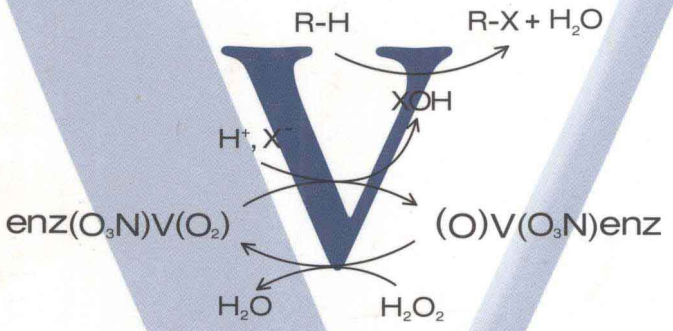
VANADIUM

Chemistry, Biochemistry, Pharmacology and Practical Applications



Alan S. Tracey
Gail R. Willsky
Esther S. Takeuchi

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Preface

This book has evolved from over a quarter-century of research that concentrated on delineating the aqueous coordination reactions that characterize the vanadium(V) oxidation state. At the beginning of this time period, only a minor amount of research was being done on vanadium aqueous chemistry. However, the basic tenets of ^{51}V NMR spectroscopy were being elaborated, and some of the influences of ligand properties and coordination geometry on the NMR spectra were being ascertained. The power of NMR spectroscopy for the study of vanadium speciation had been recognized by only one or two laboratories. This would change, and the demonstration of the great value of this technique for determination of speciation, together with the discovery that vanadium in the diet of rats could be used to ameliorate the influence of diabetes, provided the impetus for rapid growth in this area of science. The discovery of the vanadium-dependent haloperoxidases, the enzymes responsible for a host of biological halogenation and oxidation reactions, added even more impetus for understanding vanadium(V) chemistry, in particular that involving hydrogen peroxide.

This book does not follow a chronological sequence but rather builds up in a hierarchy of complexity. Some basic principles of ^{51}V NMR spectroscopy are discussed; this is followed by a description of the self-condensation reactions of vanadate itself. The reactions with simple monodentate ligands are then described, and this proceeds to more complicated systems such as diols, -hydroxy acids, amino acids, peptides, and so on. Aspects of this sequence are later revisited but with interest now directed toward the influence of ligand electronic properties on coordination and reactivity. The influences of ligands, particularly those of hydrogen peroxide and hydroxyl amine, on heteroligand reactivity are compared and contrasted. There is a brief discussion of the vanadium-dependent haloperoxidases and model systems. There is also some discussion of vanadium in the environment and of some technological applications. Because vanadium pollution is inextricably linked to vanadium(V) chemistry, some discussion of vanadium as a pollutant is provided. This book provides only a very brief discussion of vanadium oxidation states other than V(V) and also does not discuss vanadium redox activity, except in a peripheral manner where required. It does, however, briefly cover the catalytic reactions of peroxovanadates and haloperoxidases model compounds.

The book includes discussion of the vanadium haloperoxidases and the biological and biochemical activities of vanadium(V), including potential pharmacological applications. The last chapters of the book step outside these boundaries by introducing some aspects of the future of vanadium in nanotechnology, the recyclable redox battery, and the silver/vanadium oxide battery. We enjoyed writing this book and can only hope that it will prove to provide at least a modicum of value to the reader.

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Kenneth J. Takeuchi received his BS degree summa cum laude from the University of Cincinnati in 1975 and his PhD degree in chemistry from Ohio State University in 1981. He spent two years at the University of North Carolina at Chapel Hill conducting postdoctoral research in chemistry. In 1983, he accepted a position as assistant professor of chemistry at the State University of New York at Buffalo; he was granted tenure and promoted to associate professor in 1990 and promoted to professor in 1998. Professor Takeuchi was a consultant with ARCO Chemical for five years and has been a consultant with Greatbatch, Inc. for the past five years. He is an author or coauthor of 75 refereed articles and more than 140 presentations at various scientific meetings. His areas of research include coordination chemistry of ruthenium, ligand effects on transition metal chemistry, electrochemistry, materials chemistry, and battery related chemistry.

