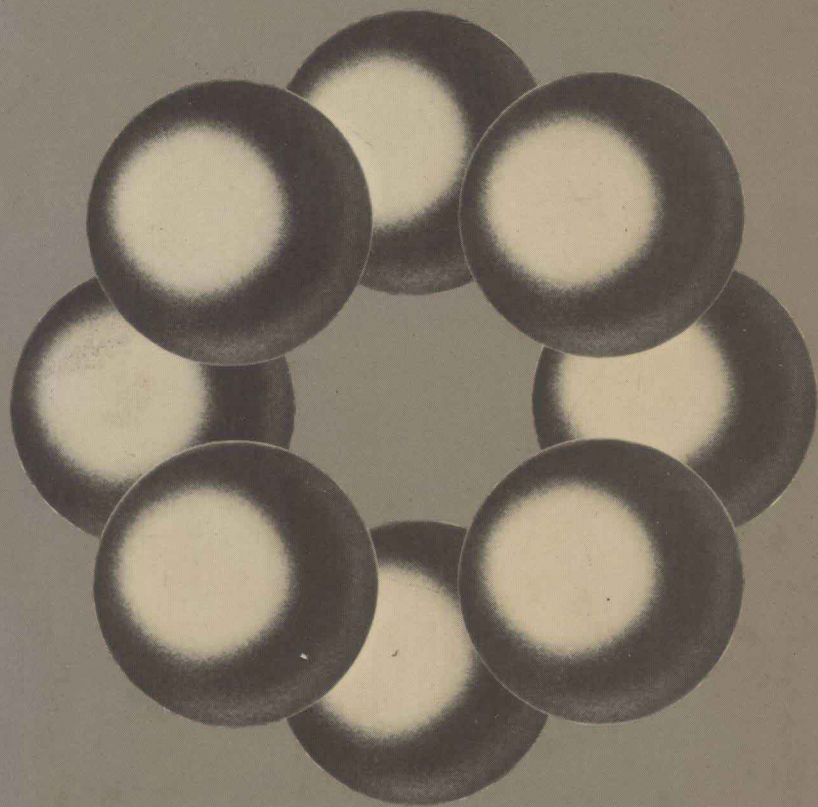


**OXFORD CHEMISTRY SERIES**

**metals  
and metabolism**

**D. A. Phipps**



D. A. PHIPPS

Department of Chemistry, Liverpool Polytechnic

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# Metals and metabolism

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## Editor's Foreword

Although the importance of metal complexes in both plants and animals has been recognized for many years, the chemistry of living systems has tended to be related to the organic rather than to the inorganic area of chemistry. The great advances in the study not only of metal complexes but more generally of metal ions in solution has altered this situation, and the importance of inorganic chemistry in relation to metabolic processes is now recognized.

This book sets out to relate, as far as is possible, the biological role of each metal to its position in the periodic table and to its appropriate 'inorganic' properties.

In some cases, this relationship is fairly well understood; in others it is, in the present state of our knowledge, decidedly tenuous. It is hoped that these contrasts will both inform and encourage the reader in an area where there is enormous scope for future development.

A. K. H.

# Preface

TO many people, the progress of science appears to be a process of fission rather than of fusion, in which the established disciplines fragment into a bewildering array of 'specialisms', arising from the limits that time imposes on each of us. Such an apparent narrowing of interest and outlook can be seen in the schisms within the broad field of biochemistry, which has recently produced yet another new area of specialization, bio-inorganic chemistry.

A close examination of this new domain, with its etymologically horrendous name, serves as a timely reminder that science may make the most successful match from the least likely partners. For many years biochemistry has been seen principally as an outgrowth of its parent, organic chemistry, and the major part of the literature has dealt with the biological implications of the properties and reactions of compounds of carbon, ranging from very small molecules of only a few atoms to the largest natural macromolecules. More recently, however, interest has been rapidly increasing in the biological roles of other elements, particularly metals; this upsurge has been preceded and aided by the rapid advances in inorganic chemistry over the last twenty years. The result is that bio-inorganic chemistry is now an established and recognized field of study. Yet the process should not be seen as a narrowing of our outlook for, far from having a 'blinkering' effect, the growth of this new area has provided both a new viewpoint on existing knowledge and the tantalizing prospect of entirely new vistas.

