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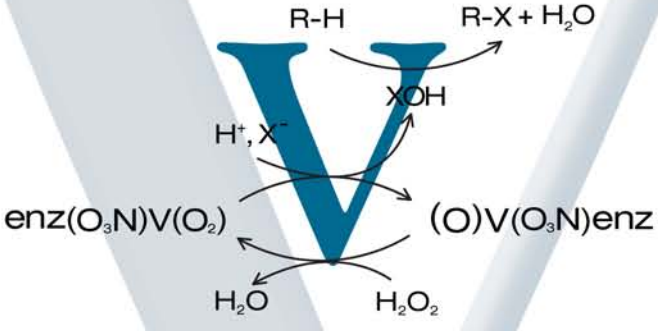

Alan S. Tracey
Gail R. Willsky
Esther S. Takeuchi

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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.

Acknowledgments

The authors are grateful to Tecla R. Atkinson of the University at Buffalo School of Medicine and Biomedical Sciences Office of Medical Computing for drawing the biological figures in chapters 10 and 11. We also thank Dr. Kenneth Blumenthal of the Biochemistry Department at the University at Buffalo and Dr. Vivian Cody of the Hauptman-Woodward Medical Research Institute, Buffalo, NY for critically reviewing chapter 11. The authors are also grateful to Drs. K. J. Takeuchi and A. Marshilok for their extensive contributions to chapter 13.

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.

Table of Contents

Chapter 1 Introduction 1

1.1 Background 1
1.1.1 Vanadium (V) 2
1.1.2 Vanadium (II), (III), and (IV) 3
References 5

Chapter 2 Vanadate Speciation 7

2.1 Techniques 7
2.1.1 Vanadium-51 NMR Spectroscopy 8
2.1.2 pH-Dependence of Vanadium Chemical Shifts 11
2.1.3 ^{51}V 2-Dimensional NMR: Correlation and Exchange Spectroscopies 12
2.1.4 ^{1}H and ^{13}C NMR Spectroscopy 13
2.1.5 ^{17}O NMR Spectroscopy 14
2.1.6 NMR Spectroscopy in Lipophilic Solutions 15
2.2 Vanadate Self-Condensation Reactions 19
2.2.1 The Commonly Encountered Vanadates 19
2.2.2 Decavanadate 25
2.3 Vanadium Atom Stoichiometry of Complexes 26
References 27

Chapter 3 Monodentate Ligands of Vanadate 31

3.1 Alcohols and Phenols 31
3.1.1 Primary, Secondary, and Tertiary Aliphatic Alcohols 31
3.1.2 Phenols 33
3.2 Amines and Acids 33
3.2.1 Aliphatic and Aromatic Amines 33
3.2.2 Carboxylic Acids, Phosphate, Arsenate, and Sulfate 34
3.2.3 Sulfhydryl Ligands 35
References 35

Chapter 4 Aqueous Reactions of Vanadate with Multidentate Ligands 37

4.1 Glycols, α-Hydroxycarboxylic Acids, and Dicarboxylic Acids 37
4.1.1 Glycols: Cyclohexane Diols, Carbohydrates, and Nucleosides 38
4.1.2 α-Hydroxy Carboxylic Acids, Maltol 43
4.1.2.1 Heteroligand Complexes 47
4.1.3 Dicarboxylic Acids: Oxalic, Malonic, and Succinic Acids 48

4.2 Hydroxamic Acids 49
4.3 Thiolate-Containing Ligands 51
4.3.1 β-Mercaptoethanol and Dithiothreitol 51
4.3.2 Bis(2-thiolatoethyl)ether, Tris(2-thiolatoethyl)amine, and Related Ligands 53
4.3.3 Cysteine, Glutathione, Oxidized Glutathione, and Other Disulfides 53
4.4 Amino Alcohols and Related Ligands 54
4.4.1 Bidentate Amino Alcohols and Diamines 54
4.4.2 Polydentate Amino Alcohols: Diethanolamine and Derivatives 54
4.5 Amino Acids and Derivatives 57
4.5.1 Ethylene-N,N′-Diacetic Acid and Similar Compounds 57
4.5.2 Pyridine Carboxylates, Pyridine Hydroxylates, and Salicylate 58
4.5.3 Amides 61
4.6 α-Amino Acids and Dipeptides 61
4.6.1 α-Amino Acids 61
4.6.2 Dipeptides 62
4.7 Other Multidentate Ligands 72
References 74

