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Theoretical Study on The Effect of Metal Ions on The Structural Properties of Base

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Abstract: Metal ions play an important role in living organisms, for example Mg^{2+} is a cofactor for many biological enzymes (including DNA and RNA synthesis), Ca^{2+} is an important component of bone composition, and metal ions such as Fe, Co, Zn, Ni and Cu also play an important role in the normal functioning of living organisms. One of the main targets of metal ions in living organisms is deoxyribonucleic acid (DNA), which is an important carrier of information stored and transmitted by organisms. The direct interaction between DNA base pairs and metal ions have a significant impact on the structure and function of DNA base pairs, which is demonstrated as following: the binding of metals to bases usually breaks the hydrogen bonds of the base pairs. The N7 atom of a purine residue or the N3 atom of a pyrimidine residue, as well as the outer ring O atom and the phosphate oxygen atom, are the preferred sites for metal binding. The binding of metals to DNA and RNA also indirectly affects the conformation of the sugar ring. REDOX active metal ions have the ability to bind to DNA and can mediate oxidative DNA damage by reacting with endogenous oxidants. According to studies of antioxidants in the field of metal-mediated oxidative DNA damage, metal ion coordination also plays a key role in the mechanism of some antioxidants. Also, metal-DNA interactions are the basis for many anti-cancer drugs, anti-viral drugs and anti-bacterial agents. Metal-mediated oxidative DNA damage is associated with a variety of diseases and conditions, and understanding the binding interactions and subsequent reactivity can facilitate the management or prevention of oxidative damage. It can be seen that the study of the effect of metal ions on the structural properties of DNA bases has far-reaching implications, providing a theoretical basis for the development of novel anticancer drugs, DNA-based metal nanodevice technologies and the fabrication of spectroscopic and reactive probes.

Keywords: Metal ions, DNA, Metal ion-DNA interactions, Density general function theory, Oxidative DNA damage.

1. Introduction

1.1. deoxyribonucleoside monophosphate(DNA)

Nucleotides are polydentate ligands, which as the basic unit of nucleic acids have a variety of potential binding sites, including nitrogen atoms on purine bases, hydroxyl atoms on ribose, and negatively charged oxygen atoms on phosphate groups. Biological macromolecules composed of multiple nucleotides are called nucleic acids, and such biological macromolecular compounds often combine with proteins to form nuclear proteins. At the same time, nucleic acids are present in all kinds of organisms, including the cells of plants and animals, as well as the cells of microorganisms. Based on their chemical composition, nucleotide order, etc., nucleic acids can be divided into two types: ribonucleic acid (RNA) and deoxyribonucleic acid (DNA).

Deoxyribonucleic acid (DNA), as the most important macromolecule in living organisms, is the main component of chromosomes and is mainly responsible for the storage and transmission of biological information. It also plays a very important role in biocatalizations. In short, the maintenance of the structure and function of organisms cannot be separated from the participation of DNA [1]. DNA is a superhelical negatively charged polymer of nucleotide units that generally has a right-handed double helix (B-DNA) structure in cells. The nucleic acid base sequences of the two chains are complementary, with the phosphate group on the outside and the base pair on the inside connected by hydrogen bonds. These four nucleotides consist of adenine (A), guanine (G), thymine (T), cytidine (C), and a sugar-phosphate group [2].

1.2. The role of metal ions in living organisms

The life activities of organisms are promoted by a series of interwoven biological reactions, and organic life depends on inorganic elements to complete many important processes. Metal ions, for example, play a vital role in the human body, where they are necessary for several cellular reactions and various metabolic and physiological functions. Studies have found that trace metal elements account for about 50% to 70% of the components of human enzymes, which can maintain the molecular structure of some proteins and nucleic acids, participate in the synthesis of hormones and vitamins, etc., and the carrier and electron transport system in the human body is composed of some metal proteins [3]. According to statistics, more than half of the proteins in the human body contain metal ions. For example, metal proteins containing Fe ions and Cu ions can act as reversible oxygen carriers during respiration [4]. Ultrattrace metal ions control the basic biological processes of living cells, and many biological reactions will not occur without the catalysis of such metal ions, and many diseases are also caused by the lack of metal ions. For example, deficiency of iron, magnesium or calcium can lead to diseases such as anemia, cardiovascular disease and osteoporosis [5]. However, once its content in the cell exceeds the optimal (natural) concentration, it will also cause some toxicity to the cell. For example, Wilson's disease and thalaseemia have corresponding excessive Cu(II), Fe(II) and other metal elements [6].

1.3. Interaction of metal ions with DNA

In addition to the concentration of metal ions, the interaction sites between metal ions and biomolecules and the

related kinetic processes also play a crucial role in life activities [6]. Metal ion complexes are essential in various biological systems, and play an important role in the biosynthesis, conformation maintenance, function play and regulation of nucleic acids. The structure and function of DNA are closely related to metal ions, which can be combined with DNA phosphate groups, sugars or base pairs [4], thus affecting base pairing and DNA double-stranded structure. Metal ions bind to DNA at multiple sites (phosphate backbone, deoxyribose and single base), and the metal ions bound at different sites can significantly affect the properties and stability of the secondary and tertiary structures of DNA.

A great deal of research has been done on the interaction of metals and complexes with DNA: In terms of experiments, there are currently literatures that use magnetic tweezers to manipulate a single DNA molecule at room temperature and analyze the DNA extendation-time curve to obtain the dynamic characteristics of the interaction between divalent metal ions and DNA, and verify that the binding law of alkali metals is consistent with Manning's theory [7]. It has also been suggested that metal cations are closely associated with several enzymatic reactions, and that DNA polymerizers incorrectly copy the template when Mg^{2+} is replaced by Mn^{2+}. Common experimental methods used to determine the bonding position of metals in nucleic acids are: conductimetry, UV-Vis spectroscopy, X-ray crystallography, nuclear magnetic resonance (NMR), and electron paramagnetic resonance spectroscopy (EPR spectroscopy).

