CHEMICAL REVIEWS

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Introduction: Inorganic and Bioinorganic Mechanisms

The mechanisms of chemical reactions in solution are of major significance in everyday chemical and biological processes. In many cases, transition metal ions and complexes play a central role in controlling the reactivity and mechanism of the chemical reaction of interest. This can be due to the actual reaction occurring at the metal center and/or the catalytic activity of the metal complex in an overall chemical process. The unique ability of transition metal ions and complexes to control the chemistry of environmental, industrial, and biological processes has increased the importance of clarifying their mechanistic behavior in simple and complex chemical processes. The role of the central metal atom or ion has received considerable attention not only in fundamental inorganic and organometallic chemistry but also in more applied areas such as in environmental, bioinorganic, and bioorganic chemistry. Such studies have contributed significantly to the elucidation of the underlying reaction mechanisms.

Rapid developments in this area over the past 10−15 years have benefited from the application of sophisticated spectroscopic techniques (Mössbauer, EPR, NMR, Raman, IR, mass spectrometry), rapid cryogenic X-ray structure determinations of reactive intermediates, matrix isolation of reactive intermediates, fast kinetic techniques, low-temperature kinetics, high-pressure kinetic and thermodynamic techniques to construct volume profiles as compared to energy profiles, and theoretical methods to analyze and predict reaction mechanisms.

The interest and advances in this area have led to regular conferences on the general topic of inorganic reaction mechanisms, such as the yearly meeting of the Inorganic Reaction Mechanisms Discussion Group of the Royal Society of Chemistry and the biannual

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Gordon Conference on Inorganic Reaction Mechanisms. In addition, recent issues of *Advances in Inorganic Chemistry* have been devoted to such topics as "Inorganic Reaction Mechanisms" (Vol. 54, 2003), "Redox-active Metal Complexes" (Vol. 56, 2004), "Relaxometry of Water−Metal Ion Interactions" (Vol. 57, 2005), and "Homogeneous Biomimetic Oxidation Catalysis" (Vol. 58, in press), which all involve the mechanistic description of chemical processes that occur in solution. In this thematic issue of *Chemical Reviews*, we focus our attention on the mechanisms of inorganic and bioinorganic processes, their interrelation in controlling the outcome of specific chemical conversions, and their close relation in terms of improving our understanding of the overall chemical process. We thoroughly believe that through the systematic clarification of reaction mechanisms, the insight gained will enable us to systematically tune the reactivity and product selectivity of chemical processes that are controlled by the interaction of the metal center with substrate molecules.

This issue consists of reviews that are more of either an inorganic or bioinorganic nature, covering a wide range of reaction types. The presentation of the contributions follows a sequence selected according to the type of reaction studied, covering both inorganic and bioinorganic aspects at the same time. In most cases the inorganic contributions focus on fundamental and model systems from coordination chemistry, whereas the bioinorganic systems deal with model either complexes to mimic certain biological processes or enzymatic systems themselves. The selected presentation should link inorganic and bioinorganic reaction types and mechanisms in order to capture the attention from individuals that would like to see where the study of inorganic systems may lead in a biological sense, and vice versa.

The study of the mechanisms of chemical reactions in solution incorporates a wide range of experimental kinetic and spectroscopic techniques, as well as the application of theoretical calculations. Idealistically, the interaction of different disciplines in chemistry should lead to a mechanistic picture that presents the momentary visualization of the chemical mechanism on the basis of all available kinetic, spectroscopic, and theoretical information on the studied system. Suggested mechanisms can only be claimed to be the best picture that presently accounts for all the available information on the reaction. Future development of even more sophisticated experimental and theoretical techniques will show whether the proposed mechanisms are indeed true presentations of the underlying chemical processes.

The 21 contributions in this issue are arranged in a specific sequence. We first present contributions dealing with ligand substitution reactions. This is the most fundamental type of chemical reaction that can occur when a metal complex is dissolved in solution in the presence of other nucleophiles. In fact, such processes are in many cases responsible for the catalytic activity of metal complexes in solution and form the basis of reaction types discussed in the subsequent sections. The next contributions are presented according to the activation of small molecules such as oxygen, nitrogen, nitrogen oxide, and hydrocarbons. Finally, the focus is shifted to electron-transfer reactions, since such reactions form an integral part of the activation of small molecules. Thus, the selected sequence presents a logical development of the topic of inorganic and bioinorganic reaction mechanisms, since ligand substitution reactions control the binding of small molecules, which is followed by the activation of the small molecule that usually involves an electron-transfer process with the metal center. Finally, two more general contributions on the application of photochemical and theoretical methods in the study of inorganic and bioinorganic mechanisms are included in this volume. At this point, the editor of this volume would like to emphasize his appreciation for the fact that the invited experts in the different areas were prepared to participate in this project and to stick to a rather tight production schedule. Without their enthusiastic support, the project could not have been realized.