Unlike the older, better-established disciplines the literature of bio-inorganic chemistry is not conveniently collected in a few major journals but is scattered about and is to be found anywhere and almost everywhere: not only in the journals of agriculture and of botany and, of course, in texts on chemistry, but also in the works on dentistry, geochemistry, medicine, nutrition, physiology, and zoology. It is a salutary lesson for the newcomer to this diversity to see the difference in emphasis and approach which specialist viewpoints bring to the same problem. This is really one of the many attractions of this new subject area; it enables us to go wandering off in fields which we might once have considered unconnected with either metals or metabolism. This freedom to browse through the fruits of other peoples' efforts is not without its price, since we must first take the trouble to learn at least the basic

elements of the professional languages of the many workers from whose efforts we are to borrow so freely.

This short book represents a chemist's view of biological events, and in producing it I have had to rely heavily on the good-natured cooperation of my colleagues, who have endeavoured to correct my many misconceptions as I have trampled through fields other than my own. In order that the new reader shall not be overwhelmed I have endeavoured to explain technical terms as they have arisen in the text, and I have also suggested some other sources to which the interested reader can go for further clarification.

Inevitably in so brief a survey of such a wide-ranging subject there are many omissions which some will consider of major importance and inclusions which others will regard as trivia. More important, the choice of subject matter is largely composed of areas of the subject for which we can put forward some chemical explanation for biological actions, and the reader should be aware that, despite what we might like to think at the present, such cases are the exception rather than the rule. And it is to exceptions that our attention should in future be directed.

*Liverpool*

D.A.P.



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# 1. Introduction

## Metals, metallic elements, and metal ions

AT the present time over 100 elements have been isolated, of which about 80 are usually described as metals.† The classification as a metal is based largely on a consideration of physical properties, and implies that the element has certain characteristics such as lustre, high density, large electrical and thermal conductivity, high melting point or considerable mechanical strength. All these characteristics are the recognizable attributes of familiar metals such as iron, but as is often the case with supposedly precise scientific definitions, this division of the elements into metals and non-metals is somewhat arbitrary, since the characteristics of each group are not mutually exclusive. Some elements, which by common consent belong quite definitely to one class, may well have properties reminiscent of the other. The low melting points of the alkalis, which are otherwise typical metals, and the high electrical conductivity of carbon (as graphite), a non-metal, are obvious examples of where difficulty in classification may arise. Indeed, in several cases it has proved impossible to place an element satisfactorily in either class, and elements such as boron and silicon have to be classified separately as metalloid or metal-like.

One disadvantage of our classification scheme is that it focuses attention on physical characteristics whilst ignoring chemical properties; though with such a large number of metallic elements, each with its own rich and varied chemistry, it would obviously be difficult to arrive at a comprehensive yet useful chemical classification. Nevertheless, such perspective is needed, since in biochemical or geochemical studies it is seldom that either physical properties or even the elemental state itself are considered, because with few exceptions the metallic elements do not occur in the native state but are found in salts or complexes of the positively charged metal ion.

Perhaps, then, a limited but useful definition of a metal is that it is an element which under biologically significant conditions may react by losing one or more electrons to form a cation, this being the functionally significant species. Of course, this is not meant to imply that metals may not react in a variety of other ways which do not fit this definition, but simply that these other reactions are normally limited to distinctly abiotic conditions.

† At least 103 elements have been definitely identified, and this number are included in most modern periodic tables.

### Typical elements

FIG. 1. The periodic table of the elements.

### *Periodicity*

Happily, whilst each metallic element is chemically distinct from the others, the differences are not random, and there is in fact considerable regularity or periodicity in the variation of their properties. Many relationships (both similarities and differences) are emphasized when the elements are arranged in the form of a periodic table such as is shown in Fig. 1. Such tables, based in principle on the original suggested by Mendeleev, are of great assistance in rationalizing and clarifying the enormous amount of experimental data now available. Some very ingenious tables have been devised using properties both of the elements themselves and also of their compounds. One table, for example, was based solely on the colours of various ions, whilst another was devised by considering solubility properties. Now, of course, it is appreciated that chemical periodicity is simply a reflection of electronic configuration, and it is on the basis of their electronic structure that the chemical and biochemical properties of the metals will be discussed.