Amy Marschilok graduated magna cum laude with a BA degree in chemistry at the State University of New York at Buffalo (UB) in 1999, and was inducted into the Phi Beta Kappa society in 2000. She completed her PhD studies in inorganic chemistry at UB in 2004, and was recognized with the 2004 UB Department of Chemistry Excellence in Teaching Award for Outstanding Teaching Assistant. Since 2004, she has worked as a senior scientist in the Battery Research and Development Group at Greatbatch, Inc. in Clarence, NY. Since 2004, she has also served as a volunteer research assistant at UB, where she assists in training undergraduate student researchers. She is coauthor of ten peer-reviewed articles and 14 research presentations.

Authors

Dr. Alan S. Tracey's research career has concentrated on two major research areas, liquid crystalline surfactant materials and the aqueous chemistry of vanadium(V), with emphasis on biochemical applications. He is the author of 150 scientific publications. He obtained his undergraduate degree in honors chemistry from the University of British Columbia and his doctorate from Simon Fraser University. After postdoctoral fellowships in Brazil, Switzerland, and Australia, he returned to Simon Fraser University. He has recently taken early retirement.

Dr. Gail R. Willsky received a BS degree in biophysics from the Massachusetts Institute of Technology, Cambridge, and her PhD from the microbiology department of Tufts University in Boston. She spent 4 years at Harvard University, Cambridge, Massachusetts, as a National Institutes of Health (NIH) postdoctoral fellow in the biology department and a research associate in biochemistry. Willsky then moved to the biochemistry department at the State University of New York at Buffalo (UB) as an assistant professor and is currently an associate professor in that department. She has been a visiting scientist at the Laboratoire de Genetique, CNRS Strasbourg, France, and in the department of physiology at the University of Southern California School of Medicine.

Her research interests originally focused on biological cell membranes, first working on phosphate transport in *Escherichia coli* and then the plasma membrane proton ATPase in *Saccharomyces cerevisiae.* While isolating vanadate-resistant mutants in yeast, she became fascinated with work showing that oral administration of vanadium salts alleviated symptoms of diabetes and switched her research focus to that area. She has pursued the insulin-enhancing mechanism of vanadium salts and complexes in cell culture, the STZ-induced diabetic rat, and human type 2 diabetic patients. The National Institutes of Health, the American Heart Association, and the American Diabetes Association have funded the work in her laboratory. Willsky has lectured all around the world and published both research articles and book chapters in this area.

Willsky is interested in education and has mentored over 75 high school, undergraduate, medical school, or graduate students in her laboratory, while developing the undergraduate program in biochemistry at UB. She also promotes women in science and is on the Executive Committee of the Gender Institute at the University at Buffalo and is the president of the Buffalo chapter of the Association for Women in Science (AWIS). She has received a Special Achievement Award from the Buffalo Area Engineering Awareness for Minorities group for her work in the Buffalo schools (in partnership with AWIS, the Women's Pavilion Pan Am 2001, and Zonta International), developing a career day program called "Imagine yourself as a scientist!" that is integrated into the middle school curriculum.

Dr. Esther S. Takeuchi is the executive director of Battery Research and Development and the Center of Excellence at Greatbatch, Inc. Since joining Greatbatch, Takeuchi has been active in lithium battery research, particularly researching cells for implantable applications. A main focus has been the development of power sources for implantable cardiac defibrillators. Takeuchi's work has been honored by several organizations. These include the Jacob F. Schoellkopf Award, given by the WNY American Chemical Society for creative research in batteries for medical applications, the Battery Division of the Electrochemical Society Technology Award for development of lithium/silver vanadium oxide batteries, the Community Advisory Council of the State University at Buffalo for outstanding achievement in science, Woman of Distinction as recognized by the American Association of University Women, and the Achievement in Healthcare Award presented by D'Youville College. She is also a fellow of the American Institute for Medical and Biological Engineering, was inducted into the WNY Women's Hall of Fame, and is an inventor credited with 130 patents. In 2004, she was inducted into the National Academy of Engineering.

