CURRENT

RESEARCH TOPICS

IN BIOINORGANIC

CHEMISTRY

Edited by

STEPHEN J. LIPPARD

DEPARTMENT OF CHEMISTRY
COLUMBIA UNIVERSITY
NEW YORK, NEW YORK

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Editor: STEPHEN J. LIPPARD
    DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY, NEW YORK, NEW YORK

Advisory Board

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Preface

Work at the interface between the areas of inorganic and biological chemistry has greatly intensified in recent years. Organization of the subject material of this growing field of bioinorganic chemistry along topical lines is fairly straightforward, if not completely satisfying. Thus whole literatures have grown up around such problems as nitrogen fixation, heme proteins, vitamin B_{12} chemistry, carboxypeptidase structure and biochemistry, metal ion transport through membranes, non-heme iron proteins, metal activation of ATP, and copper oxidases. In planning this special topics volume, some attempt was made to achieve a broader scope. For example, instead of a chapter on iron-sulfur redox proteins, it seemed desirable to have a discussion of the entire family of metallo-redox proteins. To the extent that the subject matter was amenable to such an approach, the chapters reflect this philosophy.

   The choice of topics for this particular volume was dictated by two criteria. First, it was decided to sustain the long-standing policy of this series to provide critical, comprehensive, in-depth coverage of material. This decision necessitated a high selectivity since only a few such chapters could be accomodated in a single volume. The second criterion was to assure reasonably broad coverage by including subjects that represented the various kinds of available biological ligands, namely proteins and nucleic acids and their constituents, in addition to special-function ligands such as the heme or corrin ring. To the extent that we have been successful, this book should serve as a useful introduction and guide to scientists in all fields who are interested in obtaining an overview of the emerging discipline of bioinorganic chemistry. At the same time, the individual chapters should provide current information and critical discussion of the more specialized areas for both research workers and students. Parts of certain chapters have already been adopted in manuscript form for instructional purposes at the graduate student level.

   I wish to thank the authors for their cooperation and efforts required to produce this volume. If there is sufficient positive response, future bioinorganic volumes will be scheduled in this series. As usual, comments of any kind are always welcome and will be given serious attention.

<div align="right">STEPHEN J. LIPPARD</div>

New York, New York
February 1973

Introduction

There are three major avenues of investigation in bioinorganic chemistry. The first involves direct study of the structure and function of "biometallic" molecules, an area traditionally that of the biochemist. Here one is interested in the role of metal ions in metalloenzymes, coenzymes, and proteins, as well as their function as cofactors in DNA and RNA biochemistry. In classic studies on carboxypeptidase, Vallee and co-workers recognized the importance of the zinc atom as a functional group unique among all others in the protein. By replacing the zinc with other metal ions, chemical and spectroscopic probes of the active site were made available. More recently, X-ray diffraction studies have yielded detailed structural information about several metallomacromolecules. The three-dimensional structure of a *t*RNA has just been made available through the efforts of Rich, Kim, and their associates. The critical role of magnesium ions in binding phosphate groups remote from each other in the sequence (not a new concept, incidentally) has begun to emerge, and correlates well with biochemical results from several laboratories. X-ray data serves not only to bridle the occasional untamed structural speculations derived from less direct approaches, but also provides the impetus and direction for attempts to elucidate the structure-function relationships that form our basic understanding of how biometallic molecules work. Delineation of the function of the metal ion as a structural keystone (as in the example just cited), specific reaction organizer, electron transfer agent, or substrate activator is the major objective of the direct approach, in which detailed studies are performed on specimens usually obtained directly from natural sources.

By contrast, the second major avenue involves an indirect approach, commonly the domain of the inorganic or organic chemist. Through the invention, synthesis, structure determination, physical study, and reactions of so-called "model" compounds, some insight into the workings of the natural system is sought. An additional objective might be to mimic in a simple system the catalytic function of a metalloenzyme for industrial or biomedical synthetic purposes. Current attempts to fix molecular nitrogen with homogeneous iron or molybenum catalysts exemplify this aspect. Although few doubt that important chemistry might result from this approach, serious reservation has been expressed about the relevance of such work to the understanding of natural systems. Indeed, there are purists

who believe that even to study biometallic molecule *in vitro* is to over-simplify. For instance, there are those who argue that to investigate solu-bilized components of the membrane-bound cellular redox apparatus (e.g., cytochrome *c* oxidase) is a waste of effort. This attitude stems in part from an overreaction to claims of relevance by chemists interested in riding bio-logical coattails for one reason or another. There is at least one instance where an organometallic molecule, of perfectly respectable interest for its own sake, was labeled a "model" for the nitrogenase enzyme even though it never could bind dinitrogen let alone catalyze its reduction. But un-fortunate as statements of this kind may be, it is shortsighted not to recog-nize and cultivate the growing research activities on small molecule analogs of biometallic compounds.

For the skeptical, a detailed example might be offered. The copper blue proteins characterized chiefly by Malmström, Vänngård, and their co-workers are an important class of biological oxidases. The redox, optical, and epr spectroscopic properties of these proteins have been thoroughly studied, although their detailed structures are not yet available. Even if the structures were known, the interesting task of explaining the "unusual" spectroscopic features and high redox potentials of these proteins would remain. It is worth digressing a moment to discuss the concept of unique-ness that is used with increasing frequency in this context (Vallee and Williams have formallized one aspect and called it the "entatic nature of the active site"). Since Nature could not take advantage of the redox po-tentials available among the aquo ions of the transition metals (the ferric ion, e.g., would be a good biological oxidizing agent with a reduction po-tential of -0.77 V, but it hydrolyzes at pH 7 and is thus unavailable), substitute biometallic coordination compounds evolved. In the present example, the oxidizing power of the copper(II) ion has been substantially increased by the specialized ligand environment (as yet unknown) of the protein active site. Viewed in this context, it should not be surprising if the properties of the copper(II) centers appear unusual. The uniqueness should not then be taken as some mystical force available in proteins, as has some-times been done. Rather, the properties of a biometallic molecule may be viewed as unusual in the sense that inorganic analogs with sufficiently complex ligand environments are simply not available. No one has taken the trouble to prepare them. It is therefore important that synthetic, structural, and physical studies be carried out to produce and characterize the appropriate relevant small molecules. In the case at point, copper co-ordination compounds that produce large positive reduction potentials will be deemed most relevant, and their study should contribute eventually to a fundamental understanding of how the proteins work.

Before turning to the third approach to bioinorganic chemistry, it is worth noting with approval that cooperation between inorganic and biological chemists has grown substantially in recent years. Not only are laboratories collaborating on specific problems, but there is an increasing tendency for biochemists to try their hand at preparing inorganic analogs, and for coordination chemists to establish a biological program. Surely such activities signify the emergence of a new discipline.

A third investigative avenue to this discipline involves the addition of metal ions or complexes as probes to biochemical structure and function. Here the word *addition* is emphasized as being different in kind from the *substitution* of one metal for another in a biometallic molecule. Particular examples might include spin-labels, fluorescent labels, and shift reagents, any of which might yield substantive information about the geometries and mechanistic workings of macromolecules. An especially appealing manifestation of this approach, suggested more than a decade ago by Michael Beer, is the design of heavy metal reagents to bind specifically and quantitatively to one or more (but not all) of the bases of a polynucleotide. The labeled polymer could then be sequenced by electron microscopy, the heavy metal ion serving to improve the contrast. Problems of this kind should have great appeal to inorganic as well as biochemists. At present there is not the vigorous activity in this area that it deserves.

The foregoing brief attempt to define and systematize the activities of bioinorganic chemists is of course highly subjective. Whether such a treatment will prove valid 10 years or even 10 months from now is not important. Of greater interest is that workers in the field have largely discarded parochial attitudes concerning the uniqueness of their approach to problems, and that both biological and inorganic chemists have shown a willingness to learn the techniques and literatures of the other's field. Continued activities of this kind will surely require future efforts to pull together the subject material in the now firmly established but infant discipline of bioinorganic chemistry.

STEPHEN J. LIPPARD

New York, New York
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Metalloprotein Redox Reactions

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I. INTRODUCTION

Of the myriad oxidation-reduction reactions known to modern chemistry, few can rival in efficiency, complexity, and mechanistic intrigue, the processes found in biological systems. Proteins containing transition metal ions are frequently found to be catalytic components of these most intricate of all chemical systems. The participation of metalloproteins in respiratory, photosynthetic, nitrogen fixation, biosynthetic, and metabolic processes is essential to the foundations of life. This lends further appeal to their study as unique redox agents.

The involvement of transition metal centers raises important questions regarding the mechanisms of these biological reactions. It is natural to examine the biological systems for parallels with the redox behavior of less complicated transition metal complexes. The principles which are operative in the simpler systems are not likely to be revoked, and should extend, with modification, to the biological realm. It is the purpose of this report to survey the involvement of metalloproteins as biological redox catalysts in the context of developing concepts of mechanistic behavior in both biochemistry and inorganic chemistry. A second objective is to provide access to the relevant inorganic literature for the biochemist and to the biochemical literature for the inorganic chemist. The formidable task confronting the inorganic chemist is reflected in the large number of books (1–47) devoted primarily to this topic which have appeared over the last decade, not to mention review articles and primary sources.

In Section II the redox reactions of simple metal complexes are examined since they provide insight into the finer details of mechanism. For the sake of brevity, the basic features are augmented with a degree of detail that is not needed until Section VII. The reader may wish to treat this detail lightly on first reading and return to it in connection with Section VII. Section III is devoted to mechanistic aspects of oxygen chemistry because of its biological importance. In Section IV the ways in which biological environments might affect transition metal reactivity are examined. In Section V the metalloproteins are considered in relation to their physiological activity and environment. In Section VI the physiological reactions in aqueous solution are examined. Section VII is devoted to aqueous reactions between metalloproteins and redox agents which are not directly involved with the protein in its physiological function.

II. REDOX REACTIONS OF SIMPLE METAL COMPLEXES

Reactions between two transition metal complexes resulting in complementary oxidation state changes which are usually localized on the metal centers have been extensively studied by inorganic chemists. The subject has been reviewed (48–67), most recently in two recommended articles by Linck (68, 69). It is sufficient here to survey the mechanistic patterns of these reactions which have been elucidated. (Unless otherwise specified rates will be quoted for reaction at 25°C in aqueous solution with seconds for the units of time.)