In theory, with the continuous improvement of computational level, density functional and other methods have achieved remarkable results in describing the related properties and dynamics of biomolecules. For example, results based on magnetic tweezers and AFM scanning methods combined with ion association theory analysis found that the conformational characteristics of DNA complexes are affected by the ionic strength of metal ions, DNA strand length and DNA concentration. At lower concentration of metal ions, DNA is in random linear conformation. With the increase of ionic strength, DNA presents a network coacervation structure, and the network coacervation structure continues to strengthen, which indicates that bivalent metal ions can induce mutual attraction between DNA molecules [7]. In addition, density functional method was used in other literature to analyze the binding energy of double-stranded structure between DNA base pairs under the influence of metal ions, and it was found that for purine nucleotide complexes and pyrimidine nucleotide complexes, Mg^{2+} and Mn^{2+} have stronger bonding ability than other ions [3].

1.4. The main research significance and main content of this paper

DNA-metal ion interaction covers a large number of studies from the most basic ways and characteristics of DNA-metal ion binding to the role of DNA-metal ions in medical treatment and life health. In recent years, alternative DNA base pairing mediated by metal binding is also being studied and applied in logic gates, molecular machines and nanotechnology.

This paper summarizes the effects of metal ion binding on DNA structure and the changes in binding behavior of different metal ions, with the aim of understanding the interaction of REDOX active metal ions with DNA, so as to better understand the mechanisms by which various types of oxidative DNA damage (chain breaks and base modifications) occur. In addition, based on the interaction between DNA and metal ions, the efficacy and mechanism of quinolones were discussed. Finally, recent advances in metal-mediated base pairing, which can trigger conformational changes in DNA structure, are summarized and applied to selective metal ion sensors and novel nanotechnology.

2. Theoretical Basis and Calculation Method

2.1. Hartree-Fock equation

The Hartree-Fock equation can be viewed as an ordinary Schrödinger equation for the motion of electrons. Each electron moves in a different potential field, which is obtained by electrostatic calculation of all the positive and negative charges in the system, corrected by removing an exchange charge that is equal in magnitude to the electron surrounding the electron under study. By forming a weighted average of the exchange charges and weighting and averaging the various electron wave functions at a given point in space, an average potential field can be established and all electrons are considered to be moving in it, thus greatly simplifying the Hartree-Fock method. In addition, the mean exchange charge can be further replaced by the corresponding value for the free electron gas, whose local density is equal to the actual charge density at the location in question, giving a very simple expression of the mean potential field, which still behaves qualitatively like the Hartree-Fock method. This simplified potential field has been applied to the problem of atomic structure with satisfactory results, and is also applicable to the problem of molecules and solids.

2.2. Density functional theory

Density functional theory was proposed by Hohenberg and Kohn in 1964. Electron density is regarded as a fundamental quantity in density functional theory, and the energy of the system is a functional of the electron density, while the electron density can completely determine the ground state of the system. The computational magnitude of density functional theory is usually in the range n^2-n^3 [8]. Due to the relatively small amount of computation, density functional theory calculations have great potential in solving macromolecular systems, and even living macromolecules.

According to the Kohenberg-Kohn theorem, which is the basis of density generalization theory, for a molecular system considering electron motion, the electron density $\rho(\dot{r})$ of the system determines the external potential field (i.e., the potential field generated by the nucleus) and the total number of electrons N accepted by the system, and the energy of the system is a functional $E[\rho(\dot{r})]$ of the electron density, so the density of the system determines all properties of the system. In other words, in density functional theory, the three-dimensional electron wave function $\Psi(\dot{r}_1, \dot{r}_2, \cdots \dot{r}_N)$ is replaced by the three-dimensional electron density $\rho(\dot{r})$. In some calculations, the electron density still needs to be obtained using the one-electron wave function [8]. Although density generalization theory has emphasized the importance of electron density, it is actually inseparable from the wave function. Therefore, electron density and wave function are closely related.

2.3. Comparison between Hartree-Fock method and density functional method

The comparison between Hartree-Fock method and density functional method here compares the similarities and differences between Hartree-Fock equation and Kohn-Sham equation (Table 1) [8].

Table 1. Comparison of Hartree-Fock Equation and Kohn-Sham equation [8]

HF		DFT	
$\mathbf{E = E[\psi, \overrightarrow{Rs}]}$	**(1)**	$E = E[\rho, \overrightarrow{Rs}]$	(1')
$\mathbf{\Psi = \lvert\psi_1(1), \psi_2(2), \cdots \psi_n(n)\rvert}$	**(2)**	$\rho(\dot{r}) = \sum\lvert\psi_i(\dot{r})\rvert^2$	(2')
$\mathbf{E = \int \Psi^*[\sum h_i + \sum_{i>1} \frac{1}{r_{ij}}]\Psi d\tau}$	**(3)**	$E = T[\rho] + U[\rho] + E_{xc}[\rho]$	(3')
$\mathbf{[-\frac{1}{2}\nabla^2 + Vc(\dot{r}) + \mu'_k(\dot{r})]\psi_i = \varepsilon_i\psi_i}$	**(4)**	$[-\frac{1}{2}\nabla^2 + Vc(\dot{r}) + \mu_{cc}(\dot{r})]\psi_i = \varepsilon_i\psi_i$	(4')

Unlike the Hartree-Fock method, which starts with an energy expression of the wave function of the system for a given nuclear configuration (1), DFT starts with an energy functional (1') of the electron density function. The main variable of the DFT is a physically observable measure of electron density. In the HF method, the wave function of the system is approximated as a single Slater determinant (2), the total energy is the non-relativistic Hamiltonian expected value (3), and the total energy in the DFT is exactly divided into three parts (3') : the kinetic energy term T[ρ], the Coulomb energy term U[ρ] (electrostatic energy), and the many-body interaction energy term $E_{xc}[\rho]$ (exchange-correlation energy). Where the kinetic energy term T[ρ] corresponds to the kinetic energy of the non-interacting particle system (the equilibrium system). The total electron density ρ is the superposition of the unit electron density obtained from the unit electron wave function (2') [8].

