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Interactions of Transition Metal Ions with DNA: A Review of AFM and FTIR Studies for Structural Insights and Nanostructures Fabrication

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تفاعلات أيونات العناصر الانتقالية مع الحمض النووي *DNA*: مراجعة لدراسات طيف الاشعة تحت الحمراء *FTIR* ومجهر القوى الذرية *AFM* لفهم التغير في بنية الحمض النووي وتحضير التراكيب النانومترية

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Abstract:
DNA possesses a diverse a range of chemical functionalities that allow it to interact with transition metal ions, influencing its structural stability and serving as a valuable template for nanostructure fabrication. This review focuses on the application of Fourier Transform Infrared Spectroscopy (FTIR) and Atomic Force Microscopy (AFM) to explore these interactions. FTIR offers molecular-level insights into how metal ions coordinate with phosphate groups and nitrogenous bases, while AFM visualizes the resulting nanoscale changes in DNA morphology. Investigations of metal ions such as Cu^{2+}, Ag^{+}, Ni^{2+}, Co^{2+}, Fe^{2+}, Zn^{2+}, and Rh^{3+} reveal varying binding behaviors, structural impacts, and potential applications. A comparative analysis of Cu(II) and Ag(I) interactions with DNA demonstrates that copper can cause significant structural disruption and oxidative damage, whereas silver selectively binds to guanine and adenine without inducing major conformational changes. The combined application of FTIR and AFM provides a comprehensive understanding of DNA–metal ion interactions, supporting their use in biosensing, nanowire fabrication, DNA-templated nanoparticles, and the development of metal-based therapeutic agents.

Keywords: Transition metals, DNA, FTIR, AFM, nanotechnology, nanostructures.

الملخص
يحتوي الحمض النويي DNA على مجموعة متنوعة من الخصائص الكيميائية التي تمكنه من التفاعل مع أيونات المعادن الانتقالية. تؤثر هذه التفاعلات على استقرار بنيته، مما يجعله قالبًا مهمًا لصنع الهياكل النانوية. في هذا االبحث، نسلط الضوء على استخدام مطيافية الأشعة تحت الحمراء بتحويل فوربيه (FTIR)، ومجهر القوة الذرية (AFM)، لفهم هذه التفاعلات بشكل أعمق. تساعد تقنية FTIR في معرفة كيفية ارتباط أيونات المعادن بمجموعات الفوسفات والقواعد النيتروجينية داخل الحمض النووي على المستوى الجزيئي، بينما تتيح لنا تقنية AFM رؤية التغيرات التي تحدث في شكل الحمض النووي على المستوى النانوي. أظهرت دراسات عدة لأيونات معادن مثل النحاس (Cu^{2+}) ، والفضة (Ag^{+}) ، والنيكل (Ni^{2+}) ، والكوبالت (Co^{2+}) ، والحديد (Fe^{2+}) ، والزنك (Zn^{2+}) ، والروديوم (Rh^{3+}) اختلافات في طريقة ارتباطها بالحمض النووي وتأثيرها على هيكله، بالإضافة إلى إمكانيات استخدامها في مجالات متنوعة. أظهرت المقارنات بين تفاعلات النحاس والفضة

مع الحمض النووي أن النحاس يمكن أن يسبب اضطرابات هيكلية كبيرة وأضرارًا تأكسدية، بينما ترتبط الفضة بشكل خاص بالجوانين والأدينين دون أن تُحدث تغييرات كبيرة في شكل الحمض النووي. استخدام وربط نتائج تقنيتي FTIR و AFM معًا، تمكننا من فهم وتفسير التفاعلات بين الحمض النووي وأيونات العناصر الانتقالية، وامكانية استخدامها في مجالات متعددة مثل الاستشعار الحيوي، وتصنيع الأسلاك النانوية، وتصنيع الجسيمات النانوية المعتمدة على الحمض النووي، وتطوير أدوية علاجية جديدة.

الكلمات المفتاحية: العناصر الانتقالية، *DNA*، *FTIR*، *AFM*، تقنية النانو.

1-Introduction

Transition metals are a group of chemical elements that have incomplete d-orbitals, which allow them to exhibit variable oxidation states and form coordination complexes with ligands. These properties make transition metals well-suited for various biological functions. Many vital processes in living creatures are based on the complex interactions between transition metals and biological molecules [1, 2].

Deoxyribonucleic acid (DNA) is a fundamental biomolecule that functions as the major constituent of chromosomes and the carrier of genetic information in all living cells [3, 4]. In addition to its biological role, DNA possesses structural and chemical properties that allow it to be used as a template for nanostructure fabrication. Its high aspect ratio, with a diameter of roughly 2 nm and a length that ranges from nanometers to microns, make it a good material for regulating material growth into one-dimensional structures [5, 6]. Moreover, DNA has a rich array of chemical functionalities, including its anionic phosphodiester backbone and the nitrogenous bases. These characteristics allow DNA to interact with a range of chemical species, such as transition metal ions [4, 7]. Interactions between DNA and transition metals can take place through various types of mechanisms. This involves coordinating with the oxygen atoms of the phosphate groups in the DNA backbone or with donor atoms on the nitrogen bases. Additionally, metal ions can bind to DNA by intercalating between base pairs or through electrostatic attraction [4, 8, 9]. These interactions are significantly influenced by several factors, including DNA concentration, the length and composition of DNA sequences, the type and concentration of metal ions, their oxidation states, temperature, and salt concentration [4, 10].

Such interactions have significant implications in biochemistry [11], medicine, and nanotechnology [4, 11]. Transition metal binding can induce notable changes in DNA structure, such as denaturation of the native conformation (B-form), aggregation, condensation, and disruption in base pairing and stacking [8, 12, 13]. These alterations are essential for understanding the mutagenic potential of metal ions and for the development of metal-based chemotherapeutics [14]. In addition, they are essential for the fabrication of DNA/metal-based nanostructures [4-7].

The study of metal ions binding to DNA has long been a focus of DNA nanotechnology, coordination chemistry, and bioinorganic chemistry [11]. Two powerful analytical techniques, Fourier Transform Infrared Spectroscopy (FTIR) and Atomic Force Microscopy (AFM), are commonly used to investigate these interactions [15-18]. Changes in vibrational frequencies related to DNA functional groups are detected by FTIR, revealing chemical interactions, while, morphological changes, such as condensation, aggregation, and the formation of networks or nanowires can be detected with the use of AFM imaging.

Although extensive research has been conducted on the interactions between metal ions and DNA, little is known about their molecular and structural effects. There remains a specific gap in linking FTIR-detected binding events with morphological changes observed by AFM. By combining findings from both methods, with a focus on Cu(II) and Ag(I), this review aims to elucidate their unique effects on DNA structure and highlight the implications for the creation of nanostructures and biological applications.

2. Chemical Basis of Interactions Between Transition Metal Ions and DNA

Coordination chemistry significantly controls the interaction between transition metal ions and DNA. Transition metal ions exhibit varying oxidation states and partially filled d-orbitals; therefore, they can function as flexible coordination centers for creating stable complexes with different donor atoms on the DNA molecule [2].

This section begins by explaining the functional groups in DNA that allow it to interact with transition metal ions and their complexes. It then outlines the reaction mechanisms involved in these interactions. Finally, the chemical factors influencing DNA-transition metal binding are discussed.

2.1. Chemical Functionalities of DNA Molecule

The main constituents of DNA include a ribose sugar, phosphate groups, and nitrogenous bases [3, 4]. Together, these components form nucleotides, which provide various sites for interaction with transition metal ions. These sites on DNA include the grooves of the double helix, the negatively charged phosphate groups on both strands, and the electron-donating atoms of the nitrogenous bases. A schematic representation of common metal ion binding sites on the DNA structure is shown in Figure 1. For adenine (A) and guanine (G) bases, the most frequent binding sites are the endocyclic nitrogen donors at positions N7 and N1. Additionally, although less common,

metal ion binding may occur at guanine's O6 position. In the case of pyrimidines, interactions typically involve the N3 position of thymine and cytosine [4, 19, 20].