Ideally, a complete mechanistic description of any redox reaction should provide (within the limits of the uncertainty principle) the energetic and spatial configurations of all nuclei and electrons as they move during the course of reaction. This objective is theoretically and experimentally

inaccessible. Nevertheless, the conceptual framework provides guidelines in the design of experiments and the evaluation of their results.

A rough designation of the spatial course of the nuclei during a redox reaction between simple complex ions has been made for a number of systems. The pioneering work of Henry Taube has led to a classification of redox reactions into *outer-sphere* and *inner-sphere* categories which are characterized by the geometry of the nuclei in the transition state.*

A. Outer-Sphere Reactions

1. Spatial Aspects

Outer-sphere reactions are those in which the complementary oxidation state change occurs via a path which does not involve the mutual sharing of a "bridging" ligand in the coordination spheres of both metals. An outer-sphere process is demanded when both reactants are inert to substitution over the time required for the redox reaction. This behavior is exemplified by the homonuclear "self-exchange" electron transfer reaction (70) (designated by k_{aa}):

$$Ru(NH_3)_6^{2+} + Ru(NH_3)_6^{3+} \xrightarrow[M^{-1}\ sec^{-1}]{k_{11} = 8.2 \times 10^2} Ru(NH_3)_6^{3+} + Ru(NH_3)_6^{2+} \qquad (1)$$
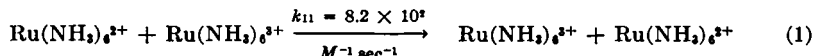
This demand is also made if only one reactant is relatively inert, provided that it does not present a binding site (usually in the form of a pair of nonbonding electrons) to the labile reactant. This is the case for the heteronuclear "cross" reaction (71) (designated by k_{ab}):

$$Cr(H_2O)_6^{2+}\ (labile) + Ru(NH_3)_6^{3+} \xrightarrow[M^{-1}\ sec^{-1}]{k_{11} = 2 \times 10^2} Cr(H_2O)_6^{3+} + Ru(NH_3)_6^{2+} \qquad (2)$$
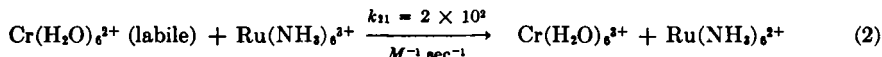
Even when these demands for an outer-sphere reaction are not in force, the lowest energy barrier to the redox process may still be presented by an outer-sphere path. However, the absence of unambiguous criteria leaves the mechanistic path of many reactions unclassified. Reactions between aquo complexes fall into this "ambiguous" category when one of them is labile to substitution over the time of the redox reaction, for example, Eq. 3, acid-independent path (72).

$$Cr(H_2O)_6^{2+} + Cr(H_2O)_6^{3+} \xrightarrow[M^{-1}\ sec^{-1}]{k_{22} < 2.5 \times 10^{-5}} Cr(H_2O)_6^{3+} + Cr(H_2O)_6^{2+} \qquad (3)$$
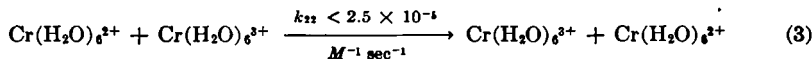
* Linck's article (69) should be consulted for a discussion of "abnormal" transition state structures such as those with expanded coordination number or ligand-ligand interactions.

Indirect arguments can sometimes be made. For example, the rate of an outer-sphere oxidation of $Cr(H_2O)_6^{2+}$ seems characteristically to be 10–60 times slower than the rate of an established outer-sphere reaction of $V(H_2O)_6^{2+}$ with the same oxidant (69, 73).

2. Energetic Aspects—The Absolute Marcus Theory

Analysis of the energy barriers to outer-sphere reactions is not complicated by contributions from bond breakage or formation. The nuclei remain within two primary bond systems. Among several related theories (56, 74) the treatment by Marcus (53, 55, 56) provides the most comprehensive framework for discussion.

For an outer-sphere reaction with $\Delta G° = 0$ the free energy of activation is formulated as a sum of contributions*:

$$\Delta G^{\ddagger} = RT \ln \frac{kT}{hZ} + \Delta G_c^{\ddagger} + \Delta G_i^{\ddagger} + \Delta G_o^{\ddagger} \qquad (4)$$

a. The Association Term. The first term of Eq. 4 accounts for the losses in translational and rotational free energy on forming the collision complex from the reactants. It has only a small enthalpy component of approximately 0.3 kcal mole^{-1} ($\frac{1}{2}RT$) at 25°C. A much larger contribution to this term comes from the entropy loss, about -13 eu at 25°C if a value (56) of $Z = 10^{10}M^{-1}$ sec^{-1} is used for the bimolecular collision rate constant.

b. The Coulombic Term. $\Delta G_c^{\ddagger}$ is the free energy change due to the electrostatic interaction between reactants at their separation distance in the activated complex, compared to that at infinite separation. In solutions of high ionic strength this term is expected to be negligibly small on a theoretical basis (56). Experimental evidence for reactions between similarly charged ions supports this expectation.

c. The Inner-Sphere Rearrangement Term. $\Delta G_i^{\ddagger}$ is the free energy change that occurs on rearranging the first-coordination-sphere ligands from their normal bond distances in the reactants to their distorted distances in the activated complex. The nature of the rearrangement barrier can be recognized from the following considerations.

Metal-ligand interaction energies for the two oxidation states of a hypothetical self-exchange couple, $ML_6^{2+/3+}$, are depicted schematically in Fig. 1. With regard to the vertical axis, the enthalpy of first-sphere interaction, ΔH_i, dominates the corresponding free energy, ΔG_i (56). To pro-

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* Other contributions, which are usually considered to be less important, can be included for special cases (56).
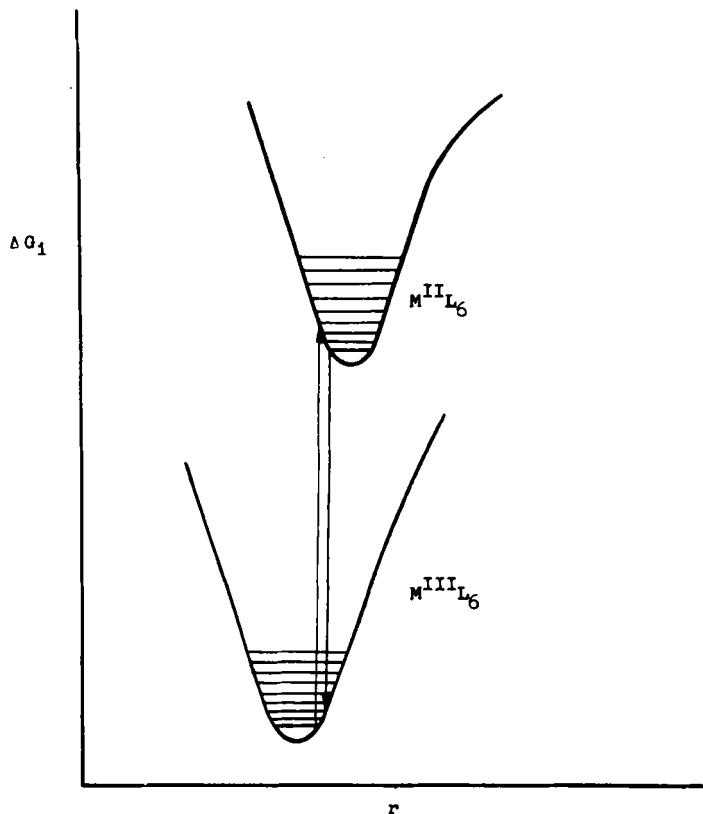
Fig. 1. Rough schematic of the energy wells for first-sphere bonding.

vide a rough frame of reference Table I contains calculated values (160) of ΔH_i for aquo ions.*

In Fig. 1 the equilibrium metal-ligand bond distances are designated as being shorter for the higher oxidation state. A specification of the nuclear positions is significant since essentially no "slow" nuclear motion can occur during the relatively "fast" transfer of an electron. Thus the Franck-Condon principle of spectroscopy, that nuclear coordinates remain

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* For comparison purposes, values of $\Delta G = -116$ kcal mole^{-1} and $\Delta H = -119$ kcal mole^{-1} have been calculated for interaction of $Fe(H_2O)_6{}^{3+}$ with an assumed number of eight water molecules in the second shell (56). This would leave $\Delta G = -314$ kcal mole^{-1} and $\Delta H = -319$ kcal mole^{-1} as the interaction energies arising exterior to the second shell (56).

unchanged during the relocation of an electron, applies to electron transfer reactions as Libby (75) first pointed out.†

The Franck-Condon principle requires that electron transfer be described by vertical transitions between the energy wells of Fig. 1. If the ground-state vibrational dimensions of the two reactants do not overlap, electron transfer between their ground states must simultaneously yield immediate products which are not in their vibrational ground states. The energy discrepancy between the two arrows corresponds to the transfer of an electron from a lower energy level in ML_6^{2+} to a higher level in ML_6^{3+}. The energy for such a transfer is not available from the surroundings because of poor coupling between slow nuclear and fast electronic motions (56).

A feasible route to the activated complex involves vibrational excitation of the complexes to levels where the vibrational dimensions overlap. A vertical transition can then occur as the result of an expansion in ML_6^{3+} and a compression in ML_6^{2+}, which are complementary. These distortions of the two coordination spheres create a situation in which the two redox orbitals on the reactants are of equal energy. The term $\Delta G_i^{\ddagger}$ represents the free energy absorbed during these first-sphere rearrangements.

d. **The Outer-Sphere Rearrangement Term.** The solvation shell exterior to the first sphere will be oriented more tightly around ML_6^{3+} than ML_6^{2+}. The term $\Delta G_o^{\ddagger}$ represents the free energy necessary to effect similar nuclear rearrangements in this solvation shell prior to electron transfer. Intuitively, $\Delta G_o^{\ddagger}$ should not differ significantly between metal complexes when the oxidation states and ligands are held constant. This

TABLE I

Enthalpies of First-Coordination-Sphere Interactions[a]

	ΔH_i, kcal mole^{-1}		ΔH_i, kcal mole^{-1}
$Ti(H_2O)_6^{2+}$	-260	$Ti(H_2O)_6^{3+}$	-584
$V(H_2O)_6^{2+}$	-267	$V(H_2O)_6^{3+}$	-610
$Cr(H_2O)_6^{2+}$	-274	$Cr(H_2O)_6^{3+}$	-662
$Mn(H_2O)_6^{2+}$	-259	$Mn(H_2O)_6^{3+}$	-655
$Fe(H_2O)_6^{2+}$	-282	$Fe(H_2O)_6^{3+}$	-629
$Co(H_2O)_6^{2+}$	-311	$Co(H_2O)_6^{3+}$	-683

[a] From Ref. 160.