Both methods require a minimum value for the value of total energy. HF method transforms the variation of the determinant wave function of a single Slater into the Hartree-Fock equation (4), which is a single particle eigenvalue equation [8]. The DFT method converts the electron density variation to the Kohn-Sham equation (4'), which is a single-particle effective Schrodinger equation for the electron wave function. The difference between the two equations (4) and (4') lies in the term μ(ṙ) : the term μ(ṙ) of the HF equation considers only the exchange interaction and is determined by the effective orbital function $\psi_i(\psi_i$ is the eigenstate of the Fokker operator), while the term μ(ṙ) of the Kohn-Sham equation takes into account all many-body effects and is independent of the orbital parameter i [9].

3. Interaction of Metal Ions and DNA

3.1. Mechanism of interaction between metal ions and DNA

The binding of metal ions to nucleic acids has been the subject of research for many years, but its mechanism of action is not fully understood. DNA is a superhelical negatively charged polymer of nucleotide units, usually found in cells in the form of right-handed double helices (BDNA). The two chains have complementary nucleic acid base sequences, with the phosphate group on the outside and the base pairs connected on the inside by hydrogen bonds. These four nucleotides are composed of adenine (A), guanine (G), thymine (T) and cytidine (C) and sugar-phosphate groups (Figure 1).

Positively charged metal ions interact directly or indirectly with sites characterized by high electron density or negatively charged DNA residues. These sites on DNA may be the backbone of two strands of negatively charged phosphates and electron donor atoms of bases, such as N and O. The main patterns of metal binding occur at N7 and O6 of guanine bases, N7 and N1 of adenine bases, and N3 of pyrimidine. Possible ways of metal bonding are shown in Figure 1 [6].

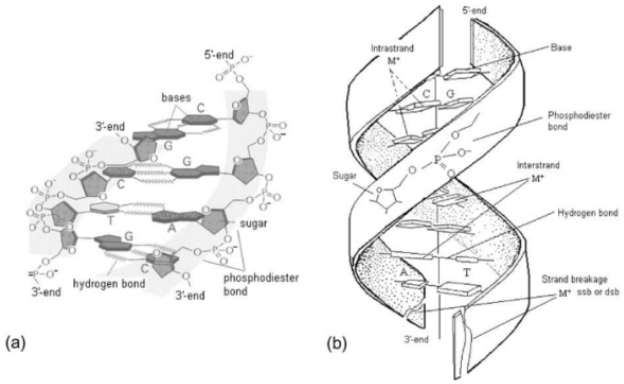

Figure 1. DNA double helix structure. (a) The complementary A-T and G-C bases are linked by hydrogen bonds, with two AT pairs and three GC pairs. (b) Metal ions may bind to one or two sites of the same chain (intra-chain) or opposite chain (interchain), or be embedded in complex forms between bases. The binding of metal ions can result in a single strand break (ssb) or a double strand break (dsb). [6]

Metal ions can bind to DNA either partially or fully hydrated, and this binding to DNA can be direct or indirect. Studies have shown that metal ions also interact between these two extremes [6]. Metal ions can exist in the body in both "free" and "bound" forms. As they move through body fluids, they are hexahydric molecules and are "free"; When they form a complex with covalent bonds, they are "bound" [2]. The following section summarizes the different metals in the periodic table and how they interact with DNA.

3.1.1. Alkali metal

Monovalent alkali metals are highly reactive and occur in nature only as cations. Alkali metals can form electrostatic or ionic bonds to DNA [2]. In general, both metal ions and nucleic acids are specifically hydrated, their hydration domains overlap, and the release of water molecules is related to the interaction between their ground states.

Spectroscopic and crystallographic data indicate that the alkali metals are concentrated on some repetitive DNA sequences. Univalent metal ions are more likely to interact with the AT-rich region of the small tank. In order to enter the trench as shown in Figure 2, they should release their coordinated water and interact directly with the base [6].

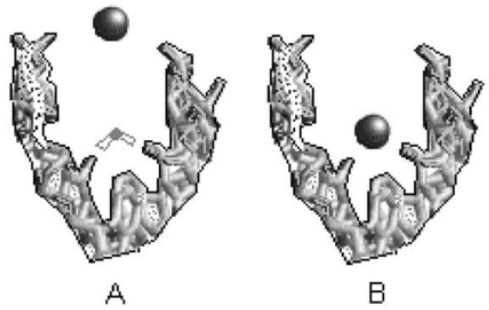

Figure 2. Monovalent cations in DNA cells [6]

Molecular dynamics (MD) simulation results are consistent with solution NMR and crystallography results, that is, it is believed that univalent cations Na^+, K^+, Rb^+, Cs^+ and NH^{4+} preferentially bind directly to the APT position (inner sphere) of the A orbital in the DNA small slot [6]. Experimental results show that when metal ions enter the small groove, the small groove will narrow, and MD simulation also shows that the coordination geometry of Na^+ in the small groove is determined by the exact location of the cation [10].

3.1.2. Alkaline earth metal

Divalent alkaline earth metals are much more reactive than alkali metals. They are more active than alkali metals, which can bind to monodentate and bidentate ligands. Among alkaline earth metals, magnesium is the most important intracellular divalent ion involved in the activation of all DNA and RNA [2]. Mg^{2+} cations not only act as specific enzymes, but also serve as a bond between nucleotides, nucleosides and their derivatives [11]. Fourier transform infrared spectroscopy, Raman spectroscopy and nuclear magnetic resonance spectroscopy show that the two positive charges of magnesium ions can attract negatively charged phosphate groups and interact with six-coordination water molecules to form hydrogen bonds. The N7 site on the nucleotide can replace one of the bound water molecules. Another can form hydrogen bonds with O6, and still others can form further hydrogen bonds (Figure 3) [6].