### *The formation of metal ions*

The energy change involved in the formation of a metal cation by removal of electrons from the neutral atom depends critically on the immediate environment of the atom. Taking the simplest case first – the isolated atom in the gas phase – the energy required (the ionization energy) can easily be determined experimentally. Not unexpectedly it varies in a periodic fashion.

A brief review of the ionization energies of the elements reveals that high values, implying electronic stability, are particularly associated with atoms and ions having filled sets of orbitals. This is the basis of a simple and successful valency theory, which explains most of the reactions of the s- and p-block metals solely on the basis of their propensity to form cations with a closed-shell configuration. These ions are particularly stable and generally do not undergo any further changes in electronic configuration, so that the ionic charge is largely independent of the local environment. In contrast, the d- and f-block transition metals readily form several ions, each of different electronic configuration and mostly not conforming to the simple closed-shell rule. The stability of these ions depends critically on their immediate environment, as is recognized by the more sophisticated valency theories used to discuss their behaviour. A knowledge of the factors affecting the relative stability of each oxidation state is of fundamental importance in understanding their biochemical roles.

In contrast to reactions in the gas phase – for which considerable amounts of energy, perhaps of the order of several thousand kilojoules per mole, are required – the formation of a metal ion in aqueous solution is much more economical. Even where the formation of the ion

## 4 Introduction

is relatively unfavourable, the reduction in the overall energy change is still considerable. With copper, for example, the first ionization energy is more than  $700 \text{ kJ mol}^{-1}$  which is over 20 times the energy required to form  $\text{Cu}^+$  in aqueous solution. In more favourable cases energy is actually released by the formation of the metal ion in water. A simplified explanation is provided in Fig.2. This shows that in solution the free energy of formation of the metal ion depends principally on the difference between two large factors, the ionization and the hydration energy; it is the balance between these which ultimately decides how many electrons will be lost from a particular atom. (Similar arguments may be advanced for the formation of ionic solids, in which the lattice energy is the counterpart of the hydration energy in solution.)

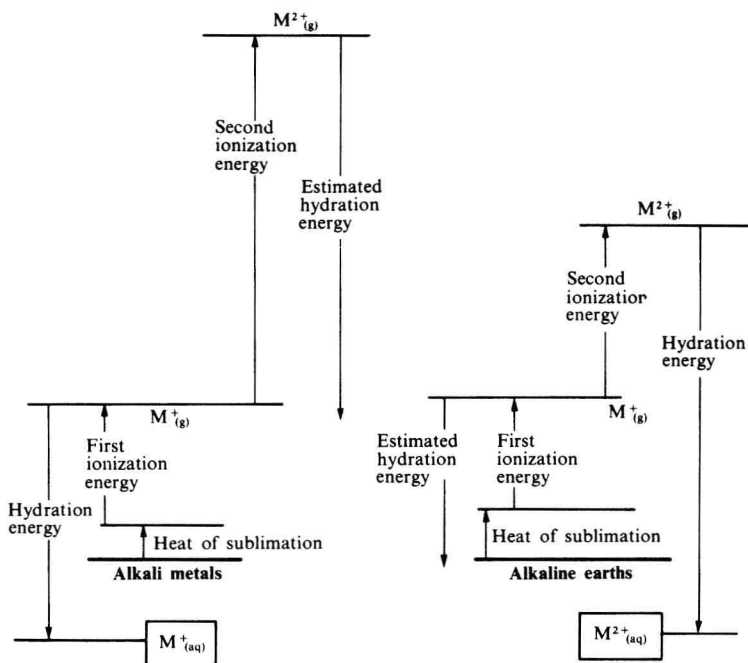


FIG. 2. The relative energy changes involved in the formation of aquated metal ions. In the case of the alkali metal the removal of more than one electron is energetically disallowed, whilst for the alkaline earth the formation of the divalent ion is the most favoured process. Similar diagrams can be drawn for other metal ions.