† This principle cannot apply to redox transformations that do not involve a temporally isolated electron transfer, for example, hydrogen-atom transfer.

conclusion has been theoretically extended to include all complexes of comparable size so long as the number of electrons transferred remains the same (56).

It should be noted that however little $\Delta G_o{}^{\ddagger}$ may contribute to *differences* in $\Delta G^{\ddagger}$ it may nevertheless impose a lower limit on $\Delta G^{\ddagger}$ for reactions involving complexes of a particular size. Theoretically, $\Delta S_o{}^{\ddagger}$ contributes little to $\Delta G_o{}^{\ddagger}$ in media of high dielectric constant such as water (56). For one-electron transfers between first-row complexes with ligands the size of water or ammonia, a value of about 3 kcal mole^{-1} can be calculated for $\Delta G_o{}^{\ddagger} \sim \Delta H_o{}^{\ddagger}$ from the available equations (56).

e. **Brief Summary.** For complexes that differ primarily in the nature of the metal-ligand bond, the calculated contributions from $\Delta G_c{}^{\ddagger}$ and $\Delta G_o{}^{\ddagger}$ remain essentially constant. In these cases, differences in $\Delta G_i{}^{\ddagger}$ have been held accountable for the bulk of observed reactivity differences with apparent success. For example, the calculated values of $\Delta G_o{}^{\ddagger}$ for the $Ru(o\text{-phen})_3{}^{2+/3+}$ and $Ru(en)_3{}^{2+/3+}$ self-exchange couples cannot differ by much more than 1 kcal mole^{-1}. Thus the rate advantage of at least 10^5 for the $Ru(o\text{-phen})_3{}^{2+/3+}$ couple has been attributed largely to a decreased $\Delta G_i{}^{\ddagger}$ (63).

The theory appears consistent with such qualitative conclusions and provides a conceptual framework for analyzing reactivity barriers in terms of their various components. Analytical expressions have been derived for these components in terms of fundamental properties of the complexes (56). At present, these seem to provide only a partial account of observed kinetic parameters.

In a provocative article, metal-ligand bond distances are reported for components of the $Ru(NH_3)_6{}^{2+/3+}$ and $Co(NH_3)_6{}^{2+/3+}$ couples with the objective of analyzing the difference of at least 10^{15} in their self-exchange rates (76). The small bond-length differences between the ruthenium species, 0.040 Å, would require inner-sphere rearrangements over small distances. These rearrangements were considered to be within reach of both ground vibrational states, leading to the conclusion that $\Delta H_i{}^{\ddagger} \sim 0$ (76).

This interpretation leaves the obstacle of explaining the *slowness* of the $Ru(NH_3)_6{}^{2+/3+}$ self-exchange. If the analytical expressions of the theory are essentially correct (56), only a $\Delta H^{\ddagger} \sim \Delta H_o{}^{\ddagger}$ of 3 kcal mole^{-1} appears extractable for comparison with the experimental value of $\Delta H^{\ddagger} = 10.3 \pm 1.0$ kcal mole^{-1} (70). In the context of this interpretation, the explanation for the reactivity difference between the $Ru(en)_3{}^{2+/3+}$ [or $Ru(NH_3)_6{}^{2+/3+}$] and $Ru(o\text{-phen})_3{}^{2+/3+}$ self-exchange couples would seemingly have to be found elsewhere than in $\Delta G_i{}^{\ddagger}$. A conceivable resolution of these discrepancies might be found if the energy wells of at least the ruthenium-amine

complexes are actually so narrow that even small rearrangements require an appreciable $\Delta H_i^{\ddagger}$.

For most outer-sphere reactions in aqueous solution of moderate ionic strength $\Delta H^{\ddagger}$ falls in the range of 3 to 11 kcal mole^{-1} (69). This would be accounted for by a $\Delta H_o^{\ddagger} \sim 3$ kcal mole^{-1} and a $\Delta H_i^{\ddagger}$ which ranges from 0 (for couples whose ground-state dimensions overlap) to 8 kcal mole^{-1} (for couples with substantial rearrangement requirements). In this view, reactivity differences that are due to variations in $\Delta H^{\ddagger}$ arise primarily from the inner-sphere term as a result of differences in bonding.

With some couples, abnormally high barriers are found, for example, $Co(NH_3)_6^{2+/3+}$. This couple is unusual since a change in ground state from low spin to high spin occurs on going from $Co(III)$ (t_{2g}^6) to $Co(II)$ $(t_{2g}^5 e_g^2)$. The high reactivity barrier has been attributed to the conversion of $Co(NH_3)_6^{2+}$ to a $t_{2g}^6 e_g^1$ excited state prior to electron transfer with a calculated $\Delta H_{sp}^{\ddagger} = 24.6$ kcal mole^{-1} (76). An additional contribution of about 8 kcal mole^{-1} would be necessary from other sources to account for the observed $\Delta G^{\ddagger} \gtrsim 33$ kcal mole^{-1}. The possibility that the high barrier might arise from unusually large inner-sphere rearrangements was excluded on the basis of a force constant calculation (76). It again would seem worthwhile to consider the possibility that the energy wells are unexpectedly narrow and present "abnormal" resistance to rearrangement in the directions required for dimensional overlap.

The source of the entropy of activation in outer-sphere reactions remains obscure. The value of $\Delta S^{\ddagger} = -11 \pm 3$ eu reported (70) for the $Ru(NH_3)_6^{2+/3+}$ self-exchange is in line with the -13 eu calculated earlier for loss of translational and rotational entropy in forming the collision complex. However, many outer-sphere reactions have entropic barriers as large as $-30 < \Delta S^{\ddagger} < -50$ eu (69). No source for such large values can be found in the theoretical formulations (56). At zero ionic strength $\Delta S_c^{\ddagger}$ can provide about -20 eu, *but* this contribution theoretically becomes negligible at the ionic strengths of most studies (51, 56). A careful study of the dependence of $\Delta S_c^{\ddagger}$ on ionic strength seems highly desirable, especially since extreme sensitivity to variations has been reported (118).

In the single case where results have been extrapolated to zero ionic strength, the calculated $\Delta G^{\ddagger}$ and $\Delta S^{\ddagger}$ are both significantly lower than observed (77a). The calculated $\Delta S^{\ddagger}$ would be even lower if a value of -13 eu for the loss of translational and rotational entropy had been used. This paper should be consulted for an enlightening analysis of the discrepancies (77a).

A large number of reactions between positive ions have large negative values for $\Delta S^{\ddagger}$ (68, 69). Newton and Baker have recognized an empirical correlation between the partial molar entropy of the transition state and

its charge (77d, 68). The higher the total charge, the more negative is the partial molar entropy. No molecular interpretation of these results seems available.

An understanding of the source of the entropy barrier is badly needed in any comprehensive pursuit of biochemical reactions since $\Delta S^\ddagger$, especially $\Delta S_0^\ddagger$, would appear to be especially sensitive to modification by biological environments. It may prove necessary to take account of changes from the bulk dielectric constant (77a) and to make allowance for specific interactions in a solvent which seems especially sensitive entropically to such interactions (201). Additional inconsistencies between observation and calculations from the theory have been noted (51, 77b,c).

A significant development which has potential for better delineating the contributions to reactivity in outer-sphere reactions is the observation of a first-order electron transfer within a relatively stable precursor ion-pair complex, $[Co^{III}(NH_3)_5OH_2 \cdot Fe^{II}(CN)_6]^+$ (89). This type of reaction presents the opportunity to evaluate ΔH and ΔS for electron transfer activation and precursor complex formation *separately*. The electron transfer act may be too rapid to be distinguished as a first-order process for many reactants. Nevertheless, the thermodynamic parameters for ion-pair formation, which do not seem widely available (90), should not vary greatly in complexes where the central metal is changed but the ligands and total charge are held constant. Thus a compilation of these values for appropriate slow, or even unreactive, complexes should make it possible to factor the contributions from precursor formation out of the activation parameters. As a result the desired extension to more reactive complexes, especially those not containing the atypical Co(III) center, seems feasible and should contribute to a resolution of some of the problems described earlier.