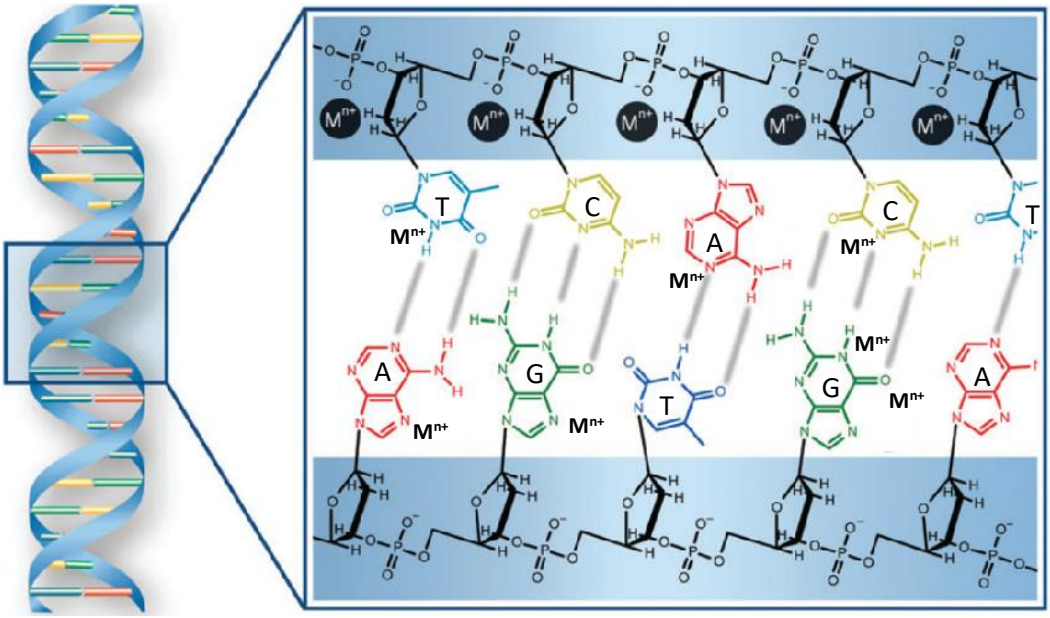

Figure 1: The structure of the DNA molecule with common metal ion binding sites [5].

2.2 Basic Interaction Mechanisms of DNA and Transition Metal Ions

Coordinative bonds and non-covalent interactions are the two main ways that DNA and metal ions interact. Coordinate inner-sphere binding represents the first type of interaction that occurs between transition metal ions and nucleic acids. In this mode of interaction, electron donor atoms from the DNA bases coordinate directly with the unoccupied orbitals of the transition metal ions. The majority of transition metals undergo chemical reactions with the N7 atoms of adenine and guanine, as well as the N3 atoms of cytosine and thymine. Compared to electrostatic or groove interactions, this type of binding is often more stable and specific. As a result of this mode of transition metal–DNA interaction, the hydrogen bonds between adjacent nucleobases may be disrupted, leading to destabilization of the DNA double helix structure [4, 14, 21, 22].

As represented in Figure 2, when transition metals bind to DNA, particularly at G–C-rich regions, they can catalyze the generation of reactive radicals from hydrogen peroxide (H_2O_2), resulting in DNA strand breaks or oxidative damage. Reactive oxygen species (ROS) produced by other metal ions, including copper (II) and iron (III), can cause oxidative damage to nucleobases or breakage of the DNA backbone [23-25].

In the second type of reaction between DNA and metal ions, the negatively charged phosphate groups on the DNA backbone can bind positively charged metal cations through electrostatic forces. For example, silver ions (Ag^+) attach to the DNA backbone through such interactions. Normally, counter ions such as sodium (Na^+) or magnesium (Mg^{2+}) ions screen the negative charges of the phosphate groups in the DNA backbone. However, in the presence of metal ions, an ion-exchange process can occur, as demonstrated by the successful loading of silver ions onto the backbone [26, 27]. Additionally, this mode of interaction involves outer-sphere binding through hydrogen bonding between coordinating ligand molecules and nucleobases and/or phosphate groups [20-22]. Divalent cobalt cations (Co^{2+}) bind indirectly to DNA through hydrogen bonds formed between the coordinating water molecules of the metal ions and the oxygen atoms of the phosphate backbone [28]. Manganese ions (Mn^{2+}) also interact through an outer-sphere mechanism, similar to that observed for Co^{2+}. Despite being comparatively weak and generally non-specific, the outer-sphere mechanism works as an initial step toward more specific binding types, such as covalent bonding or intercalation. These interactions may affect biological functions such as transcription and replication by altering the DNA's overall charge distribution and condensation state [28, 29].

Additionally, both covalent and non-covalent bonds can be formed between transition metal complexes and DNA. Covalent binding occurs when the central metal ion forms a direct bond with the phosphate backbone or a nitrogenous base. On the other hand, positively charged metal complexes can interact non-covalently with DNA through intercalation, electrostatic interactions, and groove binding within the major or minor grooves along the exterior of the DNA helix [30].

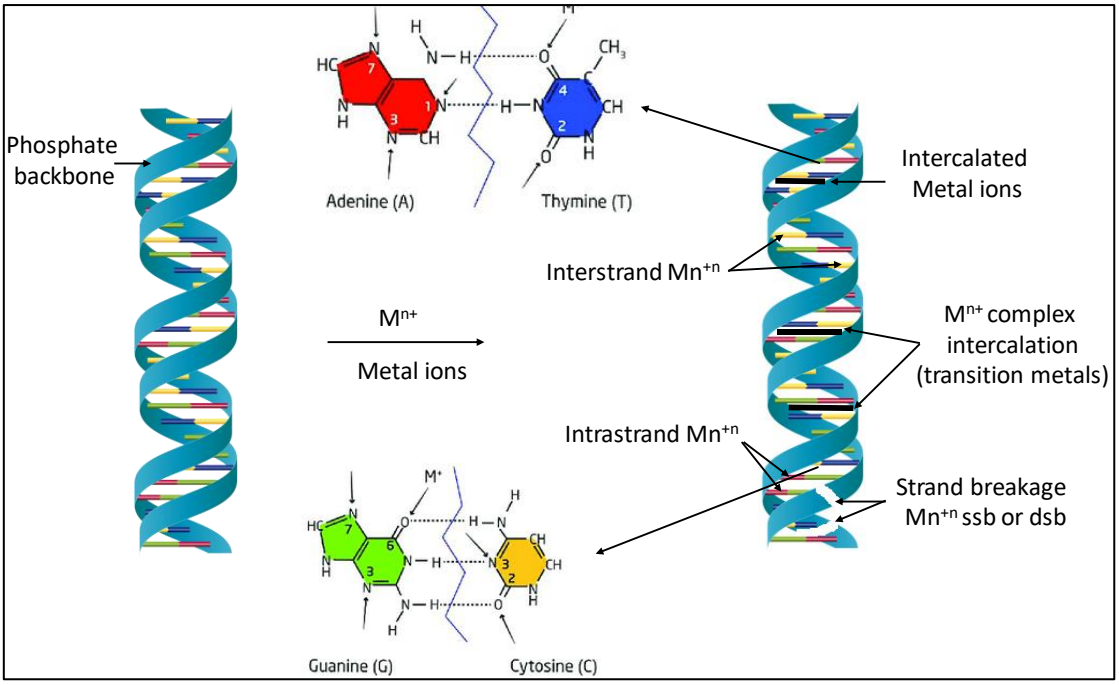

Figure 2: Metal ions can bind to one or two sites on the same strand (intrastrand) or the opposite strand (interstrand), or they can intercalate in complex form between the bases. Metal ion binding can cause either single-strand breaks (ssb) or double-strand breaks (dsb) [25].

Specific metal complexes that have a planar geometry can attach to the grooves of the DNA helix. Minor groove binding is more prevalent, particularly in AT-rich sequences, due to its narrower size and greater accessibility. However, cations can also localize within the major groove, especially in GC-rich regions. The binding of metal ions to DNA is strongly influenced by the nucleotide sequence [31, 32].

Some metal complexes can also engage in intercalative binding. In this type of interaction, planar aromatic transition metal complexes insert themselves between adjacent base pairs of the DNA double helix. The insertion disturbs the natural stacking of the base pairs, causing the helix to partially unwind. An example of this reaction mechanism is the interaction between Hg^{2+} and DNA.

