Spectroscopic Studies of Mg^{2+} & Ca^{2+}-Metal ions and Cytidine 5'-triphosphate (CTP) Interactions

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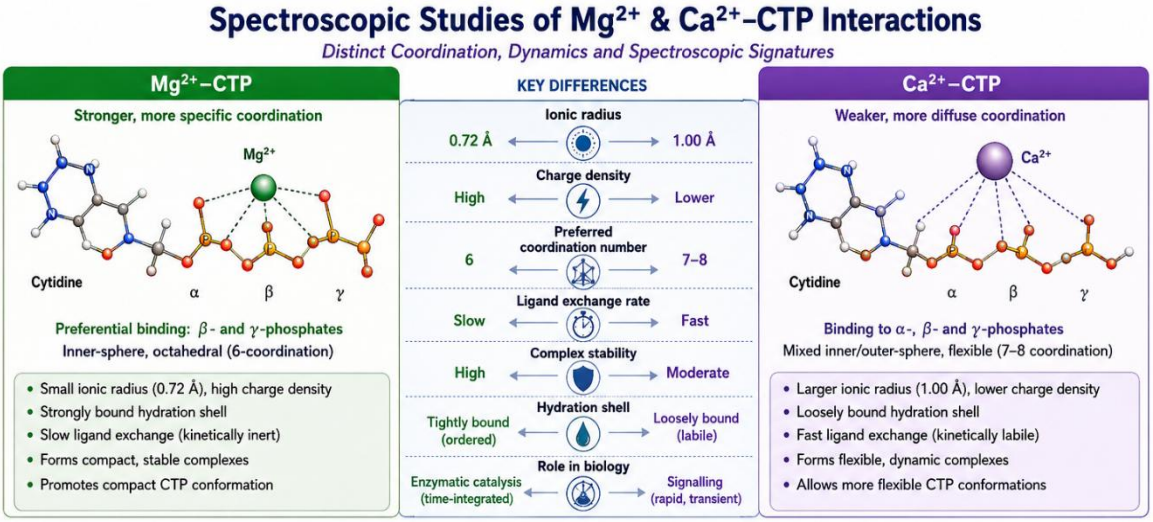
ABSTRACT

The interaction between divalent metal cations, specifically magnesium (Mg^{2+}) and calcium (Ca^{2+}), and nucleotides like cytidine triphosphate (CTP) is fundamental to numerous biological processes, ranging from enzymatic catalysis to nucleic acid stabilization. Key advances include the application of ultrafast two-dimensional infrared (2D-IR) spectroscopy to probe phosphate-ion interactions in aqueous environments and the development of high-field, dynamic nuclear polarization (DNP)-enhanced NMR techniques for challenging quadrupolar nuclei such as ^{25}Mg and ^{43}Ca. Computational approaches, particularly Density Functional Theory (DFT) and Molecular Dynamics (MD) simulations, have become indispensable for interpreting complex spectroscopic signatures and providing atomistic details of binding modes. Comparative analysis reveals that Mg^{2+} typically prefers inner-sphere coordination to the phosphate groups of CTP, forming stable tridentate complexes that are crucial for enzymatic catalysis. Mg^{2+} coordination serves not merely as structural support but actively participates in transition state stabilization and nucleophilic activation in enzymes such as 2-C-methyl-D-erythritol-4-phosphate cytidyltransferase. In contrast, Ca^{2+} exhibits more flexible binding patterns, often involving outer-sphere interactions or coordination with ribose and nucleobase moieties, making it suitable for dynamic signalling roles. Mg^{2+} possesses a high dehydration energy (~450 kcal/mol) and a rigid octahedral coordination sphere, resulting in slow ligand exchange kinetics. Ca^{2+}, with lower dehydration energy and a more flexible coordination environment (6-8 water molecules), exhibits faster exchange dynamics. Recent 2D-IR studies have provided direct evidence of these dynamics, revealing that contact ion pair (CIP) formation is rare for Mg^{2+} but more frequent for Ca^{2+} in aqueous solutions.

Current challenges include the low sensitivity of metal-direct NMR spectroscopy and the need for more accurate solvation models in theoretical studies.



Keywords: Mg^{2+}-CTP coordination, Ca^{2+}-nucleotide interactions, 2D-IR spectroscopy, DNP-enhanced NMR, DFT calculations, enzymatic catalysis, metal hydration dynamics, phosphate coordination chemistry.

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INTRODUCTION

Metal-Nucleotide Interactions and Biological Significance: Metal ions are essential components of the cellular environment, playing diverse roles in the structural integrity and functional regulation of nucleotides and nucleic acids. Among these, divalent cations—particularly Magnesium (Mg^{2+}) and Calcium (Ca^{2+})—are of paramount importance due to their high charge density and ability to neutralize the negatively charged polyphosphate backbone of nucleotides [1], [2].