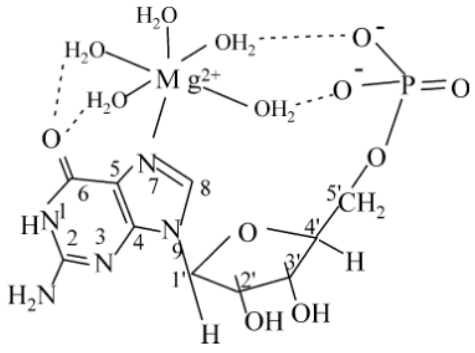

Figure 3. Proposed Structure Mg^{2+} for Mg $(H_2O)_5$-GMP Binding [6]

Cationic binding between N7 and phosphate-oxygen is accompanied by a change in DNA conformation. Studies have shown that increasing the concentration of Mg^{2+} cations transforms the B-DNA morphology into Z-DNA. B-DNA sequences are also influenced by other bivalent cations, such as Ca^{2+}, Zn^{2+}, Co^{2+}, Ba^{2+}, Mn^{2+}, and Cd^{2+} [6]. Combining X-ray and NMR data from FT-IR spectroscopy shows that when Mg^{2+} interacts with oligonucleotide GAAGCTTC, it must bind GpA and GpC at the end. Binding sites are electronegative PO_2^- groups, C=O, NH^2, N1, N3 and N7 of base residues [12].

Alkaline earth metals Ca^{2+}, Sr^{2+} and Ba^{2+} bind to DNA mainly in the form of inner sphere, while Mg^{2+} can interact with DNA to produce more outer sphere complexes due to its stable structure and high Gibbs free energy of hydration [2].

3.1.3. Transition metal

The transition metals or D-zone metals are partially filled with d orbitals, so they can be called free radicals. Transition metals interact with DNA in a more complex way, and they react with multiple different sites. Transition metals are easily separated from water molecules in the reaction to form inner complexes [2]. The binding of transition metals to bases is generally more direct, while the binding to phosphate groups is indirect. Figure 4 shows the crystal structure of the $[Co(H_2O)_6(1\text{-Mecyt})_6]^{++}$ complex. In the case of magnesium ions, 1-Mecyt interacts with cobalt ions in an exospheric manner. The same structure was also observed for Mn^{2+} ions. The results of infrared spectrum analysis show that Na^+ cations of phosphate groups are replaced by Mn^{2+} cations, and Mn^{2+} cations combine with 5'-guanosine monophosphate to form zwitterionic complexes [6].

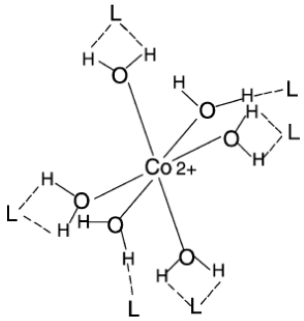

Figure 4. Structure of the $[Co(H_2O)_6(1\text{-Mecyt})_6]^{2+}$ ion. Cobalt binds to the O2 and N3 sites of 1-Mecyt by hydrogen bonding. [6]

Most transition metals react with the N7 atom of purine or the N3 atom of pyrimidine, destroying their double helix structure. Studies have shown that transition metal ions will interact with the G-C site of DNA, resulting in the oxidation of H_2O_2, thus generating free radicals to damage it [6]. Further investigation showed that the anion of the Zn^{2+} salt can determine the formation of the complex and its hydration. Therefore, the complex produced by $Zn(NO_3)_2$-$6H_2O$ combines with two water molecules to obtain a sugar conformation of C3'-endo, which is conducive to the binding of zinc and the base N7 site [6]. In addition, the complex produced by $ZnSO_4$ salt is combined with four water molecules to give a C2'-endo conformation [13]. In general, the type of anion of metal salts plays an extremely important role in the formation of complexes [6].

3.2. Metal-mediated oxidative damage to DNA

Metal ions (such as K^+, Na^+, and Mg^{2+}) are critical to the stability of DNA because they neutralize the net negative charge produced by the phosphate backbone. Many DNA interactions with metal ions are sequence specific and play a crucial role in the proper function of DNA-associated enzymes (e.g., the frequent role of Mg^{2+} as an enzyme cofactor). However, under certain conditions, these interactions can have adverse effects. Many of the cytotoxic

effects of metals result from the binding of metal ions to DNA bases. A typical example is Hg(II) ions and Hg(II) compounds, which break the hydrogen bonds between naturally occurring A-T base pairs to form T-Hg^{2+}-T pairs [14]. REDOX active metal ions have received much attention because they are ubiquitous in biological systems and can react with H_2O_2 and other endogenous oxidants to produce destructive reactive oxygen species (ROS), and an important topic in metal toxicity and carcinogenesis is metal-mediated oxidative damage to DNA. One of the most common examples is Fe(II). In the presence of aerobic metabolite H_2O_2, Fe(II) can generate hydroxyl radical ($^{\cdot}OH$) through Fenton reaction:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + {}^{\cdot}OH \quad (1)$$

Different metal ions can cause different types and degrees of DNA oxidative damage. The metal ions that produce ROS during Fenton-like reaction with H_2O_2 include Fe(II), Cu(II), Cr(III), Cr(VI), V(III), Co(II), Ni(II), Cd(II) and Zn. In the presence of reducing agents (such as ascorbic acid), Cu(II) is reduced to Cu(I), and Cu(I) can undergo Fenton-like reaction with H_2O_2 to produce Cu(II), OH^- and $^{\cdot}OH$:

$$Cu^{+} + H_2O_2 \rightarrow Cu^{2+} + OH^- + {}^{\cdot}OH \quad (2)$$

However, even without the addition of reducing agents, Cu(II) still reacts with H_2O_2 to produce ROS that behave very similar to $^{\cdot}OH$. The mechanism of oxidative damage to DNA caused by Cu(II) involves the process by which Cu(II) binds to the part of DNA containing G and is reduced to Cu(I). The ROS produced by this mechanism are thought to be Cu(I)-peroxide complexes with reactivity similar to ·OH or singlet oxygen ($^1O_2$) rather than hydroxyl radicals ($^{\cdot}OH$)[15].