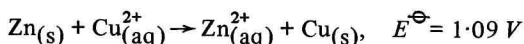
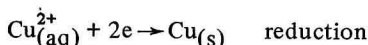
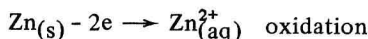
*Redox potentials*

Since the biotic milieu is predominantly aqueous (though as will be seen later the local environment of a metal ion in a living system may be effectively non-aqueous) it is pertinent to continue by examining in slightly more detail the formation and properties of the metal ion in aqueous solution. The formation is considered not because there are many significant biochemical equilibria between the metal and its ions (though a few examples are known, and are of course important in geochemical cycling) but rather because of the information such equilibria provide about the relative stability of the ions.

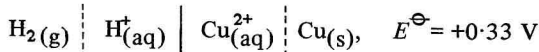
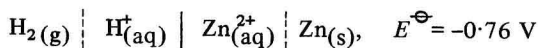
The oxidation reaction (removal of electrons) of solid metal:



is just the process which occurs at the anode of an electrochemical cell. Unfortunately, however, it is impossible to make any measurements on such a reaction in isolation, since in practice it must always be accompanied by a corresponding reduction reaction, as, for example, in the Daniell cell.



where  $E^{\ominus}$  is the e.m.f. at a defined standard state. Nevertheless it is still desirable to have some formal estimate of the contribution of each half of the reaction to the overall electromotive force of the cell. This may be done by combining each half-cell separately with a hydrogen electrode under carefully defined standard conditions and measuring the e.m.f. of each combination. The e.m.f. of the original cell may then be calculated by re-combining these two results, and since the contribution of the hydrogen cell is always removed arithmetically, it may conveniently (though arbitrarily) be set at zero.



whence  $E^{\ominus} = +0.33 \text{ V} - (-0.76 \text{ V})$ ,

$$E^{\ominus} = +1.09 \text{ V}.$$

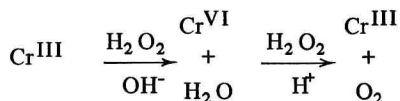
## 6 Introduction

The e.m.f.s of the two cells containing the hydrogen half-cell are then known as standard electrode potentials, or *redox* potentials.† In this fashion it is possible to set up a scale of potentials relative to the hydrogen electrode, which may subsequently be used to predict the course of reactions in solution, since the free energy change  $\Delta G^\ominus$ , is related to the cell e.m.f.  $E$ , and hence to the redox potentials themselves, by

$$\Delta G^\ominus = -nFE^\ominus$$

where  $n$  is the number of equivalents of electrons transferred during the course of the reaction and  $F$  is the Faraday.

Consequently, the information available from the redox potential may then be used to provide chemical information in a variety of situations. The redox potential for a single couple can first of all be used as guide to the relative stability of the element with respect to its cation. Thus if  $E^\ominus$  for the couple  $M_{(aq)}^{n+}/M_{(s)}$  is large and negative, as for the alkali metals, then the formation of the metal from its ion is most unfavourable, and conversely the formation of the cation is favoured. In other words, the metal is a powerful reducing agent, losing electrons easily, which is in accord with chemical experience. Clearly this argument may be reversed, and the more positive  $E^\ominus$  becomes, the more powerful an oxidizing agent is the metal ion, more readily accepting electrons to return to the elemental state. However, a cautionary note is necessary; conclusions drawn in this fashion must be treated carefully, since these reactions cannot occur in isolation, and substances which act as oxidizing agents under one set of experimental conditions may well be reducing agents under others. For example, in the reaction below, the chromium functions first as a reducing agent and then as an oxidizing agent.



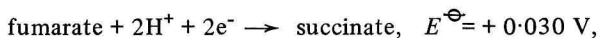
For a more detailed discussion of these reactions see p. 91.

Not surprisingly then confusion is common in the use of the terms oxidizing/reducing reagent and oxidation/reduction reaction. The reaction itself is termed oxidation or reduction *only* with respect to one of the reactants, and this should always be specified since in the course of a redox reaction the oxidizing agent is reduced whilst the reducing agent

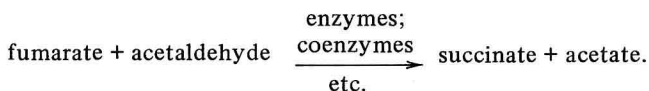
† Considerable confusion exists because of the use of two opposite (European and American) sign conventions for treating electrochemical data. In this book redox potentials will be understood to conform to IUPAC convention and are written  $M^{n+} + ne \rightarrow M$ , which are formally reduction potentials.

is itself oxidized. Thus the reaction between  $\text{Cr}^{\text{III}}$  and  $\text{H}_2\text{O}_2$  can be styled either as the oxidation of  $\text{Cr}^{\text{III}}$  or the reduction of hydrogen peroxide.

