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Conformational change induced by metal ions through coordination*

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ABSTRACT

The structure of a metal complex may be determined by the structure of the ligand or by the electronic configuration of the metal. In the latter case, the metal can induce a conformational change in the ligand. Such a conformational change is a usual result in coordination reactions, and is particularly significant in biological macromolecules, such as nucleic acids, proteins, and enzymes. We have recently obtained evidence for a mechanism that involves a metal participating in conformational changes that occur in both enzyme and substrate simultaneously.

1. INTRODUCTION

We have recently obtained evidence in our laboratory for a mechanism to assure fidelity in RNA synthesis, i.e. to guarantee that the DNA genetic code is correctly copied in RNA. This mechanism, which will be discussed below, introduces a Mg(II) switch that mediates between two enzyme conformations as well as between two substrate conformations. This multiple relationship between metal ion and ligand

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conformation in a very complex system suggests an overview of metal ions and conformational changes in ligands coordinated to them. We are particularly concerned with these effects in biological systems.

2. COORDINATION THAT DOES NOT INVOLVE SIGNIFICANT CONFORMATIONAL CHANGE IN THE LIGAND

Conformational change in the ligand upon coordination is so much a part of the metal complexation process that lack of such change almost becomes trivial. One can consider the bonding of single atoms to metals as involving no conformational change in the ligand, although there is certainly an effect on electronic configuration, as in halogenated anions such as $[CuCl_4]^{2-}$. The bonding of simple molecules or ions such as NH_3 or NO_2^-, as in $[Cu(NO_2)_6]^{4-}$, has a relatively minor effect on the ligand conformation, though even this very simple coordination involves a 1–2° change in the O–N–O bond angle [1,2].

Perhaps the most clear-cut examples of coordination not leading to conformational change are complexes of ligand molecules that are so rigid that coordination cannot promote a conformational change except through a chemical reaction. Macrocyclic ligands often provide such rigidity, as illustrated by porphyrin complexes, such as the hemes. Here, the metal must either fit into the cavity provided by the porphyrin [3–5] or else the metal coordinates even though it is pushed outside the plane of the porphyrin [4–6].

3. COORDINATION WITH CONFORMATIONAL CHANGE

Generally, coordination to a metal does result in a conformational change in the ligand, although the attention of coordination chemists is usually focused on the structure of the complex, rather than on this conformational change. As simple a ligand as ethylenediamine suffers bending of the carbon–nitrogen bonds when bound to a metal, and the presence of additional CH_2 groups in the diamine leads to further bending. In such complexes, the electronic configuration of the metal is the dominant factor in determining the structure of the complex, and the ligand accommodates to what these electrons require.

Although highly rigid macrocyclic structures such as porphyrins do not undergo conformational change on coordination, less rigid macrocyclic structures can be subjected to profound change by metal ions. Thus, a group of biologically important molecules, the ionophores, contain electron donor groups that can be organized into macrocyclic chelators by metal ions that fit the macrocycle [7]. For example, the valinomycin molecule has the carbonyls of amide groups pointing toward a K^+ ion that fits into the center of the macrocycle. The valinomycin cage specifically fits K^+ and has difficulty accommodating the smaller Na^+, so that it is very selective for K^+. In the absence of the metal ion, the K^+-coordinating carbonyls are turned

outward, so that presumably they can trap the ions, which then force the carbonyl groups inward to form the K^+-fitting macrocycle [8].

The siderophores are a group of ligands generated by microorganisms for the chelation of iron and they too form macrocyclic cages into which the metal ions can be readily fitted [9].

The importance of metal ions in mediating the conformation of ligands is of particular significance in biomacromolecules, and we shall therefore consider that effect of metals on nucleic acids and proteins.

3.1 Metal ions and nucleic acid conformation

The chemist who is unfamiliar with the nuances of nucleic acid chemistry generally thinks of DNA as a very rigid molecule. Actually, DNA and nucleic acids generally are quite flexible, their biological activity sometimes depends on this flexibility, and conversions from one conformation to another are frequently the result of metal ion binding.

The importance of metal ions on DNA conformation was first noted through the opposite effects of various metal ions on the unwinding of the DNA double helix. Some, e.g. Mg and Ca, bind primarily to the phosphate groups on the surface, and stabilize the DNA double helix by neutralizing the repulsive negative charges on these phosphate groups. Others, e.g. Al and Cu, also bind to the bases and therefore compete with the hydrogen bonding, thus disrupting the double helical structure [10,11].