The interaction of mercury (Hg^{2+}) ions with DNA provides an additional illustration of the inner sphere binding mechanism. Strong covalent T–Hg–T crosslinks can form when Hg^{2+} ions replace the hydrogen bonds in the DNA duplex, bringing two opposing thymine bases together [33, 34]. As shown in Figure 3, three T–Hg–T base pairs can form in a short trimer duplex upon binding of Hg^{2+} ions in this manner [34-36].

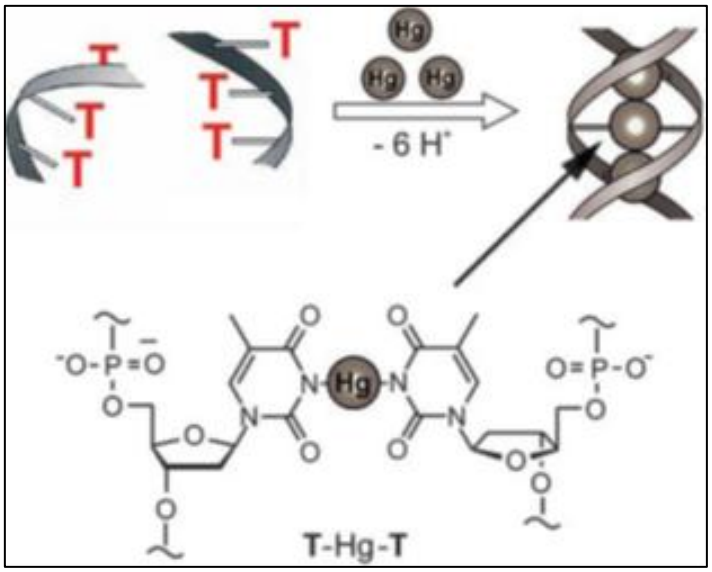

Figure 3: A diagrammatic representation illustrating how the addition of Hg^{2+} ions leads to the formation of three T-Hg-T base pairs in a small trimer duplex [34].

3. Techniques for Studying DNA-Metal Ion Interactions

Fourier transform infrared spectroscopy (FTIR), and Atomic force microscopy (AFM) are essential techniques for studying the interactions between metal ions and DNA. FTIR helps determine where and how metal ions bind by detecting changes in the chemical bonds of DNA, such as those in the nitrogenous bases and the phosphate backbone. AFM offers nanoscale images of DNA that demonstrate how metal ion binding alters the structure and form of DNA. Combining these two techniques improves our understanding of how metal ions affect DNA chemically and physically.

This section starts by explaining how FTIR can be used to understand interactions between metal ions and DNA. It then introduces AFM as a nanoscale technique for investigating structural changes in DNA upon metal ions binding.

3.1 Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy is a commonly utilized technique for analyzing molecular vibrations and chemical bonding. It works by measuring how a sample absorbs infrared light, which reveals information about its functional groups and structural changes at the molecular level.

3.1.1 Principles of FTIR

Fourier transform infrared (FTIR) spectroscopy is a type of vibrational spectroscopy that provides intrinsic information about the functional groups in a sample. It measures the absorption of infrared light, giving precise details about functional groups and structural changes at the molecular level. The principle of this technique is based on how infrared light interacts with matter. When infrared radiation passes through a sample, specific frequencies of the light that coincide with the natural vibrational frequency of the chemical bonds within the substance are absorbed. The molecules are excited to higher vibrational states as a result, and the energy differential between the two vibrational states is in the mid-infrared range. A plot of the intensity of infrared radiation as a function of energy produces a spectrum unique to each compound. FTIR spectra display absorption bands corresponding to the vibrational frequencies of atomic bonds within molecules. Since each compound contains a unique combination of atoms, no two molecules exhibit identical spectra. Therefore, functional groups and compounds can be identified by their FTIR spectra, as many functional groups possess characteristic vibrational frequencies [37, 38].

3.1.2Principle of FTIR in Biomolecular Studies

Fourier transform infrared spectroscopy is a well-known, effective, and non-destructive technique for analyzing DNA's vibrational characteristics, which are closely linked to its structural properties [39]. Studies on small quantities of biomedical material in different physical states can be performed, which is one of the main advantages of these spectroscopic methods. Another advantage is the elimination of the need for additional reagents or biochemical indicators, which significantly diminishes sample preparation time and analysis costs. Conformational changes during B–A and B–Z transitions, as well as those induced by DNA–metal ion interactions with Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Cd^{2+}, Mg^{2+}, and Pt^{2+}, can be effectively studied using IR spectroscopy [40].

The structure of the DNA molecule gives rise to a detailed FTIR spectrum, in which several bands have been attributed to specific vibrational modes of particular atomic groups. The FTIR spectrum of DNA shows four different spectral areas. Bands associated with the C=O, C=N, C=C, and N-H stretching vibrations of bases are absorbed in the 1800–1500 cm^{-1} range. These bands can be influenced by alterations in base stacking and base pairing interactions. Bands in the 1500–1250 cm^{-1} range attributed to base vibrations and base-sugar interactions are closely linked to backbone chain conformational changes and the rotation of glycosidic bonds. Between 1250 and 1000 cm^{-1}, sugar-phosphate vibrations, such as C-O stretching vibrations and PO_2^- symmetric and asymmetric stretching vibrations, are present. These vibrations exhibit a high degree of sensitivity to backbone structural changes. Bands linked to sugar vibrations that correspond to the different nucleic acid sugar puckering modes (C2'-endo and C3'-endo) are characteristic of the 1000–800 cm^{-1} range [16, 40-43]

3.1.3 FTIR Spectroscopic Indicators of DNA-Transition Metal Interactions

FTIR spectroscopy can reveal insights into structural changes and binding sites in DNA upon metal binding by observing spectrum variations. This technique identifies metal-binding sites by analyzing changes in the intensity and shifts of specific bands associated with the phosphate backbone and DNA bases [41, 44]. Typically, these changes occur in bands related to phosphate backbone vibrations (both asymmetric and symmetric stretching), functional groups of nucleobases (such as carbonyl and amino), and sugar ring vibrations. These alterations indicate coordination or structural disruptions caused by metal binding. For instance, shifts in the position or intensity of ν(P=O) bands suggest that metal ions are binding to the phosphate groups of the DNA backbone. On the other hand, alterations in base-specific bands indicate that metal ions bind to certain nucleobases [16, 18].

3.1.4 Examples of Transition Metal–DNA Interactions Investigated by FTIR

The interactions between transition metal ions and DNA have been widely studied using FTIR spectroscopy, which provides valuable insights into binding modes, coordination sites, and structural alterations. In this review,

we present examples of FTIR studies on the interactions between transition metals and DNA molecules. This includes Ag^{+}–DNA [17] and Cu^{2+}–DNA [16]. FTIR spectral comparison of metal-free and metal-bound DNA allows for the assessment of structural changes induced by transition metal ions.

3.1.4.1 FTIR Analysis of DNA-Cu^{2+} Interactions

Numerous studies have employed FTIR spectroscopy to investigate the binding of Cu^{2+} ions to DNA, providing insights into their specific effects on DNA structure. These studies have shown that the nature of the interactions varies depending on the concentration of the metal ions [22, 44-46]. Copper cations interact electrostatically with negatively charged phosphate groups of DNA at very low concentrations. Conversely, as the concentration of metal ions increases, Cu^{2+} favors coordinative bonding with the donor atoms of DNA's nucleobases. Several models have been proposed to describe the exact nature of Cu^{2+} binding to DNA. These include coordination of Cu^{2+} ions with the N7 atom of guanine and a phosphate oxygen from the DNA backbone in a 'sandwich complex,' binding between two adjacent guanines on the same DNA strand, or chelation involving both a guanine (N7, O6) and a cytosine (N3, O2) from different strands [47]. In the following, an example of FTIR analysis of the interaction between Cu(II) ions and DNA will be explained in detail.