3. Energetic Aspects—The Relative Marcus Theory

The Marcus theory has proven successful in interrelating the reactivities of self-exchange reactions with cross-reaction reactivities, all reactions being outer sphere. The cross-reaction free-energy barrier, $\Delta G_{12}^\ddagger$, is considered to arise from intrinsic barriers, $0.5\Delta G_{11}^\ddagger$ and $0.5\Delta G_{22}^\ddagger$, which each component provides in a similar fashion to its contribution to its own self-exchange reaction. (Errors accompanying the 0.5 coefficients are assumed to cancel.) In addition, the favorable free-energy change, ΔG_{12}^0, accompanying the cross reaction provides for a lowering of the activation barrier by an amount of $0.5\Delta G_{12}^0$.

$$\Delta G_{12}^\ddagger = 0.5\Delta G_{11}^\ddagger + 0.5\Delta G_{22}^\ddagger + 0.5\Delta G_{12}^0 \tag{5}$$

TABLE II

Comparison of Calculated and Experimental k_{12} Values

Reaction	k_{12}, M^{-1} sec^{-1}		Ref.
	Observed	Calculated	
$IrCl_6^{2-} + W(CN)_8^{4-}$	6.1×10^7	6.1×10^7	78
$IrCl_6^{2-} + Fe(CN)_6^{4-}$	3.8×10^5	7×10^5	78
$IrCl_6^{2-} + Mo(CN)_8^{4-}$	1.9×10^6	9×10^5	78
$Mo(CN)_8^{3-} + W(CN)_8^{4-}$	5.0×10^6	4.8×10^6	78
$Mo(CN)_8^{3-} + Fe(CN)_6^{4-}$	3.0×10^4	2.9×10^4	78
$Fe(CN)_6^{3-} + W(CN)_8^{4-}$	4.3×10^4	6.3×10^4	78
$Ce^{IV} + W(CN)_8^{4-}$	$>10^8$	4×10^8	78
$Ce^{IV} + Fe(CN)_6^{4-}$	1.9×10^6	8×10^6	78
$Ce^{IV} + Mo(CN)_6^{4-}$	1.4×10^7	1.3×10^7	78
L-Co[(−)PDTA]$^{2-}$ + Fe(bipy)$_3^{3+}$	8.1×10^4	$\geq 10^5$	79
L-Fe[(−)PDTA]$^{2-}$ + Co(EDTA)$^-$	1.3×10^1	1.3×10^1	79
L-Fe[(−)PDTA]$^{2-}$ + Co(ox)$_3^{3-}$	2.2×10^2	1.0×10^2	79
$Cr(EDTA)^{2-} + Fe(EDTA)^-$	$\geq 10^6$	10^9	80
$Cr(EDTA)^{2-} + Co(EDTA)^-$	$\simeq 3 \times 10^5$	4×10^7	80
$Fe(EDTA)^{2-} + Mn(CyDTA)^-$	$\simeq 4 \times 10^5$	6×10^6	80
$Co(EDTA)^{2-} + Mn(CyDTA)$	9×10^{-1}	2.1	80
$Fe(PDTA)^{2-} + Co(CyDTA)^-$	1.2×10^1	1.8×10^1	80
$Co(terpy)_2^{2+} + Co(bipy)_3^{3+}$	6.4×10	3.2×10	81
$Co(terpy)_2^{2+} + Co(phen)_3^{3+}$	2.8×10^2	1.1×10^2	81
$Co(terpy)_2^{2+} + Co(bipy)(H_2O)_4^{3+}$	6.8×10^2	6.4×10^4	81
$Co(terpy)_2^{2+} + Co(phen)(H_2O)_4^{3+}$	1.4×10^3	6.4×10^4	81
$Co(terpy)_2^{2+} + Co(H_2O)_6^{3+}$	7.4×10^4	2×10^{10}	81
$Fe(phen)_3^{2+} + MnO_4^-$	6×10^3	4×10^3	82a
$Fe(CN)_6^{4-} + MnO_4^-$	1.3×10^4	5×10^3	62b
$V(H_2O)_6^{2+} + Ru(NH_3)_6^{3+}$	1.5×10^3 ^{a}	4.2×10^3	70
$Ru(en)_3^{2+} + Fe(H_2O)_6^{3+}$	8.4×10^4	4.2×10^5	70
$Ru(NH_3)_6^{2+} + Fe(H_2O)_6^{3+}$	3.4×10^5	7.5×10^6	70
$Fe(H_2O)_6^{2+} + Mn(H_2O)_6^{3+}$	1.5×10^4	3×10^4	86

^{a} See Table III, footnote b.

A helpful rationalization and pictorialization of these contributions has been provided by Sutin (51). With inclusion of a correction factor, f,

$$\log f = \frac{(\log K_{12})^2}{4 \log (k_{11}k_{22}/Z^2)} \qquad (6)$$

which becomes appreciable only as K_{12}, the cross-reaction equilibrium constant, becomes large (Z is the collision frequency), Equation 5 is trans-

formed into

$$k_{12} = (k_{11}k_{22}k_{12}f)^{1/2} \qquad (7a)$$

or more usefully for one-electron transfers at 25°C,

$$\log k_{12} = 0.5(\log k_{11} + \log k_{22} + \frac{\Delta E^0}{0.059} + \log f) \qquad (7b)$$

For such reactions, each increment of 0.12 V in ΔE^0 contributes one order of magnitude to the rate.

The general applicability of Eq. 7 is confirmed by the data of Table II. The agreement, although perhaps fortuitous in some cases (56), is remarkably good except for several examples involving Co(III) [especially $Co(H_2O)_6{}^{3+}$]. Other deviations for this metal center have been noted (71, 77b, 83, 84). An important test of the relative Marcus theory involves, first, a separation of the thermodynamic contribution $0.5\Delta G_{12}^0$ from the intrinsic kinetic barriers $0.5\Delta G_{11}^{\ddagger}$ and $0.5\Delta G_{22}^{\ddagger}$, and, secondly, a partitioning of the total intrinsic barrier between the latter two in order to examine the validity of their having equal coefficients.

In a number of studies the thermodynamic contribution has been isolated and found to correspond closely to that given in Eq. 5 (78, 83, 85, 86, 88). In contrast, the contributions of the intrinsic barriers did not always comply with Eq. 5. One reason may be that the nonelectrostatic work terms involved in bringing the various reactants together may not cancel exactly (87).

We shall take as well established the $0.5\Delta G_{12}^0$ contribution to $\Delta G^{\ddagger}$ for the aqueous reactions of simple metal complexes. The extent to which this relationship extends to the reactions of metalloproteins remains an important question. It seems unlikely that so pervasive an influence in simple reactions would fail to affect the more complex reactions of metalloproteins. The extensive correlation of $k_{12} = (k_{11}k_{22}K_{12}f)^{1/2}$ with a wide variety of experimental results (Table II) suggests its provisional application in most simple systems.

B. Inner-Sphere Reactions

1. Spatial Aspects

In an inner-sphere reaction the complementary oxidation state change occurs via a path in which the reactants combine to form a single primary bond system with at least one "bridging" ligand being simultaneously bound to both metal centers. The necessary, but not always sufficient, conditions for such a mechanism are (1) that one complex possess at least

one ligand with a secondary bonding site which is sterically accessible (potentially important for metalloproteins) to the second metal center, and (2) the latter must be sufficiently labile (or able to expand its co-ordination number) to gain access to the bridging ligand during the time of the redox process.

Because reactants satisfying these conditions may nevertheless have access to a lower energy outer-sphere path, positive evidence for the inner-sphere path is required. Indirect arguments of varying plausibility have been made in support of inner-sphere paths for which no direct evidence exists. The most acceptable evidence, however, is of the type originally employed by Taube and Myers (91) in which more than equilibrium amounts of the bridging ligand are experimentally detected in the product coordination sphere of the metal center not originally associated with the bridging ligand. For this to be successful, a degree of inertness is demanded of the product with respect to the time period of both the redox reaction and observation. The approach has now been extended to certain reactions of a variety of reductants in addition to $Cr(II)$, namely $Co(CN)_5^{3-}$ (92), $Fe(H_2O)_6^{2+}$ (93), $Ru(NH_3)_5H_2O^{2+}$ (94), and $V(H_2O)_6^{2+}$ (95–97), and to one reaction in which the bridging ligand originally resides on the reductant: $Fe(CN)_6^{4-}$ reacting with $HCrO_4^-$ (the third one-equivalent step is apparently inner sphere) (98). The observation of *less* than equilibrium amounts of a potential bridging ligand in the product sphere of the metal center which brought it into the reaction should also establish the inner-sphere path, but this approach is experimentally less tractable in most systems for which the equilibrium amounts are already low and has not been exploited. The high ligand specificity in certain metalloproteins may make this diagnosis feasible provided that an inner-sphere path is operative.

For polyatomic bridging ligands the redox process can conceivably be consummated by several paths in which the incoming metal center bonds to one of several available bridging ligand atoms. Taube's terms "adjacent" attack for those reactions in which a single nucleus separates the metal centers and "remote" attack when two or more nuclei intervene between the metals apply here. Documentation of remote attack has been provided in a number of instances, the simplest involving a case where adjacent and remote bridging atoms compete, that is, the reduction of $Co^{III}-NCS^-$ complexes by $Cr(H_2O)_6^{2+}$ where $(H_2O)_5Cr-SCN^{2+}$ is generated in greater than equilibrium concentration (99). In the reaction of $(NH_3)_5Co(-NC_5H_4CONH_2)^{3+}$ with $Cr(H_2O)_6^{2+}$ two possible remote binding sites exist. The structure of the activated complex has been established as involving the bonding of $Cr(H_2O)_5^{2+}$ to the remote carbonyl group (100).

A third consideration of atomic geometry during the course of reaction deals with the question of chelation in the activated complex. The mecha-

nistic possibilities can be subdivided into several categories. The first of these involves the chelation of the incoming metal center by an originally monodentate ligand with a pendant function capable of chelation. This process can involve a remote atom in the pendant function with either a remote atom in the adjacent function, for example, $Cr(H_2O)_6^{2+}$ + $(NH_3)_5Co-OCO*CH_2CO*OH$ (61, 101) (chelating atoms starred), or with an adjacent atom, for example, $Cr(H_2O)_6^{2+}$ + $(H_2O)_5Cr-S*CH_2CO*OH$ (102).

A second possibility is for double chelation in the activated complex which involves a ligand already chelated to the first metal center but which has two remote atoms geometrically disposed for chelation to the incoming metal center as well, for example, $Cr(H_2O)_6^{2+}$ + $Co(NH_3)_4C_2O_4^+$ (103). This mode has not been extensively examined in simple systems but may be more important for certain metalloproteins. A third type of chelation involves double bridging by two cis ligands to form a single ring containing both metal centers. This could involve atoms which are either remote or adjacent with respect to the metal center bringing the ligands into reaction. Double bridging was first observed in the reaction between $Cr(H_2O)_6^{2+}$ and cis-$Cr(H_2O)(N_3)_2^+$ (104), and has since been observed in other systems (105–107).

2. Energetic Aspects

The detailed steps of an inner-sphere reaction can be cataloged according to Scheme I.