The ability of DNA binding to produce ROS metal ions makes DNA-bound metal ions an important aspect of understanding ROS production mechanisms and site-specific DNA oxidative damage associated with disease and disorders. Oxidative damage to DNA by ROS ranges from single and double strand breaks to modified DNA bases. Among them, base modifications can cause DNA strand breaks, and these different forms of DNA damage have been linked to many diseases and conditions, including kidney disease and diabetes, certain types of cancer, high blood pressure, and aging. However, in some cases, this damage is desirable, especially in chemoprevention and chemotherapy applications, if it can be targeted and controlled to prevent DNA replication in tumors [16]. G is the most easily oxidized DNA base, which exhibits the greatest degree of damage, resulting in a variety of G-based derivatives, including the recognized oxidative DNA damage marker 8-hydroxy-2'-deoxyguanosine (8-OH-dG)[17]. Transition metal ions Fe(II), Cu(II), Cr(III) and V(III) produce significant levels of 8-OH-dG in the presence of H_2O_2, and Cu(I) or H_2O_2 systems also produce significant levels of 8-OH-dG[17]. The reactive properties of free radicals suggest that they are produced near the place where they react. In general, single-strand breaks are a generalized form of damage associated with freely generated ROS in solution, and double-strand breaks are strongly correlated with 8-OH-dG levels, suggesting that they are caused by ROS generated near the G base. Figure 5 illustrates the ROS produced by free metal ions in solution and metal ions bound to the phosphate skeleton "and" or "or" single bases of DNA and the types of damage.

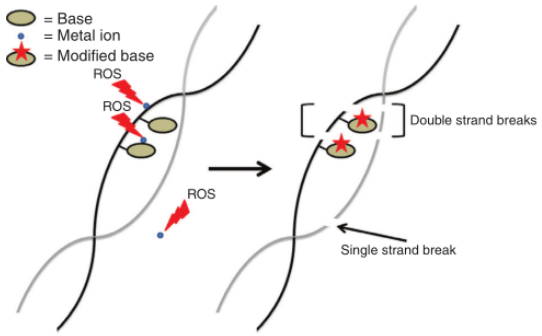

Figure 5. Description of ROS formation and oxidative DNA damage of metal ions free from solution and bound to phosphate mainchains and individual bases. The strong correlation between site-specific modifications of bases, such as 8-OH-dG, and double-strand breaks suggests that both types of damage are caused by ROS produced by DNA-bound metal ions. Single strand breaks indicate less site-specific ROS production (for example, from stray metal ions in solution). [18]

Metal-mediated DNA oxidation, especially G-base oxidation, is complex. Fleming et al. recently investigated the production of ROS from mononucleoside dG and single-stranded oligodeoxynucleotides and double-stranded oligodeoxynucleotides in Cu(II) or H_2O_2 systems where the reducing agents ascorbate and N-acetylcysteine are present. They observed a total of 10 different oxidation products of dG, including the G base itself. They propose a mechanism to explain that the main oxidation product they observed is 5-carboxamido-5-formamido-2-iminohydantoin(d2lh), which is caused by the overall two-electron oxidation of dG at the C5 position. Oxidation at the C8 site leads to the recognized marker of oxidative damage 8-oxo-dG (the oxidized form of 8-OH-dG). The coordination of Cu at the N7 position of dG appears to play an important role in the oxidation of both C5 and C8. The Cu(III)-OH at the N7 position produces the 5-OH-dG intermediate during the oxidation of C5 (resulting in the main product d2lh), and the 8-OH-dG tautomer during the oxidation of C8.

3.3. Antioxidant of coordinated metal ions

Many antioxidants function as ROS scavengers, reacting sacrificingly with ROS before the surrounding structure is damaged. However, research on antioxidants in the field of metal-mediated oxidative damage to DNA has shown that metal ion coordination plays a key role in the mechanism of some antioxidants.

3.3.1. Selenium compound

The organic selenium compounds selenocysteine and selenomethionine act as antioxidants in reactions involving Cu(I) through the coordination of Cu ions [19]. Methylselenocysteine has shown the ability to minimize oxidative damage to DNA by coordinating Cu(I) and Fe(II), while selenocysteine has shown antioxidant activity in reactions involving Cu(I) and Fe(II), and there is evidence that it forms a coordination complex only with Fe(II) [19]. The inorganic selenium compounds selenium dioxide (SeO_2) and sodium selenite [Na_2SeO_3, which dissociates in aqueous solution to form selenite ions (SeO_3^{2-})] also act as antioxidants in reactions involving Fe(II), Cu(II), and Cr(III) by coordinating these metal ions. All of these compounds exhibit varying degrees of protection, and the degree of antioxidant

behavior also depends on the identity of the metal ion. Hart et al investigated the ability of SeO_2 and SeO_3^{2-} to coordinate these metal ions before and after they have had a chance to bind to DNA by monitoring levels of site-specific oxidative DNA damage markers 8-OH-dG. In Fe(II) and Cu(II) reactions, SeO_2 and SeO_3^{2-} can reduce 8-OH-dG levels even if metal ions are first bound to DNA; These metal ions were pre-cultured with Se compounds prior to the addition of DNA, and their effectiveness as antioxidants was significantly improved. These results suggest that SeO_2 and SeO_3^{2-} are able to coordinate the binding of DNA to Fe(II) and Cu(II) and reduce oxidative damage to a certain extent.