Chapter 5 Coordination of Vanadate by Hydrogen Peroxide and Hydroxylamines 81

5.1 Hydrogen Peroxide 82
5.2 Hydroxylamines 85
5.3 Coordination Geometry of Peroxo and Hydroxamido Vanadates 87
References 95

Chapter 6 Reactions of Peroxovanadates 99

6.1 Heteroligand Reactions of Bisperoxovanadates 99
6.1.1 Complexation of Monodentate Heteroligands 99
6.1.2 Complexation of Oxobisperoxovanadate by Multidentate Heteroligands 104
6.2 Reactions of Monoperoxovanadates with Heteroligands 106
6.2.1 Complexation by Amino Acids, Picolinate, and Dipeptides 106
6.2.2 Complexation by α-Hydroxycarboxylic Acids 111
6.3 Oxygen Transfer Reactions of Peroxovanadates 114
6.3.1 Halide Oxidation 114
6.3.2 Sulfide Oxidation 116
References 118

Chapter 7 Aqueous Reactions and NMR Spectroscopy of Hydroxamidovanadate 123

7.1 Interactions of Hydroxamidovanadates with Heteroligands 123
7.2 Vanadium NMR Spectroscopy of Hydroxamido Complexes 124
References 129

Chapter 8 Reactions of Oligovanadates 131

8.1 The Smaller Oligomers 131
8.2 Decavanadate 134
References 136

Chapter 9 Influence of Ligand Properties on Product Structure and Reactivity 139

9.1 Alkyl Alcohols 139
9.2 Glycols, α-Hydroxy Acids, and Oxalate 142
9.3 Bisperoxo and Bishydroxamido Vanadates: Heteroligand Reactivity 144
9.4 Phenols 146
9.5 Diethanolamines 147
9.6 Pattern of Reactivity 149
References 150

Chapter 10 Vanadium in Biological Systems 153

10.1 Distribution in the Environment 153
10.2 Vanadium-Ligand Complexes 155
10.2.1 Amavadine 156
10.3 Vanadium Transport and Binding Proteins 157
10.3.1 Vanabins 159
10.4 Vanadium-Containing Enzymes 160
10.4.1 Nitrogenases 160
10.4.2 Vanadium-Dependent Haloperoxidases 160
10.4.2.1 Haloperoxidase Active Site 162
10.4.2.2 Haloperoxidase Model Compounds 163
References 166

Chapter 11 The Influence of Vanadium Compounds on Biological Systems ... 171

11.1 Vanadium Compounds on Biological Systems: Cellular Growth, Oxidation-Reduction Pathways, and Enzymes 171
11.1.1 Vanadium Compounds and Oxidation-Reduction Reactions 173
11.1.1.1 Vanadium-Dependent NADH Oxidation Activity 173
11.1.1.2 Vanadium Compounds and Cellular Oxidation-Reduction Metabolism 174

11.1.2 Inhibition of Phosphate-Metabolizing Enzymes by Vanadium Compounds 176
11.1.2.1 Inhibition of Ribonuclease 176
11.1.2.2 Inhibition of Protein Tyrosine Phosphatase 179
11.1.3 Effect of Vanadium Compounds on Growth and Development 180
11.1.4 Nutrition and Toxicology of Vanadium 181
11.2 Pharmacological Properties of Vanadium 183
11.2.1 Vanadium as a Therapeutic Agent for Diabetes: Overview 184
11.2.1.1 Vanadium Compounds Used for Treatment of Diabetes: Salts, Chelate Complexes, and Peroxovanadium Compounds 186
11.2.1.2 Effects of Vanadium Compounds in Biological Models 187
11.2.2 Vanadium as Therapeutic Agent for Cancer 191
11.3 Mechanism of Therapeutic and Apoptotic Effects of Vanadium 193
11.3.1 Cellular Oxidation-Reduction Reactions as Part of the Therapeutic Effect of Vanadium 193
11.3.2 Vanadium Interaction with Signal Transduction Cascades as Part of the Therapeutic Effect 194
11.4 Summary 199
Abbreviations 200
References 202

Chapter 12 Technological Development 215

12.1 Molecular Networks and Nanomaterials 215
12.2 The Vanadium Redox Battery 217
12.3 The Silver Vanadium Oxide Battery 219
References 220

Chapter 13 Preparation, Characterization, and Battery Applications of Silver Vanadium Oxide Materials 221