(1)
$$L_5M^{III}X^{m+} + M^{II}(H_2O)_6^{n+} \overset{K_p}{\rightleftharpoons} [L_5M^{III}XM^{II}(H_2O)_6]^{(m+n)+}$$
Encounter complex formation

$$[L_5M^{III}XM^{II}(H_2O)_6]^{(m+n)+} \overset{k_1}{\underset{k_{-1}}{\rightleftharpoons}} H_2O + [L_5M^{III}-X-M^{II}(H_2O)_5]^{(m+n)+}$$
Precursor complex formation

(2)
$$[L_5M^{III}-X-M^{II}(H_2O)_5]^{(m+n)+} \rightleftharpoons [L_5M^{III}-X-M^{II}(H_2O)_5^{(m+n)+}]^{\ddagger}$$
Precursor activation

$$[L_5M^{III}-X-M^{II}(H_2O)_5^{(m+n)+}]^{\ddagger} \rightleftharpoons [L_5M^{II}-X-M^{III}(H_2O)_5^{(m+n)+}]^{\ddagger}$$
Electron transfer

$$[L_5M^{II}-X-M^{III}(H_2O)_5^{(m+n)+}]^{\ddagger} \rightleftharpoons [L_5M^{II}-X-M^{III}(H_2O)_5^{(m+n)+}]$$
Successor complex deactivation

(3)
$$[L_5M^{II}-X-M^{III}(H_2O)_5^{(m+n)+}] \rightleftharpoons L_5M^{IIm+} + XM^{III}(H_2O)_5^{n+}$$
$$\downarrow \quad\quad \downarrow$$
products   products
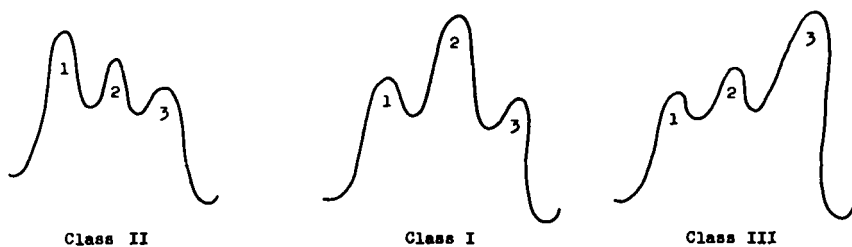Successor complex decomposition

Scheme 1

Fig. 2. Idealized classes for inner-sphere mechanisms. (Adapted from Ref. 69.)

Scheme I provides a generalized sequence for the reaction, but should not be construed as establishing each step as isolated in time in the absence of evidence.

An advantage of Scheme I is that it frequently provides for the assignment of a reaction to one of three idealized classes depending on which one of the three numerically labeled steps presents the greatest free-energy barrier. The energy contours for the three classes are depicted in Fig. 2 according to Linck's refinement of this analysis (69).
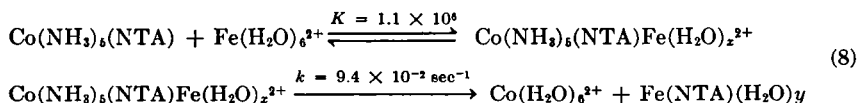
Class II reactions are those in which precursor formation is rate limiting, usually as the result of relatively slow substitution on the reactant making the new bond to the bridging ligand. The most thoroughly studied examples of this class are many reactions of the ambivalent reductant, $V(H_2O)_6^{2+}$. Substitution by water in this reductant is relatively slow, $k = 100$ sec^{-1}, $\Delta H^{\ddagger} = 16.4$ kcal mole^{-1}, $\Delta S^{\ddagger} = 5.5$ eu (108), and this is reflected in the substitution by NCS$^-$, $k = 28M^{-1}$ sec^{-1}, $\Delta H^{\ddagger} = 13.5$ kcal mole^{-1}, $\Delta S^{\ddagger} = -7$ eu (109). In anticipation of these results it was proposed that substitution into the V(II) coordination sphere to form the precursor complex, step 1, can be the rate-determining step for inner-sphere V(II) oxidations (110, 60). Since then numerous reductions by $V(H_2O)_6^{2+}$ have been assigned to Class II on the basis of the correspondence between redox and substitution processes in both rate and activation parameters (69). For cationic reactants the upper limit for assignment to this class is usually considered to be in the neighborhood of $40M^{-1}$ sec^{-1} (69).

While not always explicitly stated, the rate of step 1 depends on both an equilibrium constant K_p for pair formation and a rate constant k_1 for those substitutions on $V(H_2O)_6^{2+}$ in the pair which prove fruitful in establishing the bridged complex. Thus, $k_{obsvd} = k_1 K_p$. If no statistical factors are considered, a value of K_p as large as 0.4 for the fastest reactions of this type would bring k_1 into line with the substitution rate. This value does

not seem unreasonable (referenced to standard states of $1M$) for the ions of $1+$ and $2+$ charges involved. The slower rates reported (69) for $2+$ ions would require smaller K_p values, as expected. Values of $\Delta G_p{}^0$ which are close to zero ($K_p{}^0 = 1$) are, in fact, suggested from the fact that $\Delta H_{obsvd}{}^{\ddagger}$ and $\Delta S_{obsvd}{}^{\ddagger}$, to which $\Delta H_p{}^0$ and $\Delta S_p{}^0$ must contribute, deviate little (69) for cation-cation redox reactions from those observed for substitution alone.

For Class II reactions between ions of opposite charge a larger value for K_p is anticipated. The $k_{obsvd} = 1.3 \times 10^3 M^{-1}$ sec^{-1} reported for the inner-sphere portion (outer-sphere reaction is about 10 times more efficient) of the $V(H_2O)_6{}^{2+}$–$Co(C_2O_4)_3{}^{3-}$ reaction (111) is accommodated by a $K_p \sim 13$, which seems within reason as judged by values for large ions of $3+$ and $2-$ charge (90). The statistical factor of 6 employed (111) seems unnecessary, except, perhaps, for comparison purposes, since the presence of six carboxylate functions simply ensures their availability to a $V(H_2O)_6{}^{2+}$ undergoing substitution. Lower rates of 112 to $278 M^{-1}$ sec^{-1} have been reported for the reaction of $V(H_2O)_6{}^{2+}$ with other trinegative ions (112).

In Class I reactions formation of the precursor complex, step 1, occurs rapidly relative to electron transfer, step 2, and constitutes a rapid pre-equilibrium so that $k_{obsvd} = K_p(k_1/k_{-1})k_2$. The most striking example of this behavior involves coordination to the pendant function(s) of a monocoordinated nitrilotriacetate (NTA) ligand. In the reaction between $Co(NH_3)_5NTA$ and $Fe(H_2O)_6{}^{2+}$ saturation of the pseudo-first-order rate constant as $[Fe(H_2O)_6{}^{2+}]$ is increased implies the rapid formation of a precursor complex which decays by first-order electron transfer (113):

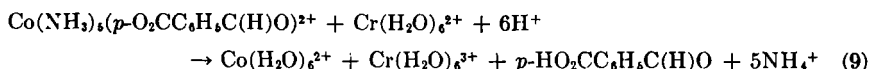$$Co(NH_3)_5(NTA) + Fe(H_2O)_6{}^{2+} \underset{}{\overset{K\ =\ 1.1\ \times\ 10^4}{\rightleftharpoons}} Co(NH_3)_5(NTA)Fe(H_2O)_x{}^{2+}$$

$$Co(NH_3)_5(NTA)Fe(H_2O)_x{}^{2+} \xrightarrow{k\ =\ 9.4\ \times\ 10^{-2}\ sec^{-1}} Co(H_2O)_6{}^{2+} + Fe(NTA)(H_2O)y \tag{8}$$

Another example is provided by the observation of $Fe(H_2O)_5Cl^{2+}$ in greater than equilibrium amounts produced by the reduction of *trans*-$Co(NH_3)_4(Cl)(H_2O)^{2+}$ by $Fe(H_2O)_6{}^{2+}$ (labile) (95). In variations on this theme a reductant can bring in the bridging ligand (98) or the metal center bringing the bridging ligand in can retain it (114), for example,

$$IrCl_6{}^{2-} + Co(CN)_5{}^{3-} + OH^- \rightarrow IrCl_6{}^{3-} + Co(CN)_6{}^{3-} + Co(CN)_5OH^{3-}$$
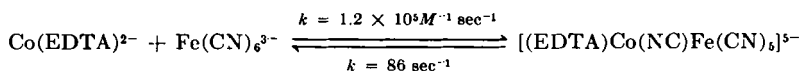
depending on the substitution characteristics of the products. In this example we are presumably verging on Class III behavior since both product metal centers are relatively inert. Depending on the donor functions involved and their lability on the product metal centers the bridging ligand

can be lost from both metal center products (115), for example,

$$Co(NH_3)_5(p\text{-}O_2CC_6H_4C(H)O)^{2+} + Cr(H_2O)_6^{2+} + 6H^+$$
$$\rightarrow Co(H_2O)_6^{2+} + Cr(H_2O)_6^{3+} + p\text{-}HO_2CC_6H_4C(H)O + 5NH_4^+ \quad (9)$$

As first suggested by Halpern (116), the classical inner-sphere reductant, $Cr(H_2O)_6^{2+}$, may, in its fastest inner-sphere reactions, border on Class II behavior. This conclusion derives from the similarities between a large number of high rate constants, 10^6 to $10^7 M^{-1}$ sec^{-1}, and a comparable calculated value for the expected upper limit for substitution-limited reaction. The rate of substitution on $Cr(H_2O)_6^{2+}$ indicated by NMR measurements (117), 10^9 to 10^{10} sec^{-1}, combined with an expected lifetime of an outer-sphere encounter complex of 10^{-11} to 10^{-12} sec, suggests that only 0.1 to 1.0% of the collisions are effective in establishing a bridge (118). When combined with a collision rate of $10^9 M^{-1}$ sec^{-1}, this yields a substitution-controlled limit in the observed range of 10^6 to $10^7 M^{-1}$ sec^{-1}. Variations within this range seem ascribable to either the expected trend for variation of K_p or the effects anticipated if the barrier to step 2 is sufficiently similar to that for step 1 that neither is solely rate limiting and mixed Class I–Class II behavior is operative. When alternate multistep pathways are consistent with the rate law (69), such as those involving proton loss either before or after precursor formation (119), a rate, calculated on the assumption of prior proton loss, which exceeds the substitution limit excessively has been used to argue in favor of proton loss from the precursor complex (120).