The most fundamental ligand substitution process that can occur on a metal center in solution is the exchange between coordinated and bulk solvent molecules. The reactivity (inert versus labile) and mechanism of solvent exchange describe the fundamental behavior of transition metal ions and complexes in solution and form the basis for complex-formation and nonsymmetrical ligand substitution reactions. Although solvent exchange reactions may at first sight be uninteresting due to the absence of an overall chemical conversion, their mechanistic understanding is of fundamental importance in all subsequently treated reaction types. In the first review by Helm and Merbach on *inorganic and bioinorganic solvent exchange mechanisms*, the authors report on detailed studies of solvent exchange reactions on main group metal ions, transition metal ions, and solvated lanthanide and actinide ions. The influence of spectator ligands on the rate and mechanism of solvent exchange reactions is also presented. In the authors' own work in this area, the application of high pressure NMR techniques and the construction of volume profiles played a crucial role in assigning the intimate nature of the solvent exchange mechanism. The bioinorganic systems described mostly deal with the development of gadolinium NMR contrast reagents in which the lability of coordinated water plays a crucial role. Richens reviews *ligand substitution reactions at inorganic centers* and mainly focuses on nonsymmetrical substitution processes dealing with complex-formation reactions. By way of introduction, he reviews the role of solvent exchange reactions and then offers a systematic survey of ligand substitution reactions on four-, five-, six-, seven-, eight-, and nine-coordinate metal centers. He also covers the influence of labilization effects caused by hydroxyl ligands, metal−carbon bonds, terminal and bridged oxo and nitride ligands, and the behavior of polynuclear clusters. The application of quantum chemical methods for the *treatment of substitution and rearrangement mechanisms of transition metal complexes* is reviewed by Rotzinger. The described chemistry includes water, ammonia, and fluoride exchange reactions, as well as ligand substitution and rearrangement (isomerization) processes. His final section is devoted to electronic structure−reactivity relationships. Much of the reported work demonstrates the good agreement between mechanistic assignments reached on the basis of volume profile analysis and those predicted theoretically. A contribution that is of fundamental importance in the description of ligand substitution reactions comes from Macchioni, who reports on the role of *ion pairing in transition metal organometallic chemistry*. The author clearly distinguishes between main group metal and transition metal complex ion pairs on the basis of the nature of the metal−ligand bond, which predominantly has a Coulombic character for main group metal ions and a covalent character for transition metal ions. The review focuses on the effect of ion pairing on the structure and reactivity of transition metal organometallic ion pairs in cases where the counterion, even when located in the first coordination sphere, still maintains most of its original charge, and consequently does not significantly share electron density with the metal center. The types of reactions covered in which ion pairing plays a crucial role include formation and heterolytic splitting of dihydrogen metal complexes, olefin polymerization, and Diels−Alder, hydrogenation, and carbonylation processes. Ligand substitution reactions also play an important role in the *chemistry and enzymology of vitamin* B_{12}. This bioinorganic topic is reviewed by Brown in an extensive report covering 400 references. In terms of the chemistry of vitamin B_{12}, its solution chemistry, photochemistry, spectroscopy, protein binding, interaction with nuclei acids, and theoretical aspects are covered. In terms of enzymology, coenzyme B_{12}-dependent enzymes, methyl transferases, and reductive dehalogenases are systematically treated. In the final contribution in this section, Weston reviews the *mode of action of bi- and trinuclear zinc hydrolases and their synthetic analogues*. Countless hydrolysis reactions are performed efficiently and selectively in biological systems through the interplay of two or three divalent metal ions in the active site of an enzyme. Ligand substitution and acid−base properties of these metal ions can induce hydrolysis reactions that under normal conditions would not occur in the absence of the metal ions. Topics covered include phosphate ester hydrolysis, metallo-β-lactamases, metallo-aminopeptidases, and biomimetic models based on bi- and tri-zinc cores.