Recent studies based on FTIR data have shown that DNA/Cu^{2+} coordination involves copper ions binding to both the oxygen atoms of the phosphate groups in the DNA backbone and the nitrogenous bases of the DNA molecule (Figure 4). The coordination of copper cations to the phosphate groups is evident from notable changes in the intensity of the band attributed to the $PO2^{-}$ symmetric stretch (1096 cm^{-1}), which is significantly reduced. Additionally, the P-O/C-O stretching in the phosphate backbone is shifted to a lower frequency (1063 cm^{-1}). It is also evident that there is a greater splitting of the P-O/C-O backbone and deoxyribose C-C stretches. Furthermore, the asymmetric $PO2^{-}$ vibration (1248 cm^{-1}) is noted to shift to a lower frequency (1242 cm^{-1}). On the other hand, evidence for the direct coordination of Cu^{2+} to DNA nucleobases is provided by changes in band positions and intensities observed in the 1300–1750 cm^{-1} region of the spectrum, which corresponds to nucleobase vibrations. These changes include a reduction in band intensity and a shift to a higher frequency (1535 cm^{-1}) of the in-plane cytosine/guanine vibration. Additionally, the guanine ring vibration shifts by -8 cm^{-1}, appearing at 1477 cm^{-1} upon Cu^{2+}/DNA complexation. The 1570–1700 cm^{-1} region of the FTIR spectrum also exhibits changes in both band intensities and positions.

The nucleobase vibrations in the 1570-1700 cm^{-1} region of the spectra also show apparent changes in band positions and intensities. The shift of C=O stretching vibrations of nucleobases to lower wavenumbers is indicative of coordination with metal ions [16].

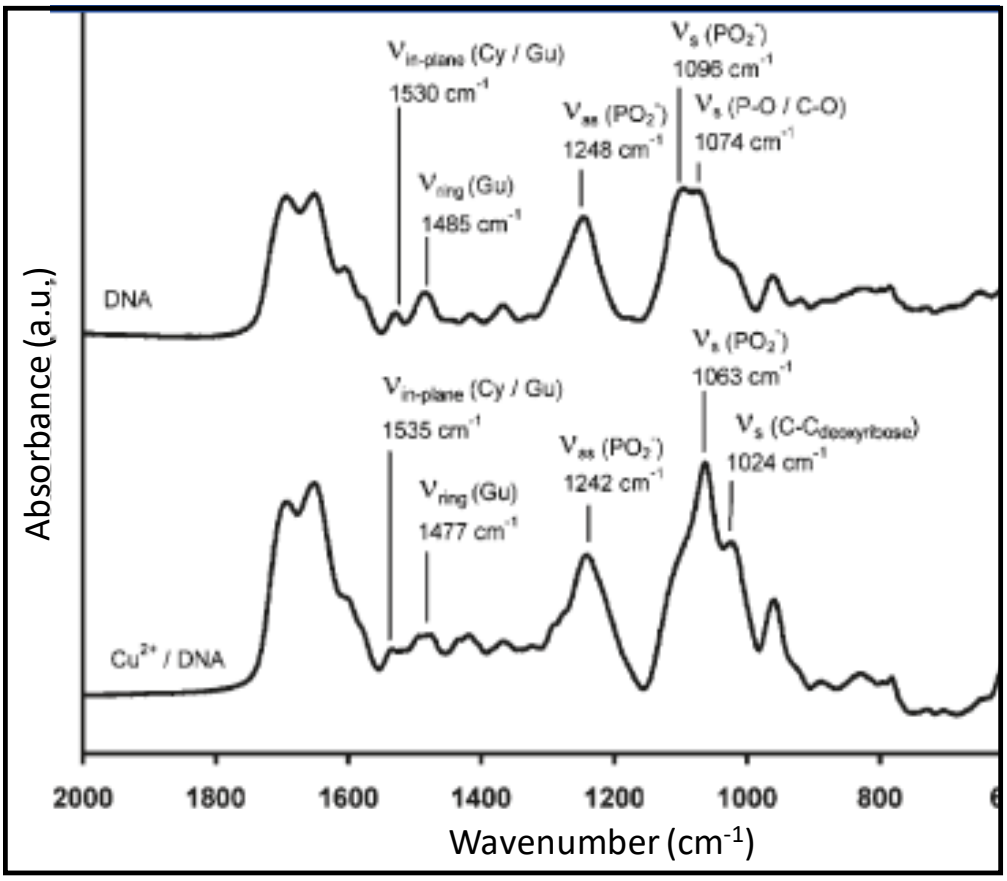

Figure 4: DNA FTIR spectra in the 600–2000 cm^{-1} range compared to the Cu^{2+}/DNA complex [16].

3.1.4.2 FTIR Analysis of DNA-Ag^+ Interactions

Silver cations (Ag^+) have gained significant interest because of their antimicrobial activity, distinctive electrochemical behavior, and strong affinity for forming stable interactions with nucleic acids. To gain insight into the coordination mechanisms and conformational changes involved, FTIR spectroscopy enables the identification of specific binding sites and structural alterations in DNA during its interaction with Ag^+ ions [17]. Instead of interacting with the phosphate backbone, Ag^+ ions, whether at high or low concentrations, are known to preferentially bind to nitrogen-containing bases in DNA. An infrared spectroscopic study of the DNA/Ag^+ complex made from a 1:5 molar ratio of Ag(I) and calf thymus DNA indicates that Ag^+ binds to guanine but not to adenine, thymine, cytosine, or the phosphate groups of the DNA backbone [17, 48].

In a comprehensive FTIR study, the interactions between DNA and Ag^+ ions were investigated across a range of molar ratios [17]. FTIR analysis indicated that at low concentrations of silver ions (Ag/DNA, r = 1/80), Ag^+ selectively binds to the N7 position of guanine, as evidenced by shifts and changes in the intensity of FTIR bands associated with guanine. These changes include an approximately 20% increase in the intensity of the band at 1717 cm^{-1} (assigned to carbonyl vibrations of guanine and thymine), along with a downshift of this band to 1712 cm^{-1}. On the other hand, the bands corresponding to in-plane vibrations at 1222 cm^{-1}, 1609 cm^{-1} (A and C), 1492 cm^{-1} (C and G), and 1663 cm^{-1} (T, G, A, and C) (PO_2^- asymmetric stretch) did not exhibit any noticeable spectral shifts. The detected changes in the spectra indicate that Ag^+ has a tendency to bind more readily to the N7 atom of guanine in G–C base pairs [49].

Moreover, the lack of alterations in the vibrational bands of cytosine at 1529 and 1429 cm^{-1} suggests that Ag(I) interacts exclusively with the N7 site of guanine, rather than forming a chelate involving both N7 and O6 without proton transfer. As the concentration of silver rises (r=1/2), the adenine peak at 1609 cm^{-1} shows a notable increase in intensity of approximately 20% compared to unmodified DNA, along with a shift to a lower wavenumber (1600 cm^{-1}), as illustrated in Figure 5. Conversely, additional bands observed at 1717, 1663, 1492, and 1222 cm^{-1} exhibited a slight decrease in intensity when interacting with Ag^+. These spectral findings may suggest that the Ag cation binds to the N7 position of adenine bases at increased concentrations.

FTIR spectral analysis shows that Ag^+ complexation does not cause a conformational change in DNA; the molecule retains its native B-form structure. Ag^+/DNA interaction did not exhibit distinct infrared spectra that are commonly linked to B-to-A or B-to-Z transitions. These spectra include shifts in the bands at 836 cm^{-1} (phosphodiester vibrations), 1222 cm^{-1} (asymmetric phosphate stretching), and 1717 cm^{-1} (carbonyl vibrations of guanine and thymine). However, minor spectral changes, including a slight shift of the 836 cm^{-1} band to 833 cm^{-1} and reduced intensity of the sugar-phosphate band at 1053 cm^{-1}, suggest indirect modifications in the sugar-phosphate backbone geometry without a full conformational change [17]. Now, it is worthwhile to make a comparative summary of FTIR Findings and the biological implications of Cu(II) vs. Ag(I)–DNA interactions, as illustrated in the table 1.

Table 1: comparison of the FTIR results with the biological consequences of interactions between Cu(II) and Ag(I) and DNA.

Aspect	Cu^{2+} interactions	Ag^+ interactions
Binding sites	Phosohate backbone + nucleobases (guanine, cytosine)	Mainly guanine (N7); adenine at high concentration.
FTIR spectral Changes	-Shifts in phosphate and base bands. -Intenisity changes	-Shifts mainly in guanine bands. - Minor backbone changes
Effect on DNA conformation	-Potential local structural changes and partial distortion due to multisite coordination. -Possible backbone and base perturbation.	No major conformational change; B-form preserved
Biological implications	-Cu(II) redox activity may cause oxidative damage and strand breaks. -Can disrupt DNA stability and functions by binding backbone and bases.	-Selective base binding likely inhibits DNA functions without structural damages. -Antimicrobial effects linked to guanine binding. -Maintains DNA structural integrity.