13.1 Introduction 221
13.2 Preparation, Structure, and Reactivity of Silver Vanadium Oxide and Related Materials 221
13.3 Battery Applications of Silver Vanadium Oxide 229
13.3.1 Primary Silver Vanadium Oxide Cells 230
13.3.2 Rechargeable Silver Vanadium Oxide Cells 236
13.4 Summary 239
References 240

Index 245

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-

ation agents [16,17]. A detailed synopsis of the coordination chemistry of V(IV) that discusses the formation and structural properties of numerous V(IV) complexes is available [18]. Details of the structure of many paramagnetic complexes are difficult to obtain, particularly so if crystalline compounds cannot be prepared for x-ray analysis. This problem has been solved to an extent by utilization of frozen solutions in electron nuclear double resonance (ENDOR) spectroscopy. This technique allows the accurate measurement of hyperfine couplings and, because these couplings are dependent on distances between interacting nuclei, provides detailed structural information. Application of this experimental technique has been discussed in detail for a variety of V(IV) complexes, including those formed from ligands such as nucleotides, amino acids, porphyrins, and other organic compounds [19].

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2 Vanadate Speciation

2.1 TECHNIQUES

Traditionally, the principal tools for the study of vanadate speciation in aqueous solution were UV/vis and electrochemistry. Unfortunately, the complex chemistry associated with vanadate has rendered much, but certainly not all, of the earlier work obsolete. The reaction solutions often contained numerous products that, *a priori,* could not be specified. Properly describing the chemistry was somewhat like doing a jigsaw puzzle without knowing what the pieces looked like or how many there were. Only with the advent of ^{51}V NMR spectroscopy in high field NMR spectrometers was there a tool in place that allowed a coherent picture of V(V) chemistry to be fully developed. The combination of potentiometry with NMR spectroscopy has proven a certain winner. Additionally, x-ray diffraction studies have provided an invaluable source of information, but it is information that, in all cases, must be used with extreme caution when attempting to describe the chemistry in solution.

Utilization of potentiometry in the study of complex equilibria is hindered by the fact that the observed electrode response derives from all reactions occurring in solution. Characterization of the system relies on the influences of hydrogen ion and reactant concentration on the measured voltage. The chemical system is then modeled and the observations compared with those expected for the model adopted. It is not unusual that there are weak differential responses for specific equilibria so that the solution potential does not adequately differentiate between alternate equilibria, and thus potentiometry might only poorly define the system. UV/vis is basically a very poor-resolution technique that often is unusable for studying equilibria if the system is at all complex. For less-complex systems, it can provide useful information and, in certain circumstances where multiple reactions are limited, can be particularly valuable, such as in the study of tight binding ligands where very dilute reactants are required in order to probe the equilibrium reaction.

An indirect method of gathering information about solution structures is provided by electrospray ionization/mass spectrometry. This technique involves ejection of a droplet of solution into an electric field chamber. As the droplet is being ejected, it becomes highly charged and essentially explodes into numerous very small charged droplets of about 10 μm in diameter. These small droplets rapidly evaporate and, in the process, release charged ions that are drawn into the inlet of a mass spectrometer. Analysis of the resultant fragmentation data provides details of molecular weight and structure. For complexes that undergo chemical changes during a millisecond or so timescale, acidity and concentration changes within the evaporating droplet can present problems in interpretation. Diligence in recognizing such factors is key to this application. This technique has proven very valuable for the study of vanadium complexes, where it has been used principally to probe model haloperoxidases complexes based on peroxovanadates [1,2]. It is reasonable to turn the argument around and use the

evidence obtained for transient species to provide evidence for possible reaction pathways, for instance, for mechanisms of oxidation by peroxovanadates.

Vanadium-51 NMR spectroscopy is generally the method of choice for studying complex equilibria or obtaining structural data. In principle, and frequently in practice, signals for all reactant and product species are observable. An NMR spectrum showing the spectral dispersion that is typical for this nucleus is shown Figure 2.1. Variation of pH or reactant concentrations usually allows an unambiguous interpretation of the information inherent in such spectra. Combination of NMR with potentiometry adds a significant degree of accuracy and redundancy to the NMR studies. This hybrid technique is particularly powerful when there is signal overlap in the NMR spectra or when certain equilibria are highly favored so that some reactant or product concentrations are poorly defined by NMR. Potentiometry is without peer when ligated ligands have noncomplexed sidechains that undergo protonation/deprotonation reactions. Such reactions often will not be easily characterized by NMR studies alone.