Not only can metal ion binding be disruptive to the well-known B-structure DNA double helix, but the degree of such binding can preferentially stabilize a variety of helical structures. Thus the binding of increments of metal ions to B-DNA can lead to the conversion of B- to Z-DNA, of Z- to "U"-DNA (where "U" is a double helix of unidentified conformation) and from "U"- to ψ-DNA (where ψ represents a three-dimensional stacking of DNA duplexes). The increasing increments of metal ions drive the equilibria $B \rightleftharpoons Z \rightleftharpoons$ "U" $\rightleftharpoons \psi$ to the right, presumably because the negative charges on the phosphate groups move closer together from B- to Z- to "U"- to ψ-DNA, so that higher concentrations of metal ions are required to stabilize the forms on the right than those on the left [12].

Different metal ions can have very different effects on the conformation of ribonucleic acids (RNA). For example, under otherwise similar conditions, the binding of Mg(II), Ni(II) and Cu(II) to poly-adenylic acid can lead to double helical, single helical, or random coil structures [13].

A very strongly binding metal such as Pt(II) can bind to specific positions on the nucleic acid molecule, and promote localized conformational changes at these positions [14]. Such localized changes can have profound effects on replication and transcription; the antitumor effect of the Pt(II) complex is apparently due to the inhibition of replication [15].

3.2 The effect of metal ions on the conformation of proteins and enzymes

Metal ions can bind to many functional groups in proteins, and therefore enzymes, in non-specific ways and thus influence the conformation of these macromolecules. The specific binding of metal ions to the active site of an enzyme is of greater interest, since that interaction involves a coordination, generally in a crevice of the molecule, that is designed for the participation of the metal in the function of the enzyme; such participation may be catalytic or structural in nature.

An important factor in determining whether metals influence the conformation of an enzyme is whether the structure of the metal–enzyme complex is determined by the electronic configuration of the metal ion or by the orientation of coordinating groups in a crevice of the enzyme protein. One can be misled into believing that the structure of a metalloenzyme can be inferred from the electronic properties of the metal, on the assumption that only those properties determine the structure. Frequently that is true. But it is also possible that the ligand organization within a macromolecular crevice can influence the structure of the complex; a clue to such influence may be provided by the failure of the electronic properties of the metal to predict the structure of the complex. It has been suggested that metal binding in enzymes may involve an "entatic" state, i.e. an energy level close to a transition state [16]. Whether or not such a state is present, a metal–complex structure that is not predicated on the electronic configuration of the metal could be the result simply of the dominance of structural features of the enzyme over those of the metal. We now consider an example of an enzyme in which the metal does not affect the conformation of the enzyme, and an example in which the metal exerts a striking conformational effect.

In carboxypeptidase A, the zinc in the active site is clearly involved in the catalytic action, and it seems to fit into its binding site without changing the conformation of the protein; there is no difference in the structure of the zinc enzyme and that of the apoenzyme [17]. Presumably the structure of the metal–enzyme complex is determined by the structure of the enzyme itself.

In concanavalin A, the addition of Ca(II) to the protein (following addition of Mn(II)) causes a major conformational change that involves a transition from a trans peptide bond to the rarely found cis peptide linkage [18]. In this case, the electronic configuration of the metal must have an influence on the structure of the metal–enzyme complex. Thus the active site metal may or may not bring about a conformational change in the protein.

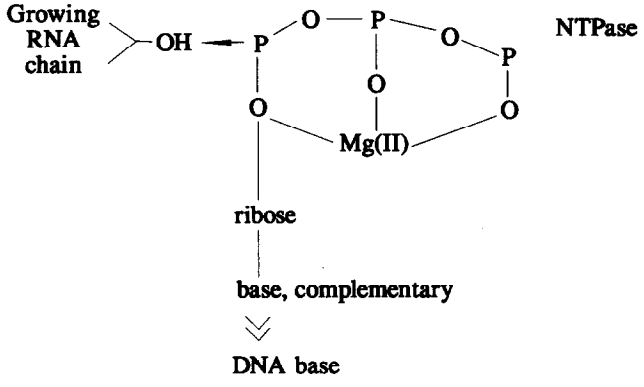
A particularly striking conformational change of very important biological significance is produced by zinc in the so-called "zinc fingers" [19]. These molecules contain finger-like groupings that are produced by the binding of zinc to cysteine and histidine ligands. The fingers fit into the grooves in the DNA double helix. The zinc itself does not bind the DNA; its purpose is to produce the fingers. The important structural feature responsible for the biological activity of the zinc fingers is induced by the presence of the metal ions.