Class III behavior is operative when decay of the successor complex, step 3, is rate determining, thereby establishing an equilibrium between it and the reactants. This reaction mode should be considered as a possibility whenever the product metal centers are both relatively inert to substitution. It has been demonstrated (98, 121, 122) or inferred (123) in several instances, for example (122),

$$Co(EDTA)^{2-} + Fe(CN)_6^{3-} \underset{k\ =\ 86\ sec^{-1}}{\overset{k\ =\ 1.2\ \times\ 10^5 M^{-1}\ sec^{-1}}{\rightleftharpoons}} [(EDTA)Co(NC)Fe(CN)_5]^{5-}$$

In considering the energetic aspects of inner-sphere reactions it is natural to make a comparison with outer-sphere reactions and to ask if there exist influences which operate in parallel fashion for the two categories. Presumably, inner-sphere reactions outside of Class I must surmount barriers which also are partially established by a need to rearrange metal-ligand configurations. The influence of the net driving force ΔG^0 on the rate is unlikely to be renounced completely for inner-sphere reactions. A correlation between the two categories does materialize but it must be considered as qualitative in nature (see Ref. 69 for a discussion and refer-

ences on this topic). A major obstacle confronting attempts at quantitative
correlations of the variety of the relative Marcus theory is that, within the
single primary bond framework of importance for inner-sphere reactions,
the intrinsic factors may well be relatively unique for each reaction (69).

C. Reactivity Influences

Reactivity patterns can be summarized succinctly by considering
selected examples which are relevant to the following domains of influence:
(1) the electronic configuration of the metal centers with special emphasis
on the symmetry of the orbitals involved in electron transfer; (2) ligand
rearrangement energy; and (3) net driving force. This approach is a varia-
tion on Linck's and is highly operational in nature; these effects are fre-
quently interdependent and the first two do not distinguish between
intrinsic and thermodynamic contributions, which seems appropriate since
they are rarely factorialized cleanly in real systems however operative
they may be. A final section deals with the participation of ligand orbitals
in the redox process.

1. Influence of the Electronic Configuration

The success of the relative Marcus theory for outer-sphere reactions
relegates questions regarding reactivity to two categories. The standard
free energy component is established by the ground-state interaction of the
ligands with the metal centers in their respective oxidation states. The
intrinsic component is derived from the inherent reactivity of a given
metal-ligand couple in its self-exchange reaction for which $\Delta G^0 = 0$. In
addition to their impact on the ground-state free energies (160), the elec-
tronic configurations of metal centers in their complementary oxidation
states have a profound effect on inherent reactivities.

The reactivity difference cited earlier for the $M(NH_3)_6^{2+/3+}$ couples of
Ru(II/III) versus Co(II/III) remains in effect, although somewhat di-
minished, as the ligands are varied, for example, k_{11} (Ru(o-phen)$_3^{2+/3+}$) >
$10^7 M^{-1}$ sec^{-1} (63), whereas k_{11} (Co(o-phen)$_3^{2+/3+}$) = $5.0 M^{-1}$ sec^{-1} (0°C)
(124). The difference can be attributed to the transferal of an electron
between t_{2g} orbitals in the former case compared to a presumed e_g trans-
feral for the latter example. While criticism can be leveled at this analysis
in view of the spin-state change in the cobalt couple the conclusions extend
to reactants which are devoid of this complicating factor. For example,
the uniform reactivity advantage of $V(H_2O)_6^{2+}$ over $Cr(H_2O)_6^{2+}$ in outer-
sphere reactions referred to earlier (69, 73) occurs in the face of a 0.16-V
deficit in ΔG^0 for the former reactant and can be rationalized in terms of

the presumed ease of transferal of an electron from a t_{2g} orbital compared to an e_g orbital.

The primary source of the reactivity advantage for π-type orbitals compared to those with σ character apparently lies in the greater rearrangement barrier presented when the orbitals associated with the transferring electron lie along the internuclear axis. Orbitals of π character are directed between the ligands where a net change of one electron affects bond distances much less; that is, they are approximately nonbonding in character. The effect of an electron change in the σ region is expected to be more strongly felt the higher the oxidation state of the metal so that the barrier presented by this effect is lower for an e_g reductant than an e_g oxidant, other things being equal. Thus, in a hypothetical series where only the electronic configuration is changed, the reactivity order is expected to be $(t_{2g} \rightarrow t_{2g}) > (e_g \rightarrow t_{2g}) > (t_{2g} \rightarrow e_g) > (e_g \rightarrow e_g)$ for outer-sphere reactions. After account is taken of variation in the other operative influences, the available experimental evidence is consistent with this ordering although in the central region it is less extensively supported than at the extremes. Table III contains representative data illustrating these effects.

For inner-sphere reactions a different pattern emerges. As can be seen in Table III, complexes with redox orbitals of σ symmetry (e_g) take greater advantage of this reaction mode, relative to the outer-sphere patterns, than do those complexes where the redox orbital is of π symmetry (t_{2g}). A comparison of the pyridine and acetato complexes of $Ru^{III}(NH_3)_5$ and $Co^{III}(NH_3)_5$ shows a reactivity enhancement by a factor of 10 greater for the Co(III) complex than for the Ru(III) complex on changing from outer-sphere to inner-sphere mechanisms (94, 69). Other examples of the efficacy of the bridging mechanism for reactants with e_g redox orbitals are evident in Table III and elsewhere (69), and it has been suggested that inner-sphere reactions are preferred when rearrangement energies are large (51). Normally, when both reactants have redox orbitals of t_{2g} symmetry, an outer-sphere path will present the lowest activation barrier.

The source of the relative inner-sphere advantage for reagents with e_g redox orbitals lies (1) in the high rearrangement barrier for outer-sphere reactions discussed above, and (2) in the way that motion of the bridging ligand away from the oxidant and toward the reductant during activation can simultaneously satisfy the large activation requirements of both metal centers (63). This motion complements the exchange of tetragonal distortions occurring between reactants on transferal of an e_g electron and can be regarded as lowering the energy of the receptor e_g orbital while simultaneously raising the energy of the donor e_g orbital (63). Increased orbital overlap in the σ-bond system may also be of importance, but this has not

TABLE III

Variations in Reactivity with Electronic Configuration[a]

	Outer-sphere reactions			Inner-sphere reactions		
Oxidant	Redox orbital	Rate, M^{-1} sec^{-1}		Oxidant	Redox orbital	Rate, M^{-1} sec^{-1}
A. $V(H_2O)_6$ as reductant ($t_{2g} \rightarrow$)						
$Co(NH_3)_6^{3+}$	e_g	3.7×10^{-4}		Usually substitution limited (Class II)		$\sim 1\text{-}40$
$Ru(NH_3)_6^{3+}$	t_{2g}	1.5×10^{3} [b]		—	—	—
$Ru(NH_3)_5L^{3+}$	t_{2g}	$\sim 3 \pm 2 \times 10^{3}$		—	—	—
$Co(NH_3)_5(py)^{3+}$	e_g	2.4×10^{-1}		—	—	—
$Ru(NH_3)_5(py)^{3+}$	t_{2g}	1.2×10^{5}		—	—	—
$Ru(NH_3)_5(O_2CCH_3)^{2+}$	t_{2g}	1.3×10^{3}		$Co(NH_3)_5(O_2CCH_3)^{2+}$ (Substitution limited)	e_g	~ 15
$Co(NH_3)_5Cl^{2+}$	e_g	7.6				
$Fe(H_2O)_6^{3+}$	t_{2g}	1.8×10^{4}		—	—	—
B. $Cr(H_2O)_6^{2+}$ as reductant ($e_g \rightarrow$)						
$Co(NH_3)_6^{3+}$	e_g	8.9×10^{-5}		$Co(NH_3)_5OH^{3+}$	e_g	1.5×10^{6}
$Ru(NH_3)_6^{3+}$	t_{2g}	2×10^{2}		$Co(NH_3)_5Cl^{2+}$	e_g	2.5×10^{5}
$Co(NH_3)_5(py)^{3+}$	e_g	4.3×10^{-3}		$Co(NH_3)_5(O_2CCH_3)^{2+}$	e_g	3.5×10^{-1}
$Ru(NH_3)_5(py)^{3+}$	t_{2g}	3.4×10^{3}		$Ru(NH_3)_5(O_2CCH_3)^{2+}$	t_{2g}	2.6×10^{4}

[a] Data are taken from the compilation by Linck (69).

[b] This is a tentative number obtained in the author's laboratory by Charles Jacks. We have not been able to duplicate the value of 80 reported in the literature (71). The new value seems more reasonable both in comparison to the values with $Ru(NH_3)_5L^{3+}$ for a variety of L (see Ref. 69) and in comparison to the value with $Cr(H_2O)_6^{2+}$.

been experimentally distinguished from other factors. The coupling of the nuclear motion to the electron transfer makes a distinction between electron transfer and group transfer difficult for many of these reactions especially at the experimental level.

2. Influence of Ligand Rearrangement Energies

The importance of $\Delta H_i^{\ddagger}$ in outer-sphere reactions has already been discussed. This factor is usually responsible for variations in the intrinsic contribution, that is, the self-exchange reactivity, as ligands are changed for a given metal couple. The influence has been successfully correlated on an empirical basis with (1) estimates of the variation in bond strength (resistance to rearrangement), and (2) estimates of the variation in the extent of rearrangement necessary for activation as the ligands are varied. Adequate examples are provided by the self-exchange rates indicated for the Ru(II/III) and Co(II/III) couples as the ligands are changed from ammonia to o-phenanthroline.

In inner-sphere reactions a distinction is made between the bridging and nonbridging ligands. Evidence supporting the requirement for substantial stretching of the metal-bridging ligand bond in the $Cr(H_2O)_6^{2+}$–$Co(NH_3)_5OH^{2+}$ reaction has been adduced through the detection of a large kinetic isotope effect, $d \ln {}^{16}O/d \ln {}^{18}O = 1.03_5$ (125). A low level of isotopic fractionation arising from the Co–N bonds, $d \ln {}^{14}N/d \ln {}^{15}N = 1.002$ to 1.003 (126), suggests that, for this example, rearrangement barriers are surmounted primarily in the bridging network. In contrast, the $Cr(H_2O)_6^{2+}$–$Cr(NH_3)_4(H_2O)Cl^{2+}$ reaction is found to have appreciable isotope fractionation from the nonbridging H_2O and the effect is larger when H_2O is trans (1.017) than when it is cis (1.007) to the bridging chloride (127). Thus both bridging and nonbridging ligands can contribute rearrangement barriers as suggested originally by Orgel (128) and Taube (48).

