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STRUCTURE-ACTIVITY RELATIONSHIPS IN MOLECULAR INORGANIC CATALYSTS: A COMPUTATIONAL PERSPECTIVE

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ABSTRACT

Molecular inorganic catalysts play a central role in modern catalysis, enabling selective and efficient transformations in energy conversion, environmental remediation, and fine chemical synthesis. Understanding how catalyst structure governs activity, selectivity, and stability is essential for rational catalyst design. Structure-activity relationship (SAR) analysis provides a conceptual framework for linking molecular features, such as metal identity, oxidation state, coordination geometry, ligand electronic properties, and steric environment, to catalytic performance. In recent decades, computational chemistry has emerged as a powerful tool to elucidate SARs in molecular inorganic catalysts, complementing experimental studies and enabling predictive catalyst design. Density functional theory (DFT), ab initio methods, molecular dynamics, and data-driven approaches have been widely applied to map reaction pathways, identify active species, quantify energetic trends, and reveal structure-property correlations. This review provides a comprehensive overview of computational strategies used to investigate SARs in molecular inorganic catalysis. Key structural descriptors, mechanistic insights, and representative case studies across redox, acid-base, and organometallic catalysis are discussed. Current challenges and emerging directions, including high-throughput screening and machine learning-assisted catalyst discovery, are also highlighted.

Keywords: Molecular inorganic catalysts, structure-activity relationships, Density Functional Theory, ligand effects, mechanistic modeling.

INTRODUCTION

Molecular inorganic catalysts, encompassing coordination complexes, organometallic species, and well-defined metal-ligand assemblies, constitute a cornerstone of homogeneous catalysis[1]. Their molecularly precise architectures distinguish them fundamentally from heterogeneous catalysts, enabling direct control over the coordination environment of the active metal center[2]. This structural definition allows systematic modulation of electronic, steric, and geometric parameters, which, in turn, govern catalytic activity, selectivity, and stability. As a result, molecular inorganic catalysts have found widespread application in diverse chemical transformations, including olefin polymerization, cross-coupling reactions, C-H activation, small-molecule functionalization, and energy-relevant processes such as electrocatalytic water splitting, hydrogen evolution, and CO_2 reduction[3].

Despite remarkable experimental advances, the rational design of high-performance molecular inorganic catalysts remains a formidable challenge. A single structural feature rarely dictates catalytic behavior; instead, it emerges from a subtle interplay among metal identity, oxidation and spin states, ligand electronics, steric environment, and reaction conditions[4]. Small changes in ligand substituent's or coordination geometry can lead to disproportionately large changes in catalytic outcomes, often in ways that are difficult to predict intuitively. Furthermore, many catalytic cycles involve short-lived intermediates and transition states that are experimentally inaccessible, limiting direct structure-function correlations[5].

In this context, structure-activity relationships (SARs) provide a robust conceptual framework for linking catalyst structure to observed reactivity. SAR analysis seeks to identify which molecular features are responsible for enhanced activity, improved selectivity, or increased robustness, thereby enabling informed catalyst optimization[6]. However, experimental SAR studies are often constrained by synthetic feasibility, time, and cost, as well as by the inherent difficulty of isolating and characterizing reactive intermediates. These limitations can obscure fundamental mechanistic understanding and slow the discovery of improved catalyst systems.

Computational chemistry has emerged as an indispensable tool for overcoming these challenges[7]. Quantum chemical methods, especially density functional theory (DFT), allow direct interrogation of electronic structure, metal-ligand bonding, and reaction energetics at an atomistic level. Computational modeling enables the exploration of complete catalytic cycles, the identification of rate and selectivity-determining steps, and the characterization of transient species that are otherwise experimentally elusive[8]. Crucially, catalyst structures can be systematically modified *in silico*, allowing individual structural parameters to be varied independently and their effects on reactivity to be quantified. This capability has transformed SAR analysis from a largely empirical exercise into a mechanistically grounded, predictive discipline.