Prior to joining Greatbatch, Takeuchi received a bachelor's degree from the University of Pennsylvania, with a double major in chemistry and history, and completed a PhD in chemistry at the Ohio State University. She also completed postdoctoral work at the University of North Carolina and the State University of New York at Buffalo.

April 19, 2007

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1 Introduction

1.1 BACKGROUND

Vanadium is a widely dispersed element that is found in about 65 minerals and generally occurs in low concentrations. Making up about 0.014% of the Earth's crust, it is the fifth-most abundant transition metal. It can be found in deposits with ores of other metals, particularly with a titanium iron magnetite ore and with the uranium ore, carnotite. Relatively high concentrations are found in certain oil and coal deposits, and consequently, they present a significant pollution hazard when such deposits are exploited. In particular, ash from gas- and oil-burning equipment often contains more than 10% vanadium. It is also found at rather high concentrations in some freshwaters and is listed as a metal of concern by the U.S. Environmental Protection Agency. It is found in ocean waters at concentrations of about 30 nmol/L, a value that varies considerably, dependent on region. Vanadium in the metallic state is used, along with other metals, as an additive to iron to form various stainless steels and is a component of some superconducting alloys. Also, it catalyzes the disproportionation of CO to C and CO_2. The vanadium oxide, V_2O_5, is a powerful and versatile catalyst that is used extensively in industrial processes and finding recent application in nanomaterials, whereas peroxovanadates are useful oxidants often used in organic synthesis and found in naturally occurring enzymes, the vanadium-dependent haloperoxidases.

The most common oxidation states of the metal are +2, +3, +4, and +5, although oxidation states of +1, 0, and −1 are well known. The oxidation states +3 through +5 can be maintained in aqueous solution, and these three oxidation states all have known biological significance, even though the function might not be understood.

Until recently, probably the best understood oxidation state of vanadium was V(IV). This situation changed with the advent of high field nuclear magnetic resonance (NMR) spectrometers, which provided the means to obtain a detailed understanding of the V(V) oxidation state. Indeed, the past 2 decades have seen the redrawing of the landscape of V(V) science, particularly where the aqueous phase is involved.

Much of the recent impetus for the studies of vanadium(V) chemistry derives from the fact that there is marked diversity in biochemical activity associated with this oxidation state. Vanadium(V) occurs naturally in vanadium-dependent haloperoxidases, but beyond this, various complexes of V(V) have powerful influences, inhibiting the function of a large range of enzymes and promoting the function of others. Additionally, vanadium oxides have a marked insulin-mimetic or insulin-enhancing effect in diabetic animals. Despite intensive investigation, the specific function or functions of the metal that leads to this behavior are not known. A great deal of research has gone into obtaining highly potent insulin-mimetic

compounds. A number of compounds have essentially the same activity, and this suggests the function is at a level not yet understood. It seems quite likely that the insulin-mimetic effect derives from the simultaneous modification of the function of a number of enzymes and that the role of the ligands is to ensure vanadium is transported effectively to the appropriate sites. The situation is somewhat different with peroxovanadates. These complexes are often exceedingly effective insulin-mimetics, at least in cell cultures. They are good oxidizing agents and function by means of an oxidative mechanism. However, unless selectivity of function can be built into them, they will probably not achieve success in animal models.

The potentially serious aspects of vanadium pollution, the function of biologically occurring enzyme systems, the role of vanadium on the function of numerous enzymes, and the associated role in the insulin-mimetic vanadium compounds are inextricably linked. The key to our understanding all such functionality relies on understanding the basic chemistry that underlies it. This chemistry is determined to a significant extent by the V(IV) and V(V) oxidation states but clearly is not restricted to these states. Indeed, the redox interplay between the vanadium oxidation states can be a critical aspect of the biological functionality of vanadium, particularly in enzymes such as the vanadium-dependent nitrogenases, where redox reactions are the basis of the enzyme functionality.