3.3.2. Sulfur compound

In studies of metal-mediated oxidative damage to DNA, the antioxidant activity of sulfur-containing compounds is also related to their ability to bind metal ions. It has been reported that cystine, cysteine, methylcysteine and methionine can form coordination complexes with Cu(I) and reduce oxidative damage of DNA. Reducing and oxidized forms of glutathione also reduce Cu(I)-induced oxidative DNA damage through a mechanism that appears to be involved in Cu(I) binding. The sulfur compound 3-carboxypropyl disulfide has no antioxidant activity against Cu(I) or H_2O_2 oxidative damage. However, it reduces Fe(II) -mediated damage through a mechanism involving metal coordination [20]. Thiocompounds methionine sulfoxide and methylcysteine sulfoxide also exhibit antioxidant activity against Cu(I) or H_2O_2 systems, and are consistent with Cu coordination.

3.4. DNA-metal complex interactions and drug interactions

Metal-dna interactions are the basis of many anti-cancer drugs, antiviral drugs and antimicrobials. Most of these species function by inserting DNA structures, a behavior that can be controlled by forming metal complexes with drugs. Common metal centers for these drugs include Ru, Os, Co, Ni, Cu, and Zn. The discovery of the chemotherapeutic metal-based drug cisplatin is one of the prime examples of manipulating metal-DNA interactions to fight disease. Cisplatin (cis-$[PtCl_2(NH_3)_2]$) is a metal complex whose effectiveness is based on the ability of platinum to form a large number of adduct complexes with the N7 atom of the G base.

3.4.1. DNA-metal complex interaction

Delivery of chemotherapy drugs as structured nanoparticles has the potential to specifically exploit the cytotoxic effects of metal complexes and metal complexes in a targeted manner. A chloro-ligand containing Cu(II) and Sn(IV) with pyrazole and phenylglycine was shown to bind to calf thymus DNA (CT-DNA) by electrostatic interaction and induce condensation into granular nanostructures. The complex also showed oxidative cleavage activity to plasmid DNA. In addition to forming a concentrated nanoform of DNA(allowing transport across the cellular barrier and resisting enzymatic degradation), a key and novel feature of the complex is reported to be its double-binding pattern to DNA, which results from Cu(II) binding to G-base N7 and Sn(IV) interacting with phosphate backbone [21]. The Cu(II), Co(II) and Ni(II) complexes $[M(H_2O)_3(SO_4)(4\text{-}CNpy)_2].H_2O$ (where 4-CNpy is 4-cyano-pyradine) exhibit the same solid phase structure. Its solid phase structure is $[M(H_2O)_4(4\text{-}CNPY)_2]^{2+}$, which is strongly bound to CT-DNA.

The absorption spectra of Cu-Sn heterobimetallic complex 1 (Figure 6) in the absence and presence of CT-DNA are shown in Figure 7. It can be seen that after adding CT-DNA to complex 1, there is a certain redshift phenomenon (3nm) in the ligand. The observed color development is due to the large positive charge binding to DNA, possibly through strong electrostatic attraction to the phosphate group of the DNA backbone, resulting in contraction and overall damage to the DNA secondary structure [21]. Due to the presence of two different metal centers, complex 1 has different specificity at the molecular level, so it has a good prospect as an anti-tumor drug.

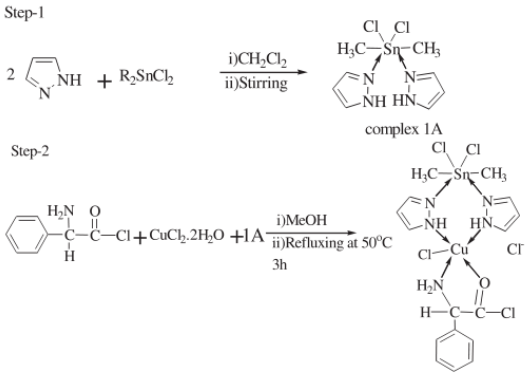

Figure 6. Synthesis diagram of heterobimetallic complexes (Complex 1) [21]

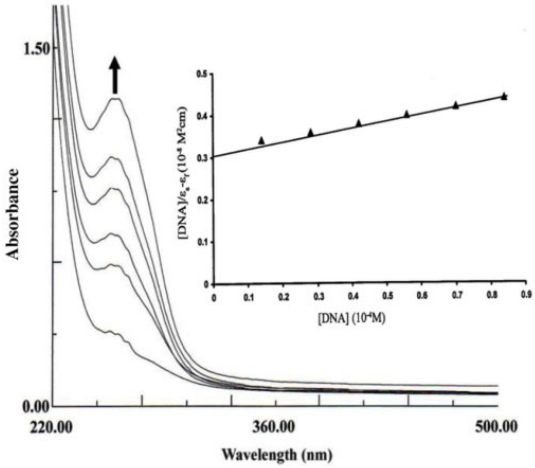

Figure 7. Absorption spectral trace of complex 1 in tris-HCl buffer after addition of CT-DNA. [21]

3.4.2. Quinolone antimicrobials

Although the mechanism of action of quinolones is not fully understood, it is generally believed that they act as inhibitors of bacterial topoisomerase by forming complexes with DNA and the bacterial enzyme topoisomerase II (DNA cyclase) or topoisomerase IV. This binding eventually leads to DNA breakage and bacterial cell death. Quinolone antimicrobials have been reviewed [22], and recent studies support the role of DNA-bound metal ions in quinolone-DNA interactions. Quinolones are able to bind to the phosphate group of DNA through the carboxyl and carbonyl parts, and it has been shown that the presence of a DNA-bound metal ion can enhance or inhibit this binding, depending on the identity of the metal ion and its concentration. Mg^{2+} ions have been reported to play a major role (cofactor) in the DNA cleave-rejoin activity of topoisomerase [23], and the presence of Mg^{2+} has been noted to have an effect on quinolone binding