However, whichever terminology is adopted, the overall course of the reaction may readily be predicted by considering the appropriate redox potentials. Moreover, redox reactions are by no means limited to metal-ion/metal couples and may equally apply to other biologically significant redox processes, for example,



From these values it is easy to deduce that fumarate is the more powerful oxidizing agent,<sup>†</sup> and acetaldehyde the more powerful reducing agent so that the reaction becomes



Clearly, a knowledge of redox potentials enables the thermodynamic probability of any reaction to be estimated, though of course no deduction can be made about the rate of such a reaction.

A second warning must now be given. Before redox potentials can be used to predict or explain the course of a reaction it is essential to ensure that the data being employed are applicable to the reaction conditions. The standard values  $E^\ominus$  apply only when all reactants have unit activity, which is not necessarily nor even likely to be true *in vivo*.<sup>‡</sup> As a consequence the actual redox potential  $E_{\text{exp}}$  will differ from the standard value, often quite markedly. For the alkali metals and alkaline earths even quite large changes in conditions such as concentration or temperature are unlikely to affect the stability of the metal ions, and it is still possible to ignore other oxidation states of these metals. However, for the transition metals the situation is quite different and the relative stabilities of different oxidation states are markedly affected by changes in environment.

Fortunately, using the Nernst equation it is relatively easy to correct for changes in redox potential caused by changes in concentration,

<sup>†</sup> A simple rule is that the couple with the more positive potential always reacts as written, and the reaction is completed by the other couple reacting in the reverse sense to that written.

<sup>‡</sup> Activity is a mathematical device employed in thermodynamics to allow for the fact that solutes of the same absolute concentration may exhibit different *effective* concentrations.



$$E(\text{exp}) = E^{\ominus} + \frac{RT}{nF} \ln \frac{a_{\text{Ox}}}{a_{\text{red}}}.$$

If the solutions are dilute then the activities may be replaced by concentrations, so that

$$E(\text{exp}) = E^{\ominus} + \frac{0.06}{n} \lg \frac{[\text{Ox}]}{[\text{Red}]}.$$

Inspection quickly shows that a decrease in the concentration of the oxidized species makes the observed potential more negative, whilst a corresponding increase makes it more positive.

It is important to emphasize that changes in concentration are not the only factors affecting the redox potential, though they are undoubtedly important. As has been suggested previously, changes in local environment can have considerable effects, particularly amongst the transition-metal ions. A change in solvent, particularly one involving a significant alteration to the polarity of the medium, is likely to have a much greater effect than even the largest variation in concentration. Similarly there will be a considerable change in redox potential if the water molecules directly bound to the metal ion are replaced by other ligands. Indeed, this latter effect is of considerable importance in regulating the redox potential of many of the transition-metal complexes, especially those containing iron, which function widely as redox reagents for living systems.

Implicit in all the previous discussion has been the assumption that in aqueous solution the metal ion is no longer independent of its surroundings, since due regard must be paid to the coordination of water molecules, as evidenced by the hydration energy. The origin of the hydration energy has been the subject of much discussion, and it is now clear that the problem is quite complex. For the alkali metals at least, the principal contribution to the hydration energy is the electrostatic attraction between the metal ions and the dipolar water molecules. The distribution of valence electrons between the oxygen and hydrogen atoms in water is unequal, and since the oxygen atom is more electronegative (electron-attracting) it carries a partial negative charge, whilst the hydrogens have a partial positive charge. As a result the water molecule acts as a dipole and there is an electrostatic attraction between the oxygen atom and the metal ions. For more highly charged ions such as  $\text{Mg}^{2+}$  and  $\text{Al}^{3+}$ , the bonding forces between the water molecules and the cation are certainly more complex. Here the electrons on the oxygen are polarized by interaction with the metal ion to such an extent that the bonding can no longer be considered to be solely electrostatic but must be at least partially covalent, as