plane-wave basis set was expanded up to a cutoff of 280 Ry. The Grimme D3 method was applied to account for dispersion interactions. The ground state energy was calculated until it converged to within 10^{-5} hartree. The positions of the atoms were updated using the BOMD approach with a time step of 0.5 femtoseconds. The temperature of the system was maintained using a Nosé-Hoover thermostat with a time constant of 1 picosecond[4-7].

Theoretical Challenges for Conventional DFT Functionals

Although DFT is commonly used because it offers a good balance between cost and accuracy for main group chemistry, most exchange-correlation (xc) approximations in DFT have issues with self-interaction errors, which come in one-electron and many-electron forms. These self-interaction errors are linked to missing constraints in DFT, such as the lack of piecewise linearity or derivative discontinuity when electrons are removed. This leads to underestimating fundamental gaps and incorrect hybridization[6].

As discussed elsewhere, a common way to improve DFT accuracy for main group methods is to include higher-order terms in the density expansion, which are often described as steps on a Jacob's ladder leading to higher chemical accuracy, while

meeting constraints from model systems or experimental data[8].

However, this approach faces challenges in open-shell transition-metal chemistry. The partially filled d shell is very sensitive to both absolute self-interaction error, known as delocalization error, and imbalances in delocalization during a reaction[9].

Exchange-correlation functionals that reduce delocalization error often increase static correlation error, which is important for transition-metal chemistry, with very few exceptions.

The best functionals for transition-metal chemistry are different from those used for main group: pure semilocal generalized gradient approximations (GGAs) are often preferred when static correlation error is present, whereas hybrid GGAs and "higher rung" functionals are usually thought to perform better for organic molecules. Also, DFT errors are usually much larger in transition-metal chemistry, and the methods used to correct these errors are different from those used in main group chemistry[10].

Conclusion

We used both computer-based calculations and lab experiments to understand how our new biocatalytic atom transfer radical cyclization works and why it shows enantioselectivity. This was done using a P450 cyclase that was developed in the lab. Computational organic chemistry has become a helpful tool in bioorthogonal chemistry, allowing scientists to gain more understanding and move this area of chemistry forward. In this review, I explain the use of computational methods in this field. I cover the main ways calculations are used and how they apply to key areas of bioorthogonal chemistry, especially cycloadditions. Using these techniques, scientists have found ways to change the electronic structure through hyperconjugation, which helps improve reactions without making the molecules unstable. For cycloadditions, methods like distortion/interaction analysis and energy decomposition analysis have been useful. These methods have helped create better-reacting bioorthogonal reagents and develop pairs of reactions that don't interfere with each other. Finally, I mention new areas like cheminformatics and machine learning, which may help in discovering and fine-tuning new reactions in the future.

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