The next section deals with the activation of dioxygen. Kryatov, Rybak-Akimova, and Schindler focus their mechanistic analysis on the *formation and reactivity of non-heme iron oxygen intermediates*. These groups have gained experience with the application of low temperature (down to −90 °C) stopped-flow techniques combined with rapid-scan spectroscopic detection. This not only enables them to study the kinetics of extremely fast reactions, but also allows detection of intermediates through the application of global analysis programs. This review covers the binding of dioxygen to the non-heme biocomplexes bleomycin and hemerythrin and to iron enzymes. The remainder of the review is devoted to model complexes of non-heme mononuclear and dinuclear iron complexes and their interaction with dioxygen, superoxide, and hydrogen peroxide. This extensive review covers more than 400 references. Structure−function relationships and reaction mechanisms of mononuclear non-heme iron inter- and intramolecular dioxygenases are reviewed by Abu-Omar, Loaiza, and Hontzeas in their contribution on the *mechanisms of non-heme iron hydroxylases*. The review mainly focuses on aromatic amino acid hydroxylases, other substrate hydroxylases, and intramolecular dioxygenases. The *structure and chemistry of cytochrome P450* is reviewed by Denisov, Makris, Sligar, and Schlichting. These authors have contributed significantly to the structural clarification of the catalytic cycle of cytochrome P450 through the application of sophisticated spectroscopic and X-ray techniques. In their extensive review of over 475 references, the authors present a systematic analysis of the enzymatic reaction cycle and go into the structural details of the seven fundamental reaction steps. A structural basis for proton transfer is presented, as well as alternative proton-transfer pathways in functionally different P450s. This review is complemented by a *theoretical perspective on the structure and mechanism of cytochrome P450 enzymes* presented by Shaik, Kumar, de Visser, Altun, and Thiel. The review presents theoretical analyses based on quantum mechanical and hybrid quantum mechanical/molecular mechanical methods that enable the study of the active species in their native protein environment. The review presents a brief summary of the available theoretical methods and describes the various species in the catalytic cycle and the principal mechanisms by which the enzyme transfers oxygen to the organic substrates. The review is illustrated with close to 50 very informative figures. *Transition metal catalyzed oxidation of organic substrates with molecular oxygen* is the last topic covered in this section by Punniyamurthy, Velusamy, and Iqbal. In these reactions, molecular oxygen is used as the primary oxidant, and reaction can proceed via oxidation based on the model of monooxygenases, free radical oxidation, oxidation of a coordinated substrate by a metal ion, and oxidation mimicking dioxygenase. The review covers aerobic epoxidation of alkenes, oxidation of alkenes to alcohols and ketones, Wacker oxidation, allylic oxidation, C−H oxidation, Baeyer−Villiger oxidation, and sulfoxidation reactions. The available literature is summarized in 16 tables and more than 90 reaction schemes.

Three reviews deal with the activation of nitrogen and its oxides in bioinorganic and model systems. Henderson reports on *mechanistic studies on synthetic Fe−S-based clusters and their relevance to the action of nitrogenases*. The author focuses on clusters with an Fe−S core which are widespread in biology, such that the mechanistic studies lead to greater understanding of the fundamental chemistry involved in the action of proteins containing such clusters. Topics covered include substitution reactions, protonation reactions, binding of substrate to clusters, transformation of substrates, mechanisms of the extracted FeMo-cofactor, and mechanisms of cluster assembly. The review is illustrated with 80 figures. Nitric oxide chemistry plays an important role in biological systems and has been treated in detail in a special issue of *Chemical Reviews* (April 2002) before. In the contribution by Ford, Fernandez, and Lim, the authors focus on *reductive nitrosylation of iron and copper models relevant to biological systems.* This group has performed detailed mechanistic studies in this area, and they review studies on ferri-heme models and proteins, iron(III) complexes, and copper(II) systems. In a final section, possible biological effects as a result of reductive nitrosylation reactions are reviewed. The interaction of nitrogen oxide and nitrogen dioxide with superoxide leading to the rapid formation of peroxynitrite and peroxynitrate, respectively, plays an important role in biological processes. A comparison of the *chemistry of peroxynitrites and peroxynitrates* is reviewed by Goldstein, Lind, and Merényi, who have contributed significantly to the mechanistic understanding of this chemistry. The formation and decomposition mechanisms for peroxynitrite and peroxynitrate are presented in detail. In addition, alkyl and metal peroxynitrites and peroxynitrates are discussed, as well as the reaction of peroxynitrite and peroxynitrate with CO_2. Finally, the biological implications of the described reactions are reviewed.