1.1.1 Vanadium(V)

The V(V) oxidation state is the major focus of this book, which concentrates particularly on the aqueous chemistry of the V(V) oxoanion, vanadate, but also describes applications in biochemistry, pharmacology, and technology. The chemistry described includes the self-condensation reactions of vanadate and its reactions with a number of mono- and oligodentate ligands and the associated coordination geometries. Mixed ligand chemistry is of particular interest and is an integral part of this discussion. Various aspects of the coordination chemistry are then drawn together, and it is shown that electron-donating properties of ligands have a significant and systematic influence on vanadium coordination and reactivity. Vanadium in its higher oxidation states has a significant effect on numerous biological processes and has various biological, nutritional, and pharmacological influences, including potential applications in treating diabetes and cancer. Possible mechanisms leading to this behavior are described. The vanadium-dependent haloperoxidases are briefly discussed, and model compounds that mimic some of the functionality of these enzymes are described. Also covered is the distribution of vanadium in the biosphere and its occurrence in terrestrial and marine organisms.

Developing technologies in vanadium science provide the basis for the last two chapters of this book. Vanadium(V) in various forms of polymeric vanadium pentoxide is showing great promise in nanomaterial research. This area of research is in its infancy, but already potential applications have been identified. Vanadium-based redox batteries have been developed and are finding their way into both large- and small-scale applications. Lithium/silver vanadium oxide batteries for implantable devices have important medical applications.

1.1.2 Vanadium(II), (III), and (IV)

The V(II), V(III), and V(IV) vanadium oxidation states are not discussed in detail in this book. These oxidation states have an important and well-developed chemistry, and additionally, all have biological significance. Perhaps the most widely recognized function associated with these oxidation states is the accumulation of vanadium by ascidians where vanadium, in its V(V) oxidation state, is enriched by means of a reductive mechanism by a factor of six orders of magnitude from its concentration in seawater and incorporated as V(III) into modified blood cells called vanadocytes. There are extensive research programs directed toward understanding the biochemistry and biological significance of V(III) both in the marine tunicates [1–3] and the polychaete worms [4]. The most important biochemical role of these oxidation states may lie in their utilization in nitrogen-fixing enzymes. Both the V(III) and V(II) oxidation states have a critical function in the redox cycling of the vanadium-dependent nitrogenases. These serve as alternative nitrogen-fixing enzymes to the more prevalent molybdenum-based systems. These nitrogenases function in situations where molybdenum is deficient, but even more importantly, they are more efficient than the molybdenum enzyme when the ambient temperature is significantly reduced [5,6]. It seems likely that they play an important role in arctic and alpine environments.

The V^{2+} (aq) oxidation state is not stable in aqueous solution. The redox potential of V^{2+} (aq) is such that hydrogen ions will be reduced to hydrogen and V^{3+}(aq) formed. However, under reducing conditions, the V(II) state can be maintained. The aqua V^{2+} ion is octahedrally coordinated with six water ligands, and octahedral coordination is characteristic of this oxidation state. The nitrogen functionality, as found, for instance, in diamines [7] and pyridines [8], provides a good ligating center and serves well as a functional group in multidentate ligands. Up to four pyridines can be complexed to a V(II) center. The complexation of pyridine is stepwise and quite favorable. One molar equivalent of pyridine reacts with vanadium(II) in aqueous solution, with a formation constant of 11 M^{-1} [8]. This compares with a very weak interaction with V(V), where a bispyridine complex is observable only under high pyridine concentrations [9].

Unlike V(II), both the V(III) and V(IV) oxidation states are stable in water. However, neither the V(III) nor the V(IV) oxidation states are easily maintained in the presence of oxygen if the pH is neutral or above, although, under acidic conditions, both these states are rather easily maintained. Somewhat surprisingly, the V(IV) species is more readily oxidized by O_2 than is the V(III) species. In aqueous acidic solution, the vanadium(III) ion exists as a hexaqua octahedral complex that can deprotonate to form the 2+ and 1+ species, dependent on pH. Additionally, di, tri and tetra polymeric forms are known. Structures have been proposed and their formation constants determined [10]. The occurrence of the various polymeric forms in the presence of sulfate has also been described and is particularly relevant to concentration of vanadium by bioaccumulators [10].