The influence of the rearrangement barrier associated with the bridging ligand is difficult to assess because of its extensive involvement with both metal centers. In several instances an ordering of bridging efficiency along a series of ligands is completely inverted on changing one or the other of the metal centers involved. The permeability of the bridging ligand to electron flow may also be influential in determining bridging efficiency (63). Reference 63 can be consulted for a detailed consideration of these points.

An example of nonbridging ligand effects is seen in the reactions of $Cr(H_2O)_6^{2+}$ with $Cr(NH_3)_5Cl^{2+}$ ($k = 5.1 \times 10^{-2}M^{-1}$ sec^{-1}) (129) and $Cr(H_2O)_5Cl^{2+}$ ($k = 9M^{-1}$ sec^{-1}) (130). This is in line with an anticipated

easier activation of the weaker $Cr-H_2O$ bonds relative to the stronger $Cr-NH_3$ bonds, although free energy effects may also be influential.

Nonbridging ligand effects exhibit stereoselectivity in that variations in the position trans to the bridging ligand produce greater changes than in cis positions. For example, in the $Fe(H_2O)_6^{2+}$ reductions of *trans*-$Co(en)_2(NH_3)Cl^{2+}$, $k = 6.6 \times 10^{-5}$, and *trans*-$Co(en)_2(H_2O)Cl^{2+}$, $k = 2.4 \times 10^{-1}M^{-1}$ sec^{-1}. The rate enhancement on going from nonbridging NH_3 to H_2O is about 10^3 greater than for the cis complexes, *cis*-$Co(en)_2(NH_3)Cl^{2+}$, $k = 1.8 \times 10^{-5}$, and *cis*-$Co(en)_2(H_2O)Cl^{2+}$, $k = 4.6 \times 10^{-4}M^{-1}$ sec^{-1} (131). This larger impact at the trans position can be attributed to a more direct involvement of the trans ligand with the antibonding σ orbital, d_{z^2}, which is associated with the bridging ligand. However, the parameter of influence appears to be the σ-bond strength (132, 69) rather than the ligand field strength as originally proposed (128).

It is worth noting that nonbridging ligand effects in inner-sphere reactions parallel the ligand effects in outer-sphere reactions (69, 133). This seems reasonable since the qualitative aspects of metal-ligand rearrangement are similar for the two types. In this regard, the partitioning of bridging and nonbridging effects as separable influences is of interest (69). The sensitivity of the parallel effects to the electronic configuration of the metal centers should be recognized (69). The relative ease of activating bonds to the nonbridging ligands differ when the redox orbitals are of π versus σ symmetry (134, 135). For further details on these effects recent reviews covering the area should be consulted (69, 68, 66).

3. Influence of the Net Driving Force

The almost universal role of the standard free energy change in influencing outer-sphere reactivities has been adequately illustrated. The extension of this influence to inner-sphere reactions is reasonably expected, at least in a qualitative sense, but little in the way of quantitative correlation has been achieved. Nevertheless, gross effects, at least, are in evidence; compare the reactivities toward $Cr(H_2O)_6^{2+}$ of $M(NH_3)_5X^{2+}$ when M is the stronger oxidant, Co(III) ($k = 2.5 \times 10^5$, 6×10^5, $1.4 \times 10^6M^{-1}$ sec^{-1} for X = F$^-$, Cl$^-$, Br$^-$) (136), and when M is the weaker oxidant, Cr(III) ($k = 2.7 \times 10^{-4}$, 5.1×10^{-2}, $0.32M^{-1}$ sec^{-1}) (129). On the basis of the isotope effects mentioned earlier it has been suggested that bonding rearrangements exterior to the bridging network might be necessary to compensate for the weaker oxidizing capacity of Cr(III) (63). In this view the contribution of the reduction potential of a couple to the rate of an inner-sphere reaction finds a natural explanation in the energies of the redox orbital which must be modified by ligand rearrangements in order to achieve energy matching prior to electron transfer. When viewed in this

light it would be surprising indeed if the standard free-energy change, as it reflects differences in redox orbital energies, did not contribute to inner-sphere reactivities.

4. Participation of Ligand Orbitals

In describing the course of redox reactions little has been said of the fate of the electron as it makes its way from an orbital primarily centered on one metal to a corresponding orbital on the other metal. For most reactions little may need to be said since they appear to involve "resonance" transfer, that is, the essentially instantaneous transfer between orbitals of approximately equal energy in the activated complex.

For outer-sphere reactions this corresponds to what is called "adiabatic" transfer. The electron transfer probability in the activated complex is sufficiently high, as the result of a resonance energy between reactants on the order of several hundred calories or more, to provide for a transmission coefficient of roughly unity in the Eyring theory (56). Suggestions have been made from time to time that the π systems of unsaturated ligands may provide a facile route for the electron to the surface of a complex where its transfer might be facilitated. The significance of any influence of this sort has not been experimentally established. In the transfer of a π electron between isonitrile complexes of manganese, $Mn(NCR)_6^{+/2+}$ the rate decreases by a factor of 16 on changing R from $-C_2H_5$ to $-C(CH_3)_3$ (137), but the apparent entropy barrier, wherein a transmission coefficient of less than unity would lie disguised, actually decreases.

In inner-sphere reactions resonance transfer corresponds to either "direct exchange" between metal orbitals or to "double exchange" wherein the bridging ligand simultaneously loses an electron to the oxidant and receives one from the reductant (138, 56). While most reactions between simple complexes seem to be consummated by resonance transfer, evidence does exist in some cases for a "chemical" mechanism (61, 63). In this mechanism a low-lying empty orbital on the bridging ligand receives the electron from the reductant and retains it for an appreciable time before passing it on to the oxidant. (Alternately, a filled ligand orbital of high energy could yield an electron to the oxidant and remain depleted for a time before accepting a replacement from the reductant. This converse has not been extensively studied; however, see induced transfer mechanisms below.) The chemical mechanism, involving the transitory reduction or oxidation of a ligand, usually to a radical, may be of special significance in some metalloprotein reactions if the metal centers cannot approach each other sufficiently for direct transfer and the intervening ligands do not allow sufficient "communication" for double exchange. It also may be
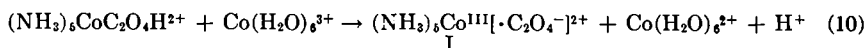
possible for insulated metal centers to allow the generation of a "protein-ligand," radical intermediate by reaction with outer-sphere reagents. The requirement, as fulfilled in the examples below, would appear to be that resonance transfer be sufficiently slow to allow the participation of suitable ligand orbitals, when available, to intervene.

Two criteria have been used to establish the credibility of this mechanism experimentally, at least for the case where the ligand is temporarily reduced. In the ligand variation approach, the rates are examined for reduction of the same metal center using bridging ligands which are as similar as possible except for the presence of a low-lying orbital in one of them. For example, the parallel reduction of $(NH_3)_5Co(O_2CCHO)^{2+}$ by $Cr(H_2O)_6^{2+}$ at a rate $(> 7 \times 10^3 M^{-1} sec^{-1})$ much faster than for reduction of $(NH_3)_5Co(O_2CCH_2OH)^{2+}$ $(3.1 M^{-1} sec^{-1})$ seems attributable to a chemical mechanism with the reducible ligand (110). In the metal center variation approach, two metal centers, with the same charge and a similar propensity to perturb the energy of the ligand orbital in question, are chosen which differ substantially in their reactivities via presumed resonance transfer mechanisms. When a certain ligand is bound to either metal center and similar rates with a particular reactant result, this is taken as evidence for the chemical mechanism. The criterion applies only in the likely case that the rate-limiting barrier is the electron transfer to the ligand orbital which is of similar energy when bound to either of the metals. However, these ordinarily dissimilar metal centers accept the electron after the rate-determining step. Thus the reduction of $(NH_3)_5CoNC_5H_4$ $CONH_2)^{3+}$ by $Cr(H_2O)_6^{2+}$ at a rate $(17.6 M^{-1} sec^{-1})$ which is only 10 times faster than the parallel reduction of $(H_2O)_5Cr(NC_5H_4CONH_2)^{3+}$ is taken as evidence for a chemical mechanism since the "normal" reactivity difference for these oxidant centers in inner-sphere reactions with $Cr(H_2O)_6^{2+}$ is on the order of 10^4 or greater (139). By way of contrast, the reduction of $(NH_3)_5Ru(NC_5H_4CONH_2)^{3+}$ by $Cr(H_2O)_6^{2+}$ occurs at a much faster rate, $k = 3.9 \times 10^5 M^{-1} sec^{-1}$, in spite of little advantage in ΔG^0. This emphasizes again the importance of the symmetry of the acceptor orbital on the metal (140). Recent reports suggest that radical intermediates can be detected under favorable circumstances (141).
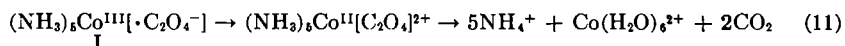
The contributions of Henry Taube to our understanding of redox processes extend to yet another arena of potential significance for metalloprotein reactions. The majority of net redox reactions in organic molecules correspond to two-equivalent processes, whereas the reactions of isolated metal centers most frequently involve changes by one equivalent. The question arises as to how facile coupling of these noncomplementary processes can be achieved. It is significant for metalloprotein reactions since they frequently are involved in the efficient coupling of a four-equivalent

oxidant, O_2, to both one-equivalent reductants (e.g., the oxidation of cytochrome c mediated by cytochrome c oxidase) and two-equivalent reductants (e.g., the oxidation of xanthine mediated by xanthine oxidase).
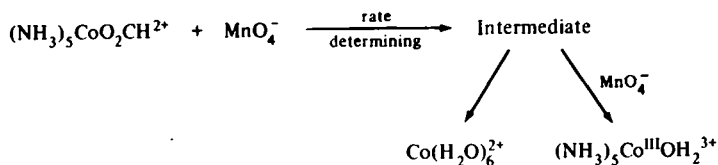
Taube first established that an external one-equivalent oxidant, for example, $Co(H_2O)_6^{3+}$ or $Ce(IV)$, could oxidize a susceptible ligand of another complex by a single equivalent

$$(NH_3)_5CoC_2O_4H^{2+} + Co(H_2O)_6^{3+} \rightarrow (NH_3)_5Co^{III}[\cdot C_2O_4^-]^{2+} + Co(H_2O)_6^{2+} + H^+ \quad (10)$$
$$\underset{I}{}$$

and thereby *induce* the otherwise much slower reduction of the internal one-equivalent oxidant (142, 143).