Although NMR is a notoriously insensitive technique, vanadium is a highly responsive nucleus, and it is quite feasible to get spectra from a few micromolar concentration of vanadium in solution. Frequently, there is no necessity for such low concentrations, and more typically NMR studies utilize 0.5 mM, and above, total vanadium concentrations.

2.1.1 Vanadium-51 NMR Spectroscopy

Vanadium-51 is a spin 7/2 nucleus, and consequently it has a quadrupole moment and is frequently referred to as a quadrupolar nucleus. The nuclear quadrupole moment is moderate in size, having a value of -0.052×10^{-28} m^2. Vanadium-51 is about 40% as sensitive as protons toward NMR observation, and therefore spectra are generally easily obtained. The NMR spectroscopy of vanadium is influenced strongly by the quadrupolar properties, which derive from charge separation within the nucleus. The quadrupole moment interacts with its environment by means of electric field gradients within the electron cloud surrounding the nucleus. The electric field gradients arise from a nonspherical distribution of electron density about the

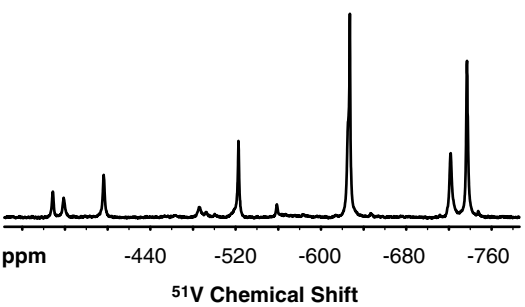


FIGURE 2.1 ^{51}V NMR spectrum showing aqueous vanadate in the presence of *N,N*-dimethylhydroxylamine and dithiothreitol. The wide spectral dispersion of the signals is characteristic of vanadium NMR spectra.

nucleus, and therefore they are influenced by ligating groups. If the electron density symmetry at the nucleus is tetrahedral or higher, the electric field gradients are zero, and there is no quadrupolar interaction.

The coordination geometry is, however, often not a good delineator of electric field gradients. Ostensibly high-symmetry molecules can give rise to significant electric field gradients at the nucleus, whereas the opposite situation may arise for low-symmetry molecules. Probably the best known, though perhaps not recognized, example of the latter behavior is the sharp NMR signals normally observed for bisperoxovanadate complexes, which typically have a pentagonal pyramidal geometry. Generally, though, it can be expected that for compounds of similar molecular weights, those with tetrahedral or higher symmetry will have sharper signals than less-symmetrical species.

The influence of the quadrupole is exhibited by efficient nuclear relaxation and, thus, broadened signals in the NMR spectrum. Because the electric field gradients will be different for every complex, signals of varying linewidth are typical of vanadium NMR spectroscopy. The variation may be small, as shown in Figure 2.1, or may be much larger, as is evident in Figure 2.2. The quadrupolar relaxation is moderated by the tumbling rate of the compound in question, so low-viscosity solvents tend to give rise to higher quality spectra. A corollary of this is that one has to be very careful in interpreting variable temperature data. Changes in linewidth as a function of temperature may well have their origin in quadrupole interactions rather than in chemical exchange. This can easily be true even if some signals within the spectrum do not undergo significant changes. Whenever possible, two-dimensional exchange spectroscopy (EXSY) should be employed to characterize exchanging systems.

Because of rapid, quadrupole-induced relaxation, NMR signals frequently are 200 or 300 Hz wide or more. This is not as severe a problem as it may at first appear because vanadium-51 has a large chemical shift range of about 3000 ppm. As illustrated in Figure 2.2, the line widths shown vary from about 130 to 1000 Hz (1.3 to 10.0 ppm with a 400 MHz spectrometer), yet the spectrum is well resolved. The fast relaxation does mean that spectra can be accumulated very rapidly. Only in atypical situations will 20 or 30 accumulations per second lead to problems of

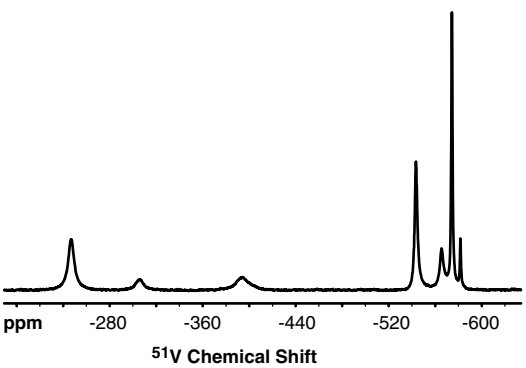


FIGURE 2.2 ^{51}V NMR spectrum showing vanadate in the presence of cysteine at pH 8.4. Signals of varying linewidth are frequently found in vanadium spectra.