Beyond static electronic structure calculations, modern computational approaches incorporate solvation effects, dynamic behavior, and environmental influences through continuum solvent models, molecular dynamics simulations, and hybrid quantum-mechanical/molecular-mechanical (QM/MM) frameworks[9]. In parallel, high-throughput computational screening and data-driven techniques, including machine learning, are increasingly being employed to extract transferable SAR descriptors and accelerate catalyst discovery. These developments have positioned computational chemistry not only as a complementary interpretive tool but as a central driver of rational catalyst design[10]. This review provides a comprehensive overview of computationally derived SARs in molecular inorganic catalysts. Emphasis is placed on fundamental

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principles linking metal-centered and ligand-centered structural features to catalytic performance, as revealed through computational studies. Representative case studies across redox, acid-base, and organometallic catalysis are discussed to illustrate how computational SAR analysis informs mechanistic understanding and catalyst optimization. Rather than exhaustively cataloging individual systems, the review focuses on transferable concepts and methodological strategies that can guide the design of next-generation molecular inorganic catalysts.

Table 1. Structural parameters governing activity in molecular inorganic catalysts and their computational descriptors

Structural parameter	Catalytic relevance	Common computational descriptors
Metal identity	Redox behavior, substrate activation	d-electron count, orbital energies
Oxidation state	Reaction energetics, mechanistic pathways	Mulliken/NBO charges, redox potentials
Spin state	Reactivity and selectivity control	Spin density, energy gaps
Coordination geometry	Orbital overlap, binding modes	Bond angles, coordination number
Ligand electronics	Metal reactivity tuning	HOMO-LUMO gap, donor-acceptor interactions
Ligand steric	Substrate access, selectivity	Buried volume, steric maps
Secondary interactions	Transition-state stabilization	Noncovalent interaction analysis

STRUCTURE-ACTIVITY RELATIONSHIPS IN MOLECULAR INORGANIC CATALYSIS

Conceptual Framework of Structure-Activity Relationships

In molecular inorganic catalysis, SARs describe how specific structural features of a catalyst influence measurable catalytic outcomes, such as activity, selectivity, and stability. Because molecular catalysts possess well-defined, tunable active sites, SAR analysis can be performed with greater precision than in heterogeneous systems[11]. The aim is to identify which structural elements control individual steps of the catalytic cycle and how these elements can be systematically optimized.

Key parameters include the identity of the metal center and its electronic configuration, which determine redox flexibility and substrate activation. Oxidation state and spin state influence the electron distribution and the accessibility of reactive intermediates, while coordination number and geometry govern orbital overlap and steric accessibility[12]. Ligand properties, such as donor atom type, denticity, and substituent effects, further modulate the electronic and steric environment of the metal center. Importantly, catalytic performance often arises from the combined effects of these parameters rather than from a single dominant feature[13].

Computational methods enable controlled variation of individual structural parameters, allowing the isolated and cooperative effects of these parameters on catalytic behavior to be evaluated. This capability is central to establishing reliable SARs and linking catalyst structure directly to mechanistic and kinetic features.

Key Structural Descriptors in Computational SAR Analysis

Computational SAR analysis relies on quantitative descriptors that capture the electronic and geometric characteristics of inorganic molecular catalysts. Frontier molecular orbital energies and compositions are widely used to assess reactivity trends, particularly in processes involving electron transfer or substrate activation[14]. Changes in these descriptors are often correlated with activation barriers and redox behavior.

Metal-ligand bond strengths and bond metrics provide insight into catalyst stability and ligand-exchange processes, while charge-distribution and spin-density analyses help track electron flow and distinguish metal- versus ligand-centered reactivity[15]. Ligand-field splitting parameters are especially relevant for transition-metal complexes, where coordination geometry and ligand identity influence spin-state energetics and reaction pathways.

Steric effects are commonly quantified using descriptors such as buried volume or cone angle, which capture the spatial environment around the metal center[16]. These parameters are critical for understanding selectivity and catalyst deactivation pathways. Together, electronic and steric descriptors provide a concise yet informative framework for correlating molecular structure with catalytic performance and for developing transferable SAR principles.