to DNA. Recent studies have shown that at low concentrations (< 3.0 mm), Mg^{2+} ions enhance quinolone-DNA binding by binding to phosphate groups on DNA and building bridges for the interaction between quinolones and phosphate groups [23]. Cu^{2+} can also increase binding interactions with several quinolones and DNA by interacting with drug molecules and DNA bases. However, for the quinolone Sparfloxacin (SPFX), which also has an amino group that can directly bind to DNA bases, the presence of Cu^{2+} reduces the binding affinity because there may be competitive binding interactions between Cu^{2+}, DNA bases, and SPFX [24]. In addition, the comparison of metal ions and their ability to enhance quinolone-DNA binding is Cr(III) and Cr(VI). The combination of Cr(III) and SPFX is not as strong as Cr(VI). However, with the increase of Cr(III) content, the SPFX-DNA binding constant increased. This is due to the fact that Cr(III) mainly binds to DNA bases at low concentrations and phosphate groups at higher concentrations, thereby increasing the SPFX-DNA binding constant. Although Cr(VI) is compatible with SPFX, its affinity to DNA is not high, and the presence of Cr(VI) has no effect on the binding constant between SPFX and DNA [25]. In the presence of Cd^{2+}, the binding interaction between SPFX and DNA is weakened, and Cd^{2+} has been reported to mainly bind DNA bases, indicating that Cd^{2+} competes with SPFX for DNA binding sites [26].

3.5. Alternative DNA base pairing using metal ion coordination

Base pairing via hydrogen bonds is essential for the correct form and function of DNA, and any disruption of this relatively powerful intermolecular force can lead to instability in DNA's double helix structure. However, researchers are beginning to ask the question: "What if hydrogen bonds were replaced by another force that attracts DNA base pairs?" "Not only is the DNA conformation different, but other properties change, including the conditions under which the DNA melts (temperature, ionic strength and pH) (i.e. strands in double-stranded DNA separate to form single-stranded DNA)." If DNA's double helix structure can be "tweaked" by the pattern and strength of base pairing, then these physical properties may have other applications. Metal ion mediated base pairing (metal-base pairing) is being investigated as an alternative to hydrogen bond base pairing. In addition to forming base pairs between naturally occurring bases, metal base pairs use synthetic ligands and bases that behave identically, allowing base pairs to be orthogonal to naturally occurring base pairs, providing an opportunity to expand genetic information and information storage capabilities. Metal-mediated base pairing involves both naturally occurring and synthetic bases and is a rapidly developing field.

Using Hg(II) and Ag(I) ions, the mismatch of natural base pairs can be achieved. As early as 1963, a 2:1 T-Hg complex (T-HG^{2+}-T) was thought to exist in disonucleotides [27], and Hg(II) and CH_3Hg(II) bind thermodynamically more favorably to the N3 of T than to the N1 of G [28]. The stabilization of this interaction was confirmed by UV melting, the specificity of Hg(II) for T-T mispairs was confirmed, and a double helix double helix structure consisting only of T-Hg^{2+}-T pairs was formed. NMR studies have shown that Hg(II) replaces the imine proton on N3 of T to form a T-HG^{2+}-T pair [29]. Recent work includes further characterization of T-Hg^{2+}-T interactions using ITC to obtain thermodynamic data. It has been reported that double T-T mismatches can be paired with two stoichiometric quantities of Hg(II), and the binding affinity of the second Hg(II) ion is more favorable than that of the first, resulting in positive cooperative binding. It has been suggested that this could be beneficial for aligning multiple Hg(II) ions in double helix DNA for nanotechnology applications. Reports also indicate that Ag(I) contains a stable double helix of C-C pairs when present and conclude that Ag(I) selectively misbinds to C-C. Dna-based Ag(I) sensors were developed [30]. The thermodynamic properties of the special C-Ag^{+}-C pair were studied by UV melting and ITC. The presence of Ag(I) only stabilizes the biphase containing the C-C mismatch, and Ag^{+} binds to the C-C pair 1:1 with a binding constant of $10^{6}{}_{M}{}^{-1}$ [31]. A notable example of artificial base pairing is the unusually stable double helix obtained by pairing an oligonucleotide-incorporated salicylic aldehyde base derivative with metal ions Cu(II) and Mn(II). In addition to base coordination, the biphasic structure was further stabilized by adding ethylenediamine as an additional crosslinker [32].

Incorporating a single metal base pair into a DNA double strand showed a significant increase in the stability of the double helix. In addition to the DNA double helix, other structures, including hairpin rings and three-stranded DNA, can be formed and manipulated by metal-mediated base pairing. Kuklenyik and Marzili demonstrated that formation of Hg(II) -mediated base pairs in oligonucleotide sequences containing different numbers of mismatched T residues affects conformational changes between hairpin and biphasic forms [33]. Using the absence or presence of metal ions to induce conformational changes between hairpin rings and double helices in these structures has a variety of applications as DNA-based metal ion sensors, devices and machines. The T-Hg^{2+}-T base pair described above is used as a component of a fluorescence-based Hg(II) sensor, where the base pair leads to a hairpin structure that increases fluorescence resonance energy transfer (FRET) between donor-acceptor groups attached to the ends of oligonucleotides. The addition of base pairs from Ag(I) demonstrated the incorporation of a 1,2,4-triazole into the oligonucleotide sequence. In the absence of Ag(I), oligonucleotides have hairpin structure, and the addition of Ag(I) causes oligonucleotides to form regular double helix structure. This conformational change is also promising as a Ag(I) sensor because the conformational change from hairpin to double helix causes fluorescence to be quenching by FRET [34]. Other examples of conformational changes based on metal-mediated base pairing include the promotion of conformational changes from random coils to hairpins by adding Ag(I) ion-paired imidazole nucleotides and T-C-rich oligonucleotides that bind Hg(II) and Ag(I). Recently, a group of nucleosides has been developed on the basis of 1,2,3-triazole combined with 1,2,4-triazole, 1,2,4-pyrazole, and 1,2,4-pyridine complements, yielding digenucleosides that form base pairs in the presence of Ag(I). The purpose of this combination of nucleosides is to further understand the various effects of stabilizing the double helix structure formed by metal-mediated base pairing [35].