$$(NH_3)_5Co^{III}[\cdot C_2O_4^-] \rightarrow (NH_3)_5Co^{II}[C_2O_4]^{2+} \rightarrow 5NH_4^+ + Co(H_2O)_6^{2+} + 2CO_2 \quad (11)$$
$$\underset{I}{}$$

The first evidence (144) provided for an intermediate, I, of the type required by this mechanism is summarized by the scheme in which the ratio

$$(NH_3)_5CoO_2CH^{2+} + MnO_4^- \xrightarrow[\text{determining}]{\text{rate}} \text{Intermediate}$$

with the Intermediate branching to $Co(H_2O)_6^{2+}$ and to $(NH_3)_5Co^{III}OH_2^{3+}$ (via MnO_4^-)

of $[Co(III)]/[Co(II)]$ produced depends on $[MnO_4^-]$. Among other recent studies (146) is a report (145) on electron transfer induced during oxidation of the ligand, pyridinemethanol, which is of interest in view of the importance of nitrogen heterocycles in biological redox processes. Fortunately, the many ramifications and opportunities presented by the phenomenon of induced electron transfer have been discussed by Taube (63) and need not be duplicated here. It is sufficient to emphasize the kinetic advantages of coupling two one-equivalent reaction centers to a two-equivalent redox transformation. This should be taken to include the probability that two-equivalent ligand reduction by one-equivalent reductants will be accomplished most efficiently if they can be closely coupled in some fashion similar to that established for ligand oxidation. An objective of certain biological systems may be to effect an efficient coupling of noncomplementary reactants.

III. MECHANISTIC ASPECTS OF OXYGEN CHEMISTRY

A substantial fraction of known metalloenzymes are oxidases which catalyze reactions between a variety of substrates and molecular oxygen, O_2. We shall take this class to include members of an oxygenase subdivision which can be further subdivided depending on whether they incorporate

both oxygen atoms of O_2 in the substrate, the dioxygenases, or whether only one of the oxygen atoms is transferred to substrate, the other being reduced to H_2O. Members of the latter subdivision are interchangeably described as mixed function oxidases or monooxygenases, with this author choosing the latter description for brevity.

Two closely related enzyme classes catalyze reactions of hydrogen peroxide. Catalases effect an extremely rapid disproportionation of H_2O_2, whereas peroxidases accomplish its utilization as an oxidant. Important studies (Section VI) have identified a number of previously known and recently discovered copper and manganese proteins as being exceptionally effective catalysts for the disproportionation of superoxide ion, O_2^-. Very recently this discovery has been taken advantage of to implicate the superoxide species as arising during the course of certain metalloprotein-catalyzed oxygenations (147). (This development has not yet been used to explore the mechanisms of purely inorganic reactions where the superoxide ion might be produced as a short-lived intermediate. The capacity of a superoxide dismutase to intercept this transient species rapidly presents an opportunity to outline the course of these reactions in more detail.) Finally, the possibility appears reasonable that the manganese centers implicated in the photosynthetic oxidation of H_2O (148) may be directly involved.

In view of these facts the chemistry of oxygen deserves our attention. Any fundamental consideration of reactions involving the conversion of oxygen between two oxidation states must take account of the inherent thermodynamic and kinetic characteristics of the states involved as well as those of any intermediate oxidation levels which arise. The inorganic aspects of the area have been reviewed elsewhere (149–155) with Taube's account (149) being characteristically incisive. It suffices to summarize briefly current understanding.

Its ubiquity notwithstanding, oxygen is characterized by an unusually varied and unique chemistry. The behavior of oxygen that is germane here is dominated by four major themes. We shall consider these briefly by entertaining stoichiometric, thermodynamic, structural, and kinetic considerations interrelatedly in that order. The initial vantage point will be taken with reference to the reduction of O_2. However, a loose application of the principle of microscopic reversibility requires that similar considerations be entertained for the reciprocal oxidations of oxygen compounds to O_2 and to the interconversion between lower oxidation states.

A. Stoichiometric Considerations

Molecular oxygen can undergo reduction by as much as four electron equivalents to yield H_2O or its equivalent oxidation state, −II. Depending

on the circumstances, only a part of this ultimate stoichiometric potential need be realized in a given reaction; that is, one- and two-electron-equivalent processes to yield O_2^- and H_2O_2 have been documented. For this reason the exploration and documentation of reactants and products stand as extraordinary prerequisites to understanding any given reaction involving oxygen, be it "biological" or "inorganic." This relates directly to the question raised in the previous section regarding the coupling of noncomplementary reagents.

B. Thermodynamic Considerations

Any realistic thermodynamic evaluation of the reactions under consideration must be made with appropriate regard to (1) the energetics of reactants and products, and also (2) the energetics of any intermediate species. A summary of the ground-state energetics is provided in the following reduction potential diagram which is applicable in aqueous solutions at pH = 7 (25°C).
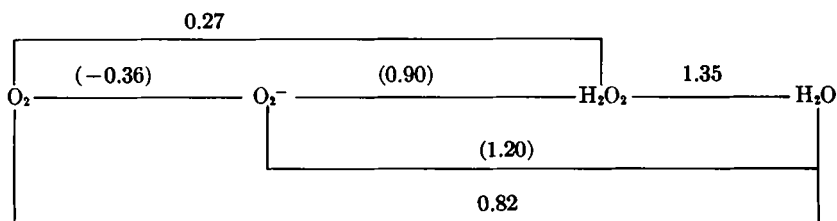
The values for the O_2/O_2^- and O_2^-/H_2O_2 couples are calculated from the value for the O_2/HO_2 couple of -0.1 V (156), using a $pK_a = 4.45 \pm 0.10$ for HO_2 (157), and should be considered subject to experimental revision. [Use of the value $E^0 = -0.32$ V for the O_2/HO_2 couple given by George (151) would revise the values in parentheses to (-0.58), (1.12), and (1.27).]

The majority of the overall oxidizing free energy available from O_2 is seen to reside in the conversion from O_2^- or H_2O_2 to H_2O. The reason lies in the extremely important fact that the one-electron reduction of O_2 is highly unfavorable. In fact O_2^- is comparable to H_2 or the ferredoxins in reducing strength. As a result, O_2 in its conversion to H_2O_2 is a surprisingly mild oxidant, being comparable to cytochrome c^{III} in this regard. In contrast, both O_2^- and H_2O_2 are much stronger oxidants than O_2.

The significance of these facts in understanding the reactions of metalloproteins with oxygen cannot be overemphasized. For example, the internal generation of the strong oxidant, O_2^-, from the milder oxidant,

O_2, may be important to the success of at least some oxygenases. The generation of O_2^- by several enzymes has been established, and will be considered later. The mechanism by which the four-equivalent oxidases (cytochrome c oxidase, laccase, ascorbic acid oxidase, and ceruloplasmin) reduce O_2 completely to water must accommodate, in some as yet unknown way, these energetic features.

In emphasizing the importance of the reduction potentials listed it is essential to note that the values apply directly only to situations where the oxygen species remain uncomplexed. Inner-sphere interactions can modify the energetics considerably and will be examined later. Also, the values are referenced to standard-state concentrations of $1M$ (except for H^+). Caution must be used in evaluating the consequences (through the Nernst equation) when concentrations differ from these values, as they will in most instances under consideration.

For example, in spite of an $E^0 = +0.1$ V for the $Ru(NH_3)_6^{3+/2+}$ couple (70), $Ru(NH_3)_6^{2+}$ could conceivably produce O_2^- from O_2 by a one-electron, outer-sphere process. The requirement for this is that O_2^- be consumed sufficiently rapidly in a subsequent reaction, say with $Ru(NH_3)_6^{2+}$, to keep its concentration below the equilibrium value. In view of the high reactivity of O_2^- this is a reasonable point to consider for a number of systems. The potential of the O_2/H_2O_2 couple ($+0.27$ V) conceivably can be utilized through single equivalent steps even with reductants weaker than O_2^-. In this way the initial one-equivalent reaction can be accomplished under certain conditions through a "borrowing" of standard free-energy from the standard potential of the second reaction.

The possibility should be explored with caution, however, since there are limits to its feasibility. The $Ru(NH_3)_6^{2+}$-O_2 reaction has now been thoroughly studied (158) with the result (over the range, $0 < pH < 6$, at 25°C)

$$-d[Ru(NH_3)_6^{2+}]/dt = (150M^{-1} \text{ sec}^{-1})[Ru(NH_3)_6^{2+}][O_2] \quad (13)$$

If the initial step were

$$Ru(NH_3)_6^{2+} + O_2 \underset{k_{-1}}{\overset{k_1 = 150}{\rightleftharpoons}} Ru(NH_3)_6^{3+} + O_2^- \quad (14)$$
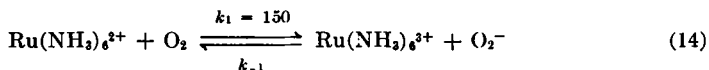
a value for $k_{-1} = 10^6 M^{-1} \text{ sec}^{-1}$ can be calculated from k_1 and $K = k_1/k_{-1} = 1.6 \times 10^{-8}$ (calculated from $\Delta E^0 = -0.46$ V using the potentials listed above).

Since there is no detectable inhibition of the rate even when $[Ru(NH_3)_6^{3+}] = 10^3[Ru(NH_3)_6^{2+}]$, the reaction of O_2^- with $Ru(NH_3)_6^{2+}$ would have to approach the diffusion-controlled limit (158). This seems