Summary Interpretation:

- Cu(II) interacts with DNA by coordinating with nucleobases and the phosphate backbone, leading to structural disruptions and potential DNA damage due to its redox activity.
- Ag(I) binds selectively, primarily targeting guanine bases while maintaining the conformation of the DNA backbone. This preserves the overall structure of the DNA but may disrupt biological processes due to its specific binding to bases.
- These differences highlight their unique biological roles: Cu(II) acts as a redox-active metal that can induce oxidative DNA damage and structural changes, while Ag(I) functions as a stable, non-redox metal that primarily inhibits DNA activity through specific base interactions, which aligns with its antimicrobial properties.

3.2 Atomic Force Microscopy Studies of Transition Metal-DNA Interactions

AFM is a powerful nanoscale technique for examining structural and conformational changes in biomolecules such as DNA [50], particularly in response to interactions with metal ions. Transition metals such as Cu^{2+}, Fe^{2+}, Ag^{+}, and Rh^{3+} have a strong tendency to bind to DNA, often leading to structural modifications, crosslinking, and even cleavage of the DNA backbone. AFM provides a direct and detailed topographical view of these modifications, enabling instantaneous analysis of DNA–metal interactions [16-18].

3.2.1 Principle and Applications

AFM is a highly effective imaging method that reveals atomic-level surface characteristics by detecting the intermolecular forces between a sharp probe tip and the sample surface as it scans line by line. Interactions at nanometer distances cause the tip to deflect, and this deflection generates detailed topographical maps. Unlike scanning tunneling microscopy (STM), AFM does not rely on electrical conductivity between the tip and the sample, making it suitable for a wide range of materials, including insulators, conductors, and biological samples. However, AFM has some limitations, such as a relatively small scanning area, sensitivity to height changes in the micrometer range, and the potential for tip deformation during scans [51-53].

AFM has the capability to function in two main modes depending on the nature of the sample: contact and tapping, figure 5. In contact mode, the tip and sample remain in continuous contact, and the tip deflects due to repulsive forces between the two, providing an image feedback signal. Although this mode offers high-resolution images, it may damage soft materials such as biological or organic specimens because of the constant pressure. The probe does not remain in contact with the sample surface when in tapping mode. This mode is primarily influenced by attractive van der Waals forces, changing the imaging environment to lessen mechanical stresses and protect delicate samples. Tapping mode is favored for examining the structural changes in DNA prior to and following the binding of metal ions [51].

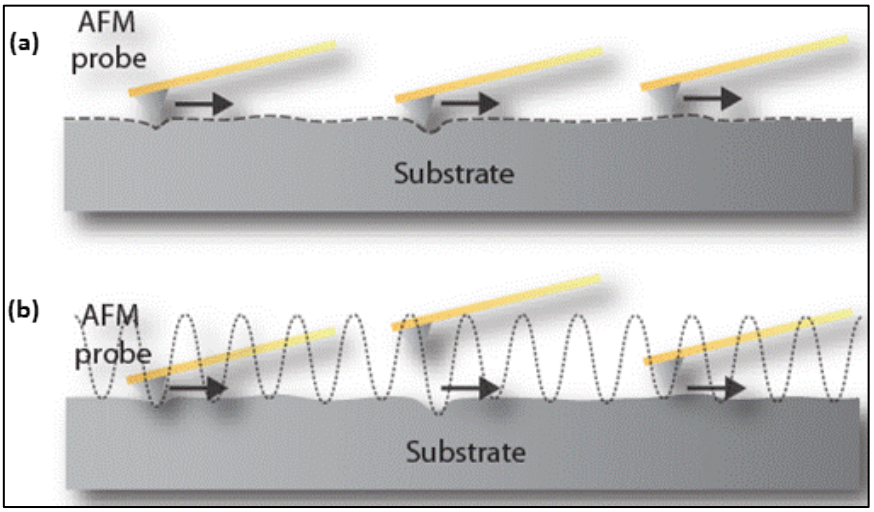

Figure 5: Schematic diagram illustrating (a) contact mode and (b) tapping mode operations of AFM techniques.

3.2.2 AFM as a Tool for Visualizing DNA–Metal Ion Interactions

AFM imaging can effectively visualize individual DNA molecules immobilized on solid substrates [54]. Using this tapping probe microscopy technique, it is possible to detect structural and morphological changes in DNA caused by metal ion binding. The alterations involve condensation, aggregation, kinking, or fragmentation of DNA strands, indicating the extent and mode of metal ion binding. The advanced capabilities of AFM allow precise measurements of variations in height, length, and curvature of DNA strands at the nanometer level, providing valuable information about the structural changes induced by metal binding [16-18].

In AFM imaging, it is essential to isolate and examine individual structures to assess their structural morphologies. Molecular combing can be used effectively align DNA structures onto silicon-based substrates [55-57]. This method enables the deposition of DNA and DNA/metal ions at densities optimal for AFM imaging, dense enough for easy identification yet sufficiently sparse to allow the analysis of individual structures [58].

3.2.3. Observed Effects of Metal Ions on DNA

To gain meaningful insight into the structural and morphological changes in DNA produced by metal binding, AFM studies should be carried out on DNA samples both before and after exposure to metal ions. The following sections discuss AFM studies of DNA before and after interaction with Cu^{2+}, and Ag^{+} ions.

3.2.3.1 AFM Studies of DNA-Cu^{2+} Interactions

The binding of Cu (II) cations to the DNA structure mainly takes place via coordination with donor atoms of the DNA bases as well as with oxygen atoms of the phosphate backbone [16]. This can induce structural and morphological alterations in DNA, including condensation, clustering, bending, or breaking apart of DNA strands [59, 60]. AFM makes it possible to directly observe how Cu^{2+} binding alters the structure and morphology of DNA [16].

In order to elucidate changes in DNA structure, AFM imaging was conducted on both bare DNA and DNA treated with an aqueous solution containing Cu^{2+}, followed by subsequent chemical reduction [16]. AFM images of DNA after chemical treatment showed noticeable changes in structural morphology, including an increase in DNA height from 1.0–1.5 nm prior to exposure to metal ions, to 2.5–7.0 nm after copper binding (see Figure 6). Such an increase in DNA height is likely as a result of the binding of copper to the DNA structure. Additionally, a number of grains were detected within the DNA strands, exhibiting a morphology similar to "beads-on-a-string" (zoomed-in region in figure 6b).

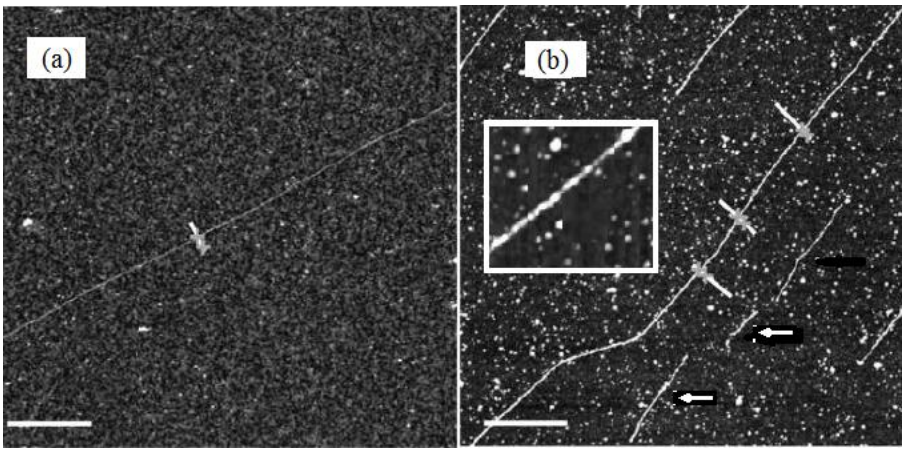

Figure 6: AFM images of DNA alone (a), and DNA after exposure to chemical treatment with $Cu(NO_3)_2$, and ascorbic acid (b). A section of DNA/Cu structure highlighting the "bead-on-a-string morphology" is shown in the inset image [16].