COMPUTATIONAL METHODS FOR SAR ANALYSIS

Density Functional Theory

DFT is the primary computational tool for investigating SARs in molecular inorganic catalysts, owing to its favorable balance of accuracy and computational efficiency[17]. DFT calculations are routinely used to optimize catalyst geometries, analyze electronic structures, and evaluate reaction pathways and activation barriers for key catalytic steps. In SAR studies, DFT enables systematic comparison of closely related catalyst structures, linking trends in reactivity directly to changes in metal identity, ligand environment, or coordination geometry[18]. Hybrid functionals and dispersion-corrected approaches are particularly important for transition-metal complexes, where both electronic correlation and noncovalent interactions strongly influence catalytic behavior.

ab-Initio and Multireference Methods

For catalyst systems involving near-degenerate electronic states, pronounced spin-state effects, or strong metal-ligand covalency, single-reference DFT methods may be insufficient[19]. In such cases, multireference approaches, including the complete active space self-consistent field (CASSCF) and second-order perturbation corrections (CASPT2), provide a more reliable description of electronic structure[20]. Although their high computational cost limits routine application, these methods are essential for establishing accurate SARs in open-shell or electronically complex catalysts, particularly when spin-state energetics decisively influence reactivity.

Molecular Dynamics and Solvent Effects

Static electronic structure calculations often neglect thermal motion and environmental influences that can affect catalytic performance. Molecular dynamics (MD) simulations, including ab initio MD, address this limitation by capturing conformational flexibility, dynamic ligand behavior, and solvent-mediated interactions[21]. Solvent effects are commonly treated with implicit continuum models for efficiency or with explicit solvent molecules when specific solute-solvent interactions are mechanistically meaningful. Including dynamic and solvation effects refines computational SAR analyses by providing a more realistic representation of the catalytic environment.

Data-Driven and High-Throughput Approaches

Recent advances in computational catalysis have enabled high-throughput screening of molecular inorganic catalysts using automated DFT workflows. By evaluating large sets of catalyst variants, these approaches allow rapid identification of structural features correlated with improved activity or selectivity. Machine learning models trained on computed electronic and steric descriptors are increasingly used to extract generalized SAR patterns and predict catalytic performance beyond the initial training set[22]. Such data-driven strategies complement mechanistic studies and represent a promising direction for accelerating catalyst discovery.

METAL-CENTERED STRUCTURE-ACTIVITY RELATIONSHIPS

Metal Identity and Periodic Trends

The identity of the metal center is a primary determinant of catalytic behavior in molecular inorganic catalysts, and computational studies have been instrumental in revealing periodic trends that underpin SARs. Variations across the transition series influence fundamental properties such as redox potential, orbital energies, and metal-ligand bond strengths[23]. Early transition metals typically exhibit strong σ-donor interactions and pronounced oxophilicity, favoring reactions involving polarized substrates and σ-bond activation. In contrast, late transition metals often display greater π-back bonding ability, which enhances activation of unsaturated substrates and stabilizes π-complex intermediates[24]. Computational SAR analyses quantify these trends by correlating metal-dependent electronic descriptors with reaction energetics, enabling the rational selection of metal centers for targeted catalytic transformations.

Oxidation States and Spin States

The ability of a metal center to access multiple oxidation and spin states is central to the versatility of many molecular inorganic catalysts. Computational investigations have shown that catalytic activity and selectivity often hinge on the relative stability and interconversion of these electronic states along the reaction pathway[25]. Subtle modifications in ligand electronic properties or the coordination environment can significantly shift oxidation and spin-state energetics, thereby altering reaction barriers and preferred mechanisms[26]. DFT and multireference calculations are particularly valuable for establishing SARs that link electronic state accessibility to observed catalytic performance, especially in redox-active and open-shell systems.

Coordination Geometry

Coordination geometry describes the arrangement of ligands around the metal center and directly influences orbital overlap, substrate binding orientation, and transition-state stabilization[27]. Computational SAR studies often correlate changes in coordination number and geometry with variations in activation barriers and reaction selectivity. Geometric distortions induced by ligand constraints can favor specific reaction pathways by stabilizing key intermediates or lowering transition-state energies[28]. By systematically comparing geometrically related catalyst structures, computational methods reveal how geometric control at the metal center translates into improved catalytic efficiency.