Complexes of vanadium(III) typically have octahedral coordination, though other coordinations are certainly not unusual, particularly with bulky ligands where trigonal bipyramidal coordination is adopted. Nitrogen- and oxygen-containing mul-

tidentate ligands such as aminopolycarboxylates are common ligands that strongly complex V(III) [11]. Complexes of such ligands are generally monomeric, but with some ligands of appropriate structure, dimeric structures are formed. Dimerization is known to occur through oxygen to give oxo-bridged dimers. However, with appropriate tridentate ligands containing an alkoxo ligating group, dimerization can occur through two bridging alkoxo oxygens to give a cyclic $[VO]_2$ core. Sulfur-containing ligands are well known to be complexed by vanadium(III). Thiolates, for instance, are good complexation agents [12,13], whereas vanadium(III)-sulfide polymers are formed during the desulfurization of crude oils.

Sulfate itself complexes V(III) and, together with appropriate V(III) ligands such as oxalate, can form crystalline V(III)-sulfate polymers, where the sulfate acts as a bidentate bridging ligand [11]. Although the polymer dissociates in solution to predominantly give the bisoxalato V(III) complex, some sulfate complexes still occur. With ligands other than oxalate, such as with aminopyridines, sulfate complexation is much more highly favored, and it may complex either in monodentate or bidentate fashion. Vanadium is also locked into the catalytic site of the vanadium nitrogenases by iron/sulfur bonds, where V(III) is involved in the redox cycle of this enzyme. There is considerable electron delocalization within $[VFe_3S_4]^{2+}$ clusters, which makes it difficult to definitively assign the vanadium oxidation state. It is, however, most consistent with the V(III) state [14]. Unlike the V(IV) and V(V) oxidation states, strong Voxo bonds do not dominate the aqueous chemistry of V(III).

Aqua vanadium(IV), like its counterparts V(III) and V(V), exists in various ionic states dependent on the pH, including $VO(H_2O)_5^{2+}$, $VO(OH)(H_2O)_4^{+}$, and the dimer, $(VOOH)_2(H_2O)_n^{2+}$. In these cationic forms, which occur under acidic conditions, V(IV) is highly water soluble. However, under mildly acidic conditions, about pH 4, where it is largely non-ionic, it forms a hydrous oxide $VO_2{\cdot}nH_2O$ ($K_{sp} \approx 10^{-22}$) that is very insoluble and precipitates from solution, thus limiting the solution concentrations to low values. It has, however, been suggested that V_2O_4 is even more insoluble [15]. Under basic conditions, the oxide can be redissolved to form the anionic species, $VO(OH)_3^{-}$. Apparently, this compound is electron paramagnetic resonance (EPR) silent, which suggests it is at least a dimeric material.

The VO^{2+} moiety is critically important to the chemistry of vanadium(IV). The V=O bond is strong, typically having a bond length of about 1.6 Å, a value similar to that found in the V(V) oxide. Vanadium(IV) does not readily relinquish the bond to oxygen, and the strength of this bond has a direct bearing on heteroligand coordination. It has a strong influence on the position of attachment of ligating groups and consequently on ligand orientation within V(IV) complexes. Square pyramidal complexation is a favored coordination mode, with the VO bond projecting vertical to the plane of the remaining coordinating atoms. The open position opposite the VO bond provides a site for complexation by strongly complexing ligands so that six-coordinate species can form.

Mono-, di-, tri-, and tetradentate ligands of various types readily form complexes with VO^{2+}. Typical ligating functional groups are *O*, *N*, and *S*, so it is not surprising that this oxidation state of vanadium has been found to have a strong influence in biochemical systems. Such biochemically relevant ligands as oxidized and reduced glutathione, ascorbic acid, nucleotides, and monosaccharides are all good complex-