These grains are created as a result of a substantial portion of the DNA strands being split and subsequently collapsing [60, 61]. Moreover, figure 6b shows structures with small lengths (indicated by the white arrow). The appearance of such small fragments can be attributed to non-specific cleavage, resulting in the breaking of DNA strands [59, 60].

Furthermore, AFM imaging shows that the attachment of Cu(II) ions to DNA results in the formation of an irregular network structure (see Figure 7b). This irregularity likely arises from the ability of Cu^{2+} to coordinate with the electron-rich sites on the bases, disrupting base pairing and locally destabilizing the double helix. Such disruption creates of nucleation sites that can interact with other base regions, and as crosslinking increases, a DNA network structure is formed [62].

3.2.3.2 AFM Studies of DNA-Ag^{+} Interactions

AFM enables the direct observation of structural alterations in DNA when it interacts with silver(I) ions. The binding of Ag^{+} causes structural changes and compaction or aggregation of DNA strands, likely due to its interaction with nitrogen atoms in DNA bases, which partially disrupts base pairing and helix stability [63, 64].

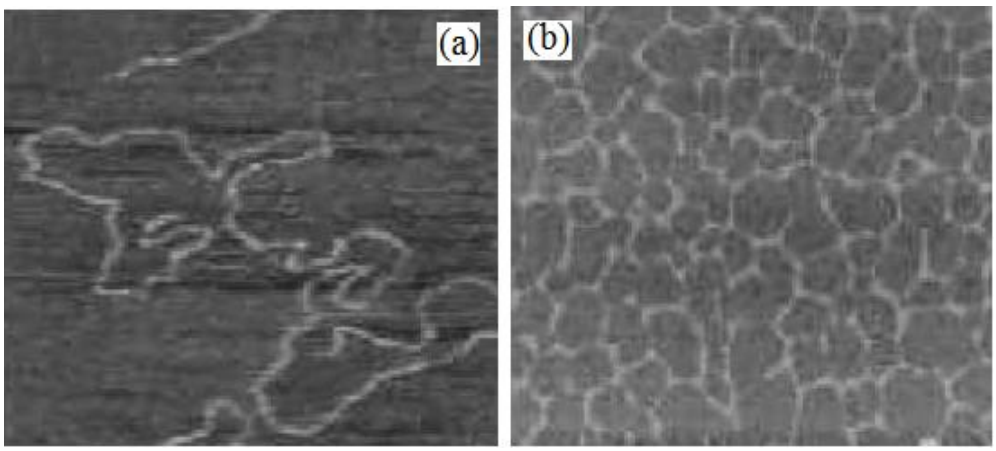

Figure 7: AFM image of DNA alone (a), and DNA-Cu(II) ions [62].

In the study of DNA interaction with Ag(I) ions, AFM imaging reveals significant morphological changes upon Ag^+ binding. AFM images of DNA/Ag^+ complexes at different metal ion concentrations are depicted in Figure 8. Prior to exposure to Ag^+ ions, DNA molecules exhibited a random coil structure with a height of 0.18 nm (Figure 8a). In contrast, after chemical treatment with Ag^+ ions, the DNA structure showed notable alterations. At low Ag^+ concentration (Figure 8b), DNA maintained a predominantly linear structure with a height of 1.25 nm but showed signs of partial collapse and compaction. As the concentration of Ag^+ increased (Figure 8c), the DNA gradually formed globular, particle-like structures with a height of 1.52 nm, indicating pronounced compaction and eventual strand condensation. Overall, the increase in DNA/Ag^+ complex height suggests enhanced molecular compaction [63].

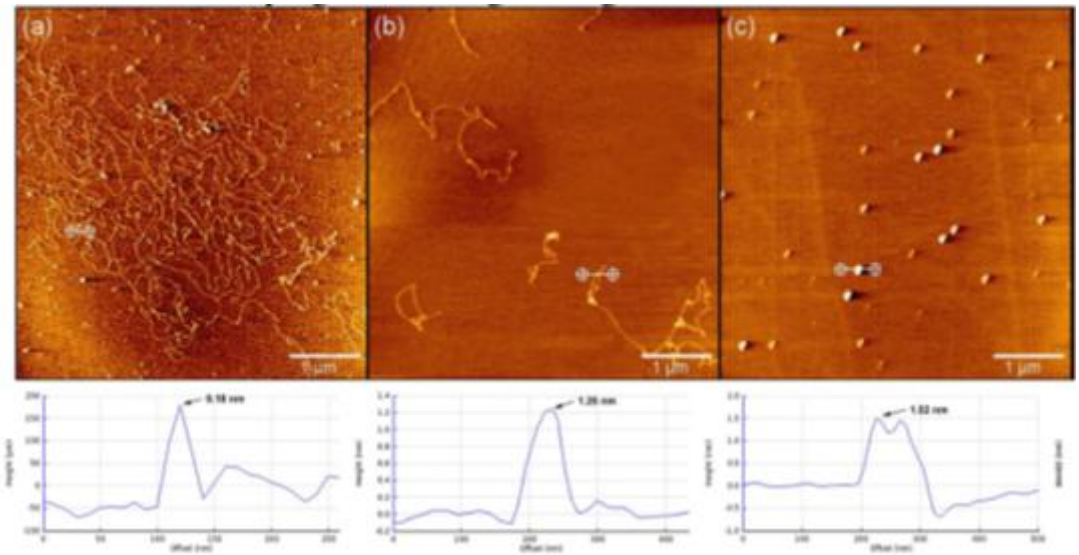

Figure 8: Selected AFM images of (a) bare DNA, (b) DNA/Ag^+ complexes at [Ag^+] = 1 μM, and (c) DNA/Ag^+ complexes at [Ag^+] = 10 μM. Corresponding cross-sectional profiles are shown below each image [63].

FM imaging shows that binding Ag^+ to poly(dGdC) does not alter the DNA's contour length or height. Although the overall structure remains stable, Ag^+ binding is likely to cause a shift in one nucleotide along the strand, bringing the C–C and G–G bases into alignment between the strands. These incompatible pairs are held together through Ag^+ coordination, showing a thermodynamic preference for C–Ag^+–C and G–Ag^+–G pairings instead of the conventional GC base pairs [65].
A comparative summary of the AFM Findings of Cu(II) vs. Ag(I)–DNA interactions is presented in table 2.

Table2: Comparison of the AFM results for Cu(II) vs. Ag(I)–DNA interactions

Feature	DNA-Cu^{2+} Interactions	DNA-Ag^+ Interactions
Principal sites of binding	Interacts with the oxygen atoms of the phosphate backbone and donor atoms of DNA bases.	Primarily binds to the nitrogen atoms of DNA bases; it can create mismatched pairs C–Ag^+–C and G–Ag^+–G.
Morphological Effects	Causes condensation, clustering, bending, and fragmentation of DNA strands; produces "beads-on-a-string" morphology	Induces compaction and aggregation; at higher concentrations forms globular, particle-like structures
Height Changes	Increases from ~1.0–1.5 nm (bare DNA) to 2.5–7.0 nm after Cu^{2+} binding	Increases from ~0.18 nm (bare DNA) to ~1.25 nm at low [Ag^+], and ~1.52 nm at high [Ag^+].
Fragmentation	Significant strand breakage and formation of small fragments due to non-specific cleavage.	No major fragmentation reported; compaction without extensive breakage.
Network formation	Creates irregular, uneven DNA network structures via crosslinking from multiple Cu^{2+} coordination sites	Maintains general contour length at low [Ag^+], but shifts nucleotide alignment (C–C and G–G base pairing) without extensive network formation
Helix Stability Impact	Disrupts base pairing, locally destabilizing double helix; nucleation sites lead to network growth	Partially disrupts base pairing; promotes non-canonical C–Ag^+–C and G–Ag^+–G alignments, altering pairing specificity

According to AFM investigations, Ag^+ mostly promotes regulated compaction and altered base pairing with little disruption of the backbone, while Cu^{2+} causes substantial DNA damage and network formation.

4. Linking AFM and FTIR Results of DNA-Metal Ions Interactions

It is crucial to understand the interactions between metal ions and DNA in order to explain their roles in biological function, structural alterations, and possible nanotechnological applications. To understand such reactions, FTIR and AFM can be used as complementary techniques. With remarkable resolution and accuracy at the nanoscale, AFM can offer crucial information about DNA structural changes [66]. FTIR spectroscopy can provide insight into structural modifications of DNA upon metal ion binding and help identify specific binding sites by analyzing changes in the intensity and position of DNA-related bands [41, 67].