perturbed signal intensity. Difficulties with very broad lines often arise if the species of interest have a high molecular weight or the solvents are of high viscosity. Both such situations slow the tumbling of the vanadium nucleus and increase the rates of quadrupole-induced relaxation. Under such conditions, it is possible that the signals are so broad that they cannot easily be observed. Molecules that for one reason or another have very large electric field gradients about the nucleus might also give atypically broad lines even in low-viscosity solvents.

It can generally be expected that spectra from samples of about 1 mmol/L concentration will be obtained within a short period of time. Spectra corresponding to concentrations of 10 or so μmol/L can be detected within a few hours if the signals are not excessively broad. Because of the linewidths of the signals, small data set sizes can routinely be used when acquiring and processing the spectra. Optimum signal to noise in a processed spectrum is obtained with a matched filter. Therefore, line-broadening factors corresponding to the linewidth at half height of the sharpest signal in the spectrum should be used. Typically, a line-broadening factor of 40 or 50 Hz serves well. When there is good signal to noise, resolution enhancement by means of a Lorentzian to Gaussian transform can provide useful information in situations where signals are partially resolved.

As a result of the short relaxation times of most vanadate species, ^{51}V 2D exchange spectroscopy is limited to dynamic processes that occur within a few tens of milliseconds. This timescale is conveniently lengthened to 1 sec or longer in cases where proton (or other) NMR spectroscopy can be employed, for instance, in ligand exchange reactions.

Because vanadium-51 has a spin of 7/2, the NMR signal generally observed is actually a composite seven-part signal deriving from transitions between all the nuclear spin states as defined by the selection rule that $\Delta m = \pm 1$. For typical solution spectra, the nuclear relaxation corresponding to the individual transitions of each chemically distinct nucleus is more or less the same, and correspondingly broadened signals are observed. However, in the slow-motion regime, the nature of the relaxation pathways between the various spin states can lead to a situation in which all transitions other than that corresponding to the –1/2 to +1/2 transition are broadened beyond observation. This occurs when the nuclear tumbling is greatly slowed, as found when vanadium is bound to proteins. This leads to the possibility of using vanadium NMR spectroscopy to directly observe and characterize complexation to proteins [3,4].

The chemical shift reference standard for ^{51}V NMR spectroscopy is $VOCl_3$, which provides a sharp signal either as a neat liquid or in nonreactive organic solvents. Unfortunately, it is not a nice compound to work with and is hydrolytically unstable. Generally, oxovanadium trichloride is used as an external reference as the neat liquid. An alternative is to calibrate a secondary reference such as a vanadate solution at pH 8 and use the signal from tetravanadate as the secondary reference frequency. Except for the preliminary calibration, this eliminates the possibility of breaking the sample of $VOCl_3$ in the NMR probe. Additionally, unless the magnetic field or the radio frequencies of the spectrometer drift significantly, the broad signals of vanadate complexes mean that little is gained by locking or even shimming the

magnet. Samples can then be prepared in protonated solvents and the spectra obtained in an unlocked mode of acquisition. This greatly expedites sample turn-around time. Note that when running in unlocked mode, the magnet cannot be shimmed, because the shim coils alter the magnetic field strength and the chemical shift calibration will then be incorrect.

There is a direct relationship between the electronegativity of ligating groups and the chemical shift. The relationship is similar for four, five, or six coordinate complexes with chemical shifts moving to higher field with increased substituent electronegativity [5]. Although apparently this is true when using a gross scale of electronegativity, it is not necessarily true when looked at under a finer scale within a series of homologous compounds, as for instance in alkyl alcohols (see Section 9.1). Also, ligands such as catechols, which give rise to low energy charge transfer bands, have a large influence on the electronic environment about the nucleus and consequently strongly influence vanadium chemical shifts. Correlations, based on the Ramsey formulation, clearly show the relationship between such charge transfer transitions and the observed chemical shifts [6].