LIGAND-CENTERED STRUCTURE-ACTIVITY RELATIONSHIPS

Electronic Effects of Ligands

Ligand electronics are a key determinant of the performance of molecular inorganic catalysts[29]. The donor strength, π-acceptor ability, and substituent effects of ligands modulate electron density at the metal center, influencing redox potentials, substrate activation, and overall reaction energetics[30]. Computational analyses provide quantitative insight into these effects by evaluating frontier molecular orbitals, metal-ligand covalency, and charge transfer between the metal and ligands. Systematic in silico variation of ligand electronics enables the identification of trends that correlate with catalytic activity and selectivity, supporting rational ligand design.

Steric Effects and Secondary Interactions

Steric properties of ligands dictate accessibility of the metal center and can significantly influence reaction pathways. Bulky ligands can prevent undesired side reactions, guide substrate orientation, or stabilize transition states, thereby affecting selectivity and turnover rates[31]. Computational descriptors such as buried volume, cone angle, and steric contour maps are widely used to quantify these effects. Additionally, secondary interactions, such as hydrogen bonding, π-π stacking, and van der Waals contacts, can modulate reactivity, and their contributions can be analyzed through noncovalent interaction (NCI) mapping and energy decomposition analyses[32].

Non-Innocent and Redox-Active Ligands

Redox-active or non-innocent ligands introduce additional complexity by participating directly in electron-transfer events. These ligands can alter the traditional metal-centered view of SARs, as catalytic cycles may involve both metal- and ligand-based redox steps[33]. Computational methods are essential for disentangling these contributions, providing insights into the relative energies of ligand- versus metal-centered states and their influence on activation barriers[34]. Understanding such ligand-mediated effects enables the design of cooperative metal-ligand systems with enhanced reactivity, selectivity, or multi-electron-transfer capability.

MECHANISTIC SARS IN REPRESENTATIVE CATALYTIC REACTIONS

Redox Catalysis

Redox reactions, such as oxidation and reduction processes, provide a clear context for applying SARs in molecular inorganic catalysis. Computational SAR studies link metal-ligand electronic structures to experimentally observed redox potentials and activation barriers[35]. By systematically varying metal identity, oxidation state, and ligand environment in silico, researchers can predict trends in catalytic efficiency and selectivity. Representative applications include water oxidation and hydrogen evolution, in which the relative stability of high-valent intermediates and electron-transfer pathways are strongly influenced by both metal-centered and ligand-centered factors[36]. Such mechanistic insights are invaluable for the rational design of catalysts capable of multi-electron transfer and energy conversion.

Acid-Base and σ-Bond Metathesis Catalysis

In acid-base catalysis and σ-bond metathesis, SARs often reflect the cooperative interplay between metal centers and ligands. Computational studies have shown that proton shuttling, bond

polarization, and transition-state stabilization are highly sensitive to ligand electronic properties, geometry, and flexibility[37]. For example, the presence of basic ligand sites or hydrogen-bond donors can lower activation barriers by facilitating proton transfer or stabilizing reactive intermediates[38]. These findings enable precise tuning of catalytic pathways, particularly in metal-ligand cooperative systems where both components contribute directly to reactivity.

Organometallic Transformations

Organometallic catalytic cycles, including cross-coupling, insertion, and elimination reactions, illustrate SARs in processes governed by discrete mechanistic steps such as oxidative addition, migratory insertion, and reductive elimination[39]. Computational SAR analysis enables systematic correlation of ligand properties-steric bulk, electronic donation, or π-acceptor character-with key kinetic barriers. For instance, bulky ligands can favor reductive elimination by destabilizing high-coordinate intermediates, while electron-rich ligands may accelerate oxidative addition. These studies provide a mechanistic rationale for ligand selection and optimization, guiding the development of catalysts with improved activity, selectivity, and substrate scope.