By combining the structural and morphological findings obtained from AFM imaging with the specific binding site information delivered by FTIR, the reaction mechanism between metal ions and DNA, as well as their effects on DNA structure, can be elucidated. For example, compact globular forms of DNA condensation may be detected in AFM, while FTIR data reveal alterations in the intensity and/or band position of the phosphate stretching bands, suggesting the binding of metal cations to the phosphate groups of the backbone. Similarly, FTIR can confirm the binding of metal ions with donor atoms in DNA bases by detecting changes in the spectral features of the base-related bands, while AFM concurrently shows disruption of base pair hydrogen bonding and destabilization of the double helix. The impact of metal ions on DNA structure, which is significant in areas spanning from biophysics to nanomedicine, can be demonstrated using the combination of AFM and FTIR techniques.

4.1 Correlating FTIR and AFM Findings on DNA-Ag^+ Interactions

AFM enables direct observation of structural changes in DNA upon binding with Ag^{+1} ions. The interaction occurs because Ag^+ binds to nitrogen atoms in DNA bases, partially disrupting base pairing and helix stability. This disruption leads to structural alterations, resulting in DNA strand compaction or aggregation. Ag^+ binding induces significant structural changes in DNA, as demonstrated by AFM imaging. At low metal ion concentrations, DNA maintains a linear shape with a height of 1.25 nm; however, it begins to exhibit signs of partial collapse and compaction. As the concentration of Ag^+ increases, there is a clear trend toward further compaction and eventual strand condensation, resulting in the gradual formation of globular, particle-like structures [63, 64].

FTIR studies, in turn, offer molecular-level indications of DNA-Ag^+ interactions. Ag^+ ions, regardless of their concentration, preferentially bind to nitrogen-containing bases in DNA [17, 68, 69]. Silver primarily binds to the N7 site of guanine at low Ag^+ concentrations, as shown by FTIR analysis of DNA–Ag^+ interactions. This is demonstrated by a downshift (from 1717 to 1712 cm^{-1}) and an increase in the strength of guanine-related bands. As the Ag^+ ion concentrations rise, the adenine peak at 1609 cm^{-1} shows a notable increase in intensity, along with a shift to a lower wavenumber (1600 cm^{-1}). This suggests that the Ag cation attaches to the N7 position of adenine bases. Remarkably, despite these interactions, the DNA maintains its B-form structure. This is evident from slight changes in the intensity and position of the sugar-phosphate backbone-related bands that are detected [17].

Integrating AFM and FTIR findings provides a comprehensive understanding of the changes in DNA structure induced by Ag(I) cations. At low concentrations of metal ions, AFM imaging reveals a linear-shaped structure of DNA with partial collapse and compaction. With increasing Ag(I) concentration, further compaction and eventual strand condensation result in the gradual formation of globular, particle-like structures. These alterations in DNA morphology are in accordance with FTIR data. By analyzing FTIR spectra, it is found that Ag(I) cations interact with nitrogen-containing bases in DNA. At low metal ion concentrations, the FTIR spectrum of the DNA/Ag^+ complex reveals a spectral alteration in the guanine-related bands, indicating that silver binds especially to the N7 site of guanine. As the Ag^+ ion concentration increases, the adenine band shows a downshift with a rise in intensity, suggesting further interaction with adenine.

Although these interactions take place, the DNA retains its B-form structure, with only minor changes observed in the sugar-phosphate backbone bands. Combined AFM and FTIR results indicate that of silver cations binding disrupts base pairing and induces subtle backbone changes detectable at the molecular level by FTIR. These molecular changes corresponding to the compaction and condensation observed at the nanoscale with AFM.

4.2 Linking FTIR and AFM Results of Interactions Between DNA and Cu^{2+} Ions

The binding of Cu(II) cations to DNA mainly occurs via coordination with donor atoms of DNA bases and the oxygen atoms of the phosphate backbone. This interaction induces structural and morphological modifications in DNA, including condensation, clustering, bending, and fragmentation of the DNA strands. AFM allows direct imaging of these changes by comparing bare DNA with DNA treated with an aqueous solution containing Cu^{2+} ions followed by chemical reduction. AFM images of DNA/Cu structures reveal noticeable changes in structural morphology, such as an increase in DNA height, suggesting metal ion binding. Furthermore, many grains shaped like "beads-on-a-string" were found inside the DNA strands, indicating strand breakdown and cleavage. The reason for these structural disturbances is that Cu^{2+} coordinates with bases that have many electrons, which destabilizes base pairing and encourages crosslinking, creating asymmetrical DNA networks [16].

FTIR spectroscopy is a widely used technique for clarifying copper-DNA interactions, providing valuable molecular insights. The FTIR data reveal that DNA/Cu^{2+} coordination occurs when copper ions bind to the oxygen atoms of the phosphate groups in the DNA backbone and to the nitrogenous bases of the DNA molecule. This coordination is supported by several spectral changes: the P–O/C–O stretching shifted to 1063 cm^{-1}, the asymmetric PO_2^- vibration shifted from 1248 to 1242 cm^{-1}, and the PO_2^- symmetric stretch significantly decreased at 1096 cm^{-1}. Evidence of Cu^{2+} coordination with DNA nucleobases is indicated by reduced intensity and frequency shifts in the 1300–1750 cm^{-1} region of the spectrum, corresponding to nucleobase vibrations. Specifically, the in-plane vibrations of cytosine and guanine shift to higher wavenumbers, while the frequency of the guanine ring vibration decreases. The combination of AFM and FTIR techniques provides a comprehensive understanding of the molecular and structural effects of Cu(II) on DNA. This dual approach enhances our knowledge of metal-DNA interaction mechanisms and their applications in fields such as nanostructure development, metal-based medicines, and biosensors.

5. Technological and Medical Applications Based on DNA-Metal Ion Interactions

5.1 DNA-Directed Fabrication of Nanostructures

The design and creation of DNA-based nanostructures have been made possible by the interaction between metal ions and DNA [70]. Specifically, DNA has been used as a programmable framework for the creation of two- and three-dimensional nanostructures due to the coordination of metal ions or metallo-ligands to specified sites within DNA. These modified DNA structures demonstrate enhanced thermal stability, with melting temperatures up to 40 °C higher than those of native DNA [71].

There is encouraging potential for using DNA in nanotechnology through the creation of metal-mediated base pairs, which are formed by inserting metal ions (such as Ag^+, Cu^{2+}, and Hg^{2+}) between DNA base pairs [70]. A self-complementary DNA oligonucleotide containing three central imidazole nucleotides adopts a hairpin shape in the absence of metal ions. However, when Ag(I) ions are introduced, imidazole–Ag^+–imidazole base pairs are formed, resulting in the formation of a duplex [72]. DNA-metal nanostructures offer significant potential, especially for developing molecules with customized electrical properties [70]. The following section discusses the fabrication of one-dimensional nanostructures based on metal ion-DNA interactions, along with their applications.

5.1.1 Fabrication and Applications of One-Dimension Nanostructures

Due to its unique characteristics, DNA is an ideal material to use as a guide for creating one-dimensional nanostructures (1-D NSs). With a diameter of 2 nm and lengths varying from nanometers to microns, DNA molecules are high-aspect-ratio structures, making them ideal for regulating material growth into 1-D shapes [5, 6, 73]. Moreover, there are numerous methods to seed DNA with various chemical species, due to the diverse chemical functionalities provided by nucleosides and anionic phosphodiester groups. Transition metal ions are among the chemical species that can be attached to the DNA structure through coordination with donor atoms of phosphate backbone and/or nitrogenous bases. The interaction between metal ions and DNA is a key step in fabricating various one-dimensional nanostructures (1-D NSs), such as one-dimensional metallic copper nanostructures (Cu-NSs) [16], metallic iron nanowires (Fe-NWs) [18], and metallic rhodium nanowires (Rh-NWs) [74], through metal ions binding and subsequent conversion. These nanostructures have distinctive shapes that make them especially useful electronics, photonics, and sensing applications [7, 75, 76].