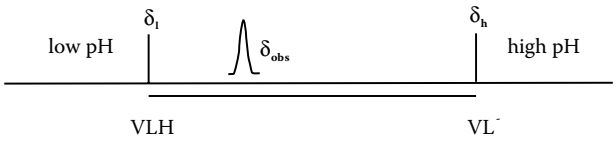
Vanadium undergoes J-coupling interactions when suitably substituted. The interactions are often not large or are decoupled by fluctuations in the quadrupole interaction. An example of such a coupling is the ^{17}O to ^{51}V J-coupling in the vanadate trianion, which is 62 Hz [7]. J-couplings have been used in the assignment of NMR signals to complexes occurring in solution. A particularly nice example of this is found in a study of peroxovanadates, where the V to V J-coupling was used in 2D correlation spectroscopy (COSY) spectra to assign vanadium signals to the pairs of vanadiums in asymmetrically substituted peroxo divanadates [8].

2.1.2 pH-Dependence of Vanadium Chemical Shifts

A common characteristic of vanadium NMR spectra is that chemical shifts vary with pH. The source of this behavior is generally an equilibrium reaction that is dependent on pH. Such equilibria can involve ligand reactions, but generally these are slow on the ^{51}V NMR timescale. However, an equilibration that is almost always fast is the protonation/deprotonation reaction. Exceptions that might be observed will generally involve changes in coordination geometry that accompany the changes in protonation state. This equilibrium can be critical to the solution chemistry that is observed and can be written simply, as in Equation 2.1, for a generic vanadate complex, VLH.

$$VLH \rightleftharpoons VL^- + H^+ \quad [VLH]K_a = [VL^-][H^+] \tag{2.1}$$

The ^{51}V NMR spectrum for this equilibrium will be characterized by a low pH limiting value, a high pH limiting value, and a pH region where the chemical shift will be sensitive to the pH of the solution. Scheme 2.1 provides a sketch of this behavior. It is evident that the chemical shift is determined by the limiting chemical shifts and the acidity constant (K_a) of VLH. This relationship can be inverted and the pH-dependence of the chemical shift used to provide the $-\log K_a$ (pK_a) of the complex of interest, as described by Equation 2.2.



$$P(VLH) = (\delta_h - \delta_{obs})/(\delta_h - \delta_l) \qquad (PVL^-) = (\delta_{obs} - \delta_l)/(\delta_h - \delta_l)$$

SCHEME 2.1

In Scheme 2.1, P(VLH) and $P(VL^-)$ represent the molar fractions of the two species.

$$pH = \log((\delta_{obs} - \delta_l) / (\delta_h - \delta_{obs})) + pK_a \tag{2.2}$$

From a pH-variation study, a plot of pH versus $\log((\delta_{obs} - \delta_l) / (\delta_h - \delta_{obs}))$ will then provide a graph with an intercept equal to the pK_a of the complex. Note that Equation 2.2 has a slope of 1. This is a useful property of this equation, as it provides a convenient check on the accuracy or interpretation of the titration experiment and can be utilized when analyzing the results of an experiment where only a partial titration curve is obtained.

A practical consequence of the pH dependence of chemical shifts is that the charge state of the various species referred to should be provided when chemical shifts are quoted. Because it is not unusual for chemical shifts to be different by 30, 40, or more ppm, dependent on protonation state, for situations of intermediate charge state, the pH of the solution should also be reported. The latter is particularly important when the pH of the medium is close to the pK_a of the species of interest.

In the context here, there is nothing special about H^+, and in principle, Scheme 2.1 and Equation 2.2 can be applied to any fast ligation interaction by making the appropriate changes to reflect a ligand, L, rather than H^+, i.e., –log [L] for pH and –log K for pK_a, thereby leading to Equation 2.3.

$$\log((\delta_{obs} - \delta_V) / (\delta_P - \delta_{obs})) = n \log[L] + \log K \tag{2.3}$$

In this case, the slope will be dependent on the number of ligands required for product formation. An example of the application of this equation is provided by the reaction of acetic acid with vanadate, where there is formation of a bisacetato vanadate [9].

2.1.3 ^{51}V 2-Dimensional NMR: Correlation and Exchange Spectroscopies

The magnitude of the nuclear electric quadrupolar interaction is dependent on the orientation of the molecular-fixed electric field gradient tensor in the applied magnetic field. Consequently, molecular tumbling causes fluctuations in the quadrupolar interaction. These fluctuations generally cause decoupling of the J interaction. However, under circumstances where the quadrupolar coupling is not very large because