3.3 Multiple conformational effects of metal, enzyme and substrate

We noted in the Introduction that we have recently obtained evidence for a mechanism of fidelity in RNA synthesis that involves the RNA polymerase enzyme, and also a Mg(II) that binds the enzyme to the substrate [20].

This enzyme brings together the DNA template containing the genetic code, the incoming substrate NTP (nucleoside triphosphate) that should contain the complementary base to the DNA base to be copied, and the growing RNA chain with a terminal OH group, to which the α-P of the triphosphate group of the NTP must form a bond in order for RNA elongation to occur.

(a)



(b)

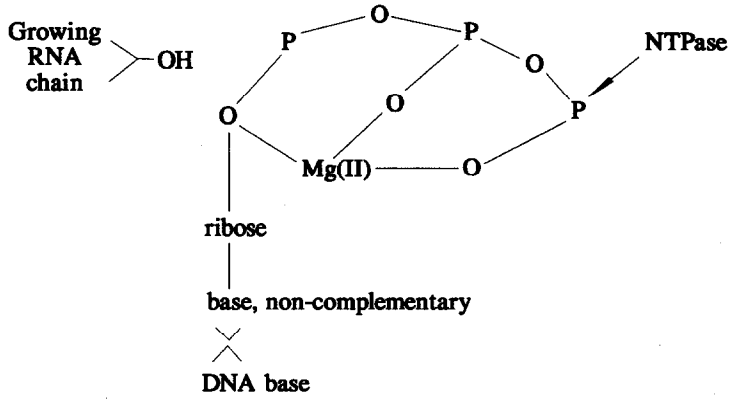


Fig. 1. Scheme for proposed mechanism of fidelity in RNA synthesis, showing a Mg(II) switch between conformers of RNA polymerase enzyme and substrate (see text).

In our mechanism, the enzyme recognizes whether or not the incoming NTP contains the right (complementary to DNA base), or the wrong (non-complementary) base. If it is right (Fig. 1(a)), then the enzyme assumes a conformation that causes the α-P to come close to the terminal OH of the growing RNA chain, thus enabling bond formation. If it is wrong (Fig. 1(b)), the enzyme assumes a different conformation that moves the α-P away from the terminal OH, thus preventing bond formation. The focal point of the conformational change is the Mg(II) bound to triphosphate and the enzyme, and the Mg moves the triphosphate back and forth, toward or away from the terminal OH, depending on whether the NTP base is complementary or non-complementary to the DNA base.

In this mechanism, the movement of magnesium triphosphate away from the terminal OH also moves it toward an NTPase enzyme that destroys the NTP. Moreover, this movement brings about a conformational change in the NTP. (Evidence for this mechanism comes from a difference (for right and wrong bases) in the distance of the Mg(II) from a Zn(II) near the terminal OH site, constancy of Mg–P distances but not Mg–ribose and Mg–base distances, and preferential attack of the NTPase on *non*-complementary bases. Not all aspects of this mechanism have been confirmed.)

The conformational change in the enzyme differs from those discussed previously in this review in that it may not be induced by the metal; but the movement of the metal caused by the enzyme conformational change induces a conformational change in the NTP substrate. Thus the metal ion is involved in multiple conformational changes in both enzyme and substrate simultaneously.

4. TRIBUTE TO PROFESSOR JOHN C. BAILAR, JR.

I know of no University Professor who has touched the lives of his students more intimately than Dr. John C. Bailar, Jr. It was always clear that, with his deep dedication to science and his particular interest in the furtherance of coordination chemistry and inorganic chemistry in general, and his many major contributions to these topics, he always emphasized the importance of the scientist. The welfare of his students was paramount. I personally owe him a deep debt of gratitude for the many ways in which he was concerned with my welfare as his graduate student and thereafter throughout my life. Through his example he taught me not only the science, but also how to deal with scientists in a mutually beneficial manner. I owe him so much, and I know that so many of his students and associates share these sentiments with me.

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