The fabrication of 1D-NSs composed of metallic or binary inorganic compounds through interactions between metal ions and DNA typically involves a two-step process. In the first step, metal ions (e.g., Ag^+, Fe^{2+}, Cu^{2+}, Rh^{3+}) bind to DNA through both covalent and noncovalent interactions. The second step involves a chemical reduction or precipitation process, resulting in the formation of continuous metallic or inorganic one-dimensional nanostructures (1D-NSs), see figure 9 [5, 77].

For fabricating 1D nanostructures composed of metal-based compounds, such as metal oxides or metal sulfides, a DNA/metal ion (DNA/M^{n+}) complex is first prepared by treating DNA with M^{n+} ions under controlled conditions. The DNA/M^{n+} system is then converted into 1-D nanostructures of the desired metal oxide or sulfide through the addition of appropriate precipitation agents, such as hydroxide or sulfide anions, respectively. DNA-metal ion interactions cab be considered a novel strategy in bottom-up nanofabrication and have been successfully used to fabricate a number of 1-D binary semiconductor nanostructures [5, 77].

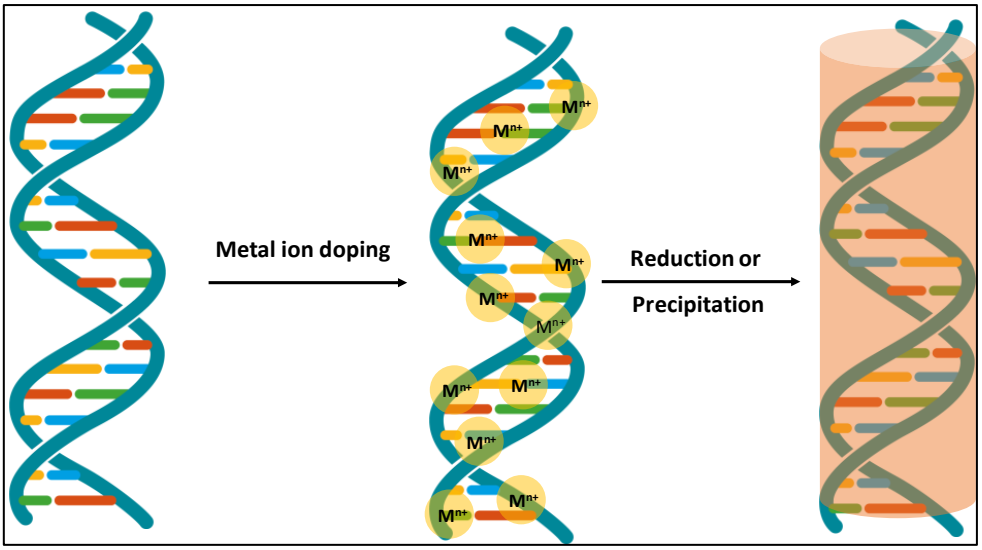

Figure 9: Scheme presenting the two-step process used for the fabrication of DNA-templated metallic and binary inorganic 1-D nanostructures.

Metal oxides such as Cu_2O/DNA [78], and Fe_3O_4/DNA nanowires [58] represent one class of binary semiconductors synthesized using DNA-templated nanofabrication. This class of materials could be technologically significant in the field of nanotechnology. Magnetite nanowires Fe_3O_4/DNA nanowires are particularly attractive for a range of applications, including the delivery of medications, diagnostic imaging, and bioseparation, due to their special electrical, optical, and magnetic characteristics [79-85]. CdS/DNA [86] and CuS/DNA [87] are examples of metal sulfide nanostructures with linear geometries created based on metal ion-DNA interactions. These binary compounds have potential applications in chemical detectors, biological probes, photonics, and semiconductor technology [88-90].

By first doping the metal ion of interest and then reducing it to the zerovalent metal, the two-step method for creating one-dimensional metal nanostructures takes advantage of DNA's metal-ion binding capabilities. Seeding DNA with metal ions can be achieved either by stretching DNA on a substrate or by combining DNA with the applicable metal cations in solution [77]. Subsequent chemical [16, 74] or electrochemical reduction [18] of metal-bound DNA results in the formation of metal nanoparticles along the DNA strand. Under favorable conditions, these nanoparticles will eventually merge to form a nanowire-like morphology [5]. The use of doping/reduction methods has been employed for the formation of a range of 1-D metal nanostructures including, silver [91], palladium [92-95], copper [16, 96, 97], iron [18], and rhodium [74].

FTIR spectroscopy has been performed on DNA/M^{n+} complexes to confirm the binding of metal ions to DNA [16, 18]. The FTIR spectra show shifts and intensity changes in vibrational bands associated with the phosphate groups and nitrogenous bases of the DNA structure. AFM imaging has been employed on the DNA/metallic system after reduction confirms the formation of continuous 1-D nanostructures [74, 77].

When metals are confined to the nanometer scale, they exhibit a range of unique properties that are not always present in their bulk counterparts [98-103]. These properties include photothermal properties [104], fluorescence [105], and optical properties such as plasmon resonance bands [106]. They also offer a method to further reduce the size of existing technologies, including electronics [107]. Moreover, metal nanostructures have distinctive properties in nanoelectronics and photonics, making them good candidates for use in numerous fields including catalysis [108], energy storage [109], nanobiomedicine [110],and nanorobotics [111].

5.2 Application of DNA/Metal Ions Complexes in Medicine

Platinum-based metal complexes are already used in anticancer therapy, and other metal complexes are being investigated for clinical applications. These drugs function by creating cross-linking adducts with DNA, which causes structural alterations such folding or kinking that prevent DNA transcription and disrupt biomolecular recognition. Compared to Pt(II) compounds like cisplatin (figure 10), Pt(IV) complexes such as iproplatin and tetraplatin (figure 10), display potential as anticancer medicines. Their octahedral structure may decrease susceptibility to substitution reactions, thereby reducing toxicity and improving therapeutic effectiveness. The development of improved metal-based anticancer treatments has been motivated by the limitations of platinum-based drugs, such as their reduced efficacy and adverse side effects [70]. Two medications based on ruthenium have advanced to various phases of clinical trials. Additionally, several other metal complexes, including various metal ions, are currently undergoing clinical evaluation [112, 113].

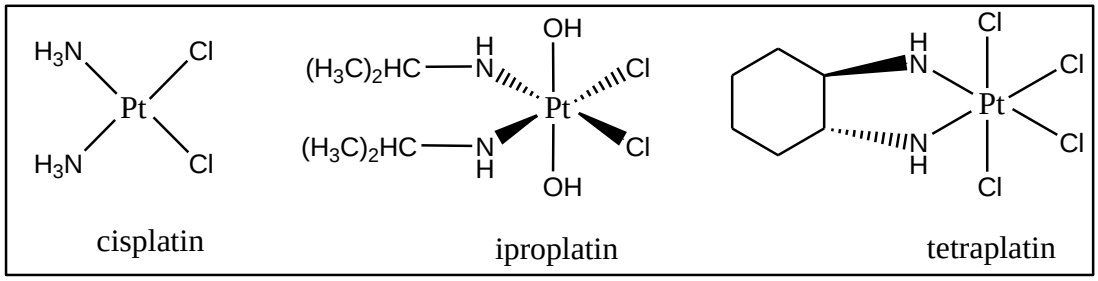

Figure 10: Structures of platinum drugs.

6. Conclusions

Transition metal ions interact with DNA through various mechanisms, including direct coordination with the backbone phosphate groups and the bases donor atoms, electrostatic forces, and binding within the grooves of the helix. These interactions can significantly change the shape of DNA, stability, and function. FTIR and AFM provide complement understandings: FTIR identifies the binding locations and chemical nature of interactions, whereas AFM discovers the resulting changes in DNA structure. When comparing Cu^{2+} and Ag^{+} ions, their effects on DNA are significantly different. Silver binds more precisely to guanine and maintains the DNA B-form, whereas copper frequently binds at many sites, often causing structural disruption and oxidative damage. Recognizing these differences is important for both biomedical research and the precise fabrication of DNA-templated nanostructures. Insights from combining AFM and FTIR deepen our knowledge of how metals interact with DNA, and they open up exciting applications in nanotechnology, sensing, and novel metal-based therapies. To gain a better understanding of DNA–metal ion interactions, future research should combine unconventional spectroscopic, imaging, and computational techniques. Linking laboratory results to biological significance can be enhanced by extending research to less-studied metals and carrying out in situ tests in physiological conditions.

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