Two reviews can formally be classified as dealing with C−H activation. *Mechanistic aspects of C−H activation by Pt complexes* are extensively reviewed (over 330 references) by Lersch and Tilset. The primary focus of this review is on the C−H bond activation in the Shilov catalytic cycle, and the discussion is limited to the mechanistic behavior of molecular entities that exist in solution. Topics that are covered include fundamental mechanistic aspects, Shilov-type chemistry, the "Catalytica" system, and reactions at Pt complexes with phosphine and nitrogen donor and anionic N donor ligands. Examples of applications in synthesis are also covered. Aromatic cyclometalation reactions frequently observed in Pt(II) chemistry are not included in this review. This is done for Pd complexes in an impressive contribution by Dupont, Consorti, and Spencer, who review the *potential of palladacycles that are more than just precatalysts*. Palladacycles are an interesting class of modular organometallic complexes that are useful stoichiometric agents in organic transformations and powerful catalyst precursors for a host of coupling reactions. They also have applications in medicinal and biological chemistry, material science, photoluminescence, total synthesis, and ligand resolution and as chiral catalysts for enantioselective reactions. The authors review almost 340 references and illustrate their account with 44 figures and 75 reaction schemes.

The subsequent section deals with electron-transfer processes. As in the case of ligand substitution reactions where solvent exchange processes form the fundamental basis for mechanistic discussions, self-exchange electron-transfer reactions play a similar role in the mechanistic description of redox processes, since they represent the most fundamental electron-transfer reaction that can occur. In the contribution by Swaddle, the focus is on *homogeneous versus heterogeneous self-exchange electron-transfer reactions*, based on the insight gained from high-pressure effects. The author is a world authority on this topic and presents an extensive review of almost 350 literature references. The author stresses the experimental challenges and interpretational difficulties associated with the study of electrode reaction kinetics, and therefore, he devotes two sections of the review to the methods of measuring electrode reaction rates and basic theoretical background. The emphasis in the remainder of the review is placed on mechanistic insights gained from high-pressure effects on homogeneous and heterogeneous electron-transfer processes in aqueous and nonaqueous media. The *redox chemistry of nickel complexes in aqueous solution* is reviewed by Zilbermann, Maimon, Cohen, and Meyerstein, who are active researchers in this area. The redox chemistry of nickel complexes is relevant to industrial, environmental, and bioinorganic (enzyme) issues. The authors focus their review on the $Ni^{3+/2+}$, $Ni^{2+/+}$, $Ni^{4+/2+}$, and $Ni^{4+/3+}$ couples and on the effect of different donor atoms and chelate structures on the redox behavior of these systems. In the third contribution, Simmonneaux and Bondon review the *mechanism of electron transfer in heme proteins and models* and focus on insight gained from the use of NMR techniques. An introductory section is devoted to NMR methods employed to study electron-transfer processes, followed by the study of self-exchange electron-transfer, multiheme intraprotein electron-transfer, and interprotein electron-transfer processes. In the selected systems from more than 300 references, iron porphyrins, heme proteins, and various cytochromes are the reactants that participate in the electron-transfer process.

This special issue of *Chemical Reviews* is concluded with two more general reviews on the application of photochemical and theoretical methods in the elucidation of inorganic and bioinorganic mechanisms. Szaciłowski, Macyk, Drzewiecka-Matuszek, Brindell, and Stochel present an extensive review of more than 770 references on the frontiers and mechanisms of *bioinorganic photochemistry*. By way of introduction, the authors cover the general area of inorganic photochemistry and its role in transition metal chemistry and supramolecular structures. Subsequently, they review the interaction of light and metal compounds in medicine, and present biochemical and bioanalytical applications of inorganic photochemistry. In a third and final section, they focus on the interaction of light and metals in homogeneous and heterogeneous systems in the environment. Ziegler and Autschbach review *theoretical methods of potential use for studies of inorganic reaction mechanisms* in their authoritative contribution. Being experts in this area, they present a systematic account of potential energy surfaces and electronic structure theory, the exploration of potential energy surfaces, the influence of environmental effects on potential energy surfaces, the description of excited states, the application of spectroscopic methods, and the determination of reaction rates from potential energy surfaces.

With these high class contributions, we are convinced that we have succeeded in covering the latest understanding of inorganic and bioinorganic reaction mechanisms. The reviews all highlight further work that needs to be done to improve our understanding of such processes, and it is our sincere hope that this issue will stimulate further exciting work in this area. The combination of mechanistic work on fundamental inorganic systems with that on more applied bioinorganic systems presents a challenging research area for synthetic, instrumental, and theoretical chemists. So let us all keep up the good and exciting work on the elucidation of inorganic and bioinorganic mechanisms!

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