CHALLENGES AND LIMITATIONS

Despite significant progress enabled by computational SAR analyses, several challenges persist in accurately predicting and rationalizing the performance of molecular inorganic catalysts. A major limitation is the treatment of electronic correlation, particularly for open-shell or multi-reference systems, where single-reference methods such as standard DFT may fail to capture the correct spin-state energetics or near-degenerate electronic configurations. Multireference and high-level ab initio methods can address these issues; however, they are often computationally prohibitive for larger or more flexible catalysts.

Dynamic effects, including ligand flexibility, conformational changes, and thermal fluctuations, add another layer of complexity. Static calculations may not fully capture the influence of these factors on substrate binding, transition-state stabilization, or overall reaction pathways. While molecular dynamics and enhanced sampling techniques can provide insights into such effects, integrating them with accurate electronic structure calculations remains resource intensive.

Solvent and environmental interactions further complicate SAR predictions. Implicit solvation models may inadequately capture specific hydrogen-bonding or noncovalent interactions, while explicit solvation requires careful selection of solvent configurations and significantly increases computational cost. These factors can lead to discrepancies between computed reaction energetics and experimental observations.

Finally, translating computationally derived SARs into experimentally realizable catalysts requires careful validation. Synthetic accessibility, ligand stability, and unanticipated side reactions may limit the practical applicability of theoretically optimized systems. Discrepancies between predicted and observed catalytic activities underscore the need for systematic benchmarking, standardized protocols, and iterative feedback between computation and experiment to refine predictive models. Addressing these challenges is essential for reliable mechanistic interpretation and the rational design of next-generation molecular inorganic catalysts.

EMERGING TRENDS AND FUTURE PERSPECTIVES

The integration of computational chemistry with high-throughput screening, machine learning, and automated workflows is rapidly transforming the analysis of SARs into molecular inorganic catalysis. Machine learning models, trained on computed electronic, steric, and mechanistic descriptors, enable rapid prediction of catalyst performance across large chemical spaces, reducing reliance on time-consuming trial-and-error synthesis. These approaches are particularly effective at identifying non-intuitive SAR trends that may be overlooked by traditional mechanistic analysis.

Future research is expected to focus on predictive catalyst design, where multiple objectives, such as activity, selectivity, and stability, are optimized simultaneously. Multi-objective computational frameworks that combine electronic structure calculations with data-driven modeling enable the exploration of trade-offs among competing properties and guide the selection of promising catalyst candidates. Coupling these predictive approaches with experimental validation in an iterative workflow will further accelerate catalyst discovery and improve the reliability of computational SARs.

Advances in the interpretability of machine learning models and data-driven analyses are also critical. By elucidating which structural features most strongly influence catalytic performance, these approaches can provide mechanistic insight rather than serving solely as black-box predictors. Integrating electronic, steric, and dynamic descriptors into interpretable frameworks will enhance understanding of cooperative metal-ligand effects, spin-state contributions, and solvent-mediated influences, ultimately supporting the rational design of next-generation molecular inorganic catalysts.

CONCLUSIONS

Computational approaches have become indispensable for understanding and guiding SARs in molecular inorganic catalysts. By providing detailed molecular-level insight into electronic structure, coordination geometry, ligand-metal interactions, and reaction mechanisms, these methods enable systematic correlations between catalyst features and activity, selectivity, and stability. Computational SAR analyses not only rationalize experimental observations but also enable predictive tuning of catalyst structures before synthesis, reducing trial-and-error and accelerating discovery.

Integration of advanced electronic structure methods, molecular dynamics, solvation modeling, and high-throughput workflows has broadened the scope of SAR studies to include complex catalytic systems, including open-shell, redox-active, and multistep reaction pathways. Incorporating machine learning and data-driven models further enhances the ability to identify non-obvious structure-function relationships and optimize multiple catalytic properties simultaneously.

Looking ahead, continued methodological advances, coupled with tighter integration between computation and experiment, are expected to improve predictive accuracy, deepen mechanistic understanding, and guide the rational design of next-generation molecular inorganic catalysts. Computational SAR analysis thus serves not only as a tool for interpreting existing systems but also as a framework for designing catalysts with tailored reactivity and selectivity for emerging chemical transformations.

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