Metal-mediated natural base pairing also gives rise to DNA-based logic gates. Applications include CdSe or ZnS quantum dots with functional nucleic acid groups, using Ag(I) and Hg(II) ions as inputs, and PCR amplification only when Hg(II) and Ag are available to form T-Hg^{2+}-T and C-Ag^{+}-C base pairs [36]. A unique development of DNA-based logic gates involves the use of gold nanoparticles (auNPs) that have been modified with T-rich or C-rich oligonucleotide chains.

The addition of Ag(I) and Hg(II)(inputs) leads to a conformational transition (due to the formation of C-Ag^{+}-C and T-HG^{2+}-T base pairs), resulting in a modified auNP aggregation and a distinct color change in the visible region of the electromagnetic spectrum. The addition of EDTA and NH_4OH can reverse this aggregation to capture Hg(II) and Ag(I), respectively. YES, AND, INHIBI and XOR colorimetric logic gates are built on top of these auNPs and do not require targeted design or changes to DNA sequences. The output is colorimetric and visible to the naked eye, and the modified auNP polymerizes in a selective manner on the basis of Ag(I) and Hg(II) [37]. Metal-based DNA base pairs also hold promise in molecular machines and artificial genetic circuits, Liu and Sadler recently conducted a computational study, Supports the possibility of producing DNA nanowires by using Cu(I) ions to form multiple adjacent base pairs (three adjacent G-Cu^{+}-C base pairs and two adjacent A-Cu^{+}-T base pairs) [38].

4. Summary and Prospect

4.1. Content summary

Metal ions are necessary for many biologically related processes. For example, Mg^{2+} and Zn^{2+} are cofactors in enzymatic reactions. The structure of DNA, including its phosphate skeleton, the deoxyribose of the O atom, and the bases containing the N and O atoms, make it a natural target for binding metal ions. The DNA-metal interaction depends on many different factors, including the type of metal ion, its form, REDOX activity, and the actual location where it binds to the DNA macromolecule. In view of the basic characteristics of the interaction between DNA and metal ions, this paper summarizes as follows: The base pairing in DNA produces a double helix structure, which is accompanied by a small gap "small groove" rich in AT and a large "main groove" rich in GC. These grooves allow metal ions, small molecules, and complex ions to interact directly with DNA bases. Metal ion binding exists at multiple sites (phosphate backbone, deoxyribose, and single base), and the binding of metal to base usually breaks the base-pair hydrogen bond, making the double helix unstable. Spectral and X-ray data indicate that N7 atoms of purine residues or N3 atoms of pyrimidine residues as well as outer ring O atoms and phosphate oxygen atoms are preferred sites for metal binding. In general, monovalent cations mainly interact with the phosphate group of the main chain. Divalent metal ions can interact with both phosphates and bases, and (mostly transitional) metal ions have significant affinity with bases. Binding of metals to DNA and RNA also indirectly affects the conformation of sugar rings, which may be the reason why some metal ions affect DNA synthesis and replication processes.

Regarding the role of DNA-metal ions in disease and human health, this paper summarizes the links between the interaction of metal ions with DNA and oxidative damage to DNA as follows: REDOX active metal ions are ubiquitous in biological systems, and in addition to their innate ability to bind to DNA, they can also produce damaging reactive oxygen species (ROS) by reacting with H_2O_2 and other endogenous oxidants. In addition, DNA double helices, hairpin rings, and three-stranded DNA structures can all be formed and manipulated by metal-mediated base pairing. Many antioxidants act as ROS scavengers, reacting with ROS sacrificially before the surrounding structure is damaged. Metal ion coordination plays a key role in the mechanism of certain antioxidants, and some sulfur (S) and selenium (Se) compounds act as antioxidants by including mechanisms that coordinate the metal ions that produce ROS. Metal-dna interactions are the basis of many anti-cancer drugs, antiviral drugs, and antimicrobials, most of which work by inserting DNA structures, with common metal centers in drugs including Ru, Os, Co, Ni, Cu, and Zn.

4.2. Future work prospect

Although a large number of theoretical studies on metal ions and biomacromolecule fragments have been reported, many studies in this area are based on the interaction of metal ions with bases and their derivatives, as well as the interaction of metal ions with phosphodiester analogues. But there is still a long way to go in perfecting the interaction between nucleotides and metal ions. Future studies are expected to elucidate the role of metal ion binding and ROS clearance in the mechanism of antioxidant action, thereby making more efficient use of antioxidant activity. In addition, specific metal-DNA interactions also contribute to improving the effectiveness of anti-cancer, antiviral, and antimicrobial agents, and future advances are likely to utilize selective metal ions binding to DNA as a way to target drug therapy. The use of metal complexes to concentrate DNA into nanoparticles has also shown promise as a means of selective drug delivery. The relevant content is essential for in-depth understanding of basic life processes and the development of anti-cancer drugs. At the same time, the application of metal ion and DNA interaction in nanotechnology, molecular machine manufacturing, etc., is also expected to be further developed, including DNa-based sensors for catalytic cracking of DNA substrates and metal ions, so as to more effectively utilize the influence of metal ions on DNA base pairing.

4.3. Innovation point

Based on a lot of reading of relevant literature, this paper summarized relevant scientific research and theoretical analysis, including the interaction between metal ions and DNA, the interaction between REDOX active metal ions and DNA, and the reduction of oxidative DNA damage by antioxidants by coordinating metal ions that produce reactive oxygen species. And the latest progress of metal-mediated base pairing is discussed systematically. The prospects of the interaction between DNA and metal ions in medicine and other fields are also discussed. In this paper, the interaction between metal ions and DNA and its research progress are explained by the method of cross analysis of physical problems, biology and chemistry, which can provide guidance for the development and innovation of practical applications such as pharmaceutical and molecular nanotechnology.

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