Biological Significance of Mg^{2+} and Ca^{2+}: Magnesium is the most abundant divalent cation in cells, with total concentrations in the millimolar range, though the free concentration is significantly lower. It serves as a vital cofactor for thousands of enzymes, including those involved in DNA replication, transcription, and energy metabolism [15], [29]. The role of Mg^{2+} extends beyond simple charge neutralization, it is actively involved in the chemistry of phosphate transfer, stabilizing the transition states through precise coordination with the triphosphate tail of ATP and CTP [6], [16]. The structure of Adenosine 5'- triphosphate is shown below:

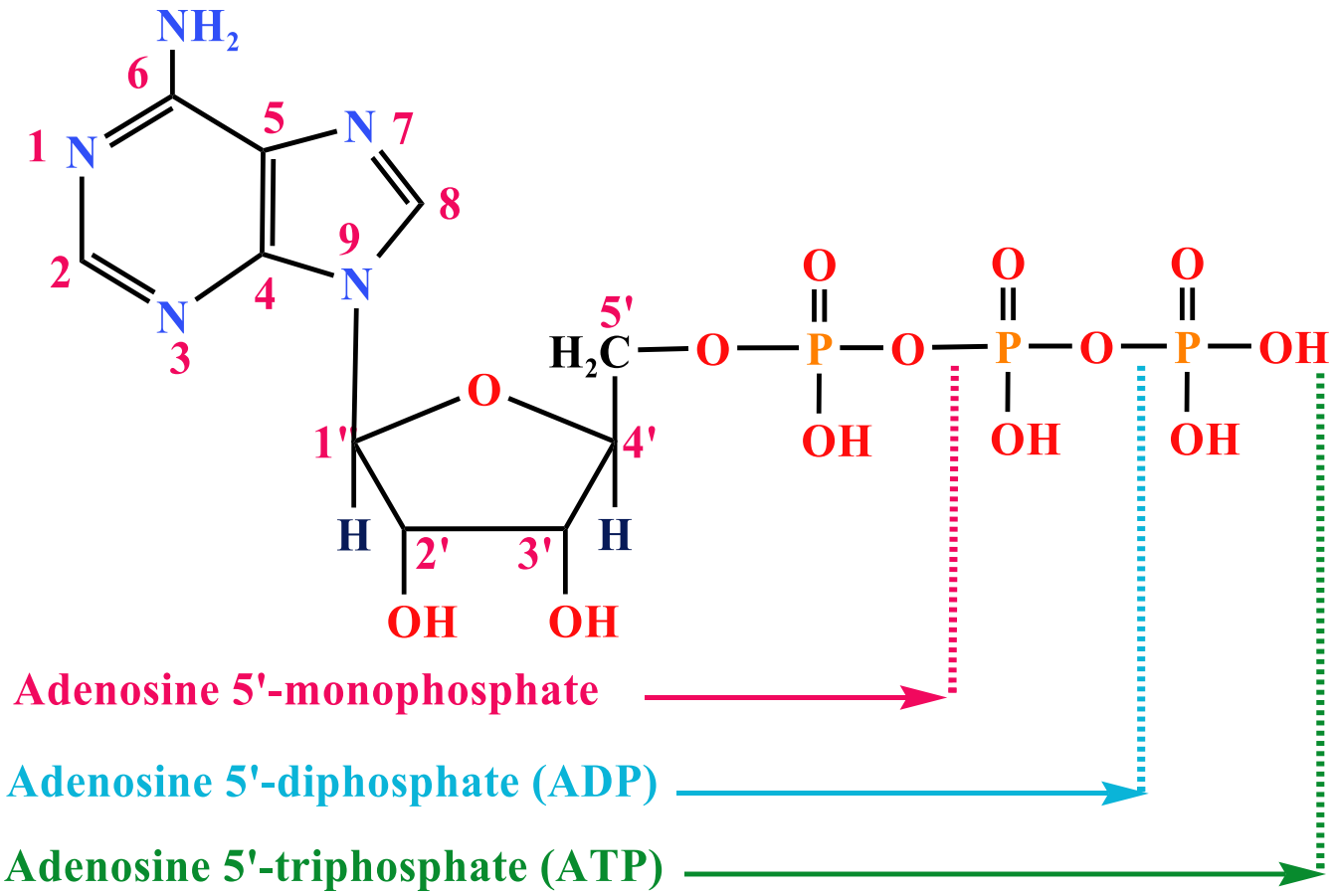

Figure 1. Chemical Structure of Adenosine

Calcium, while often maintaining lower intracellular concentrations (nanomolar range for free Ca^{2+}), plays a critical role in signalling and structural stabilization. In specific compartments or during signalling events, Ca^{2+} concentrations can rise, leading to competition with Mg^{2+} for nucleotide binding sites [15], [27]. This competition is a key regulatory mechanism in cellular signalling and is influenced by the differential hydration energies and ionic radii of the two cations [16], [30]. For instance, the preference of cellular triphosphates for Mg^{2+} over Ca^{2+} is dictated by the charge and denticity of the phosphate ligand, as well as the solvent exposure of the binding pocket [16].

The Role of Cytidine Tri-Phosphate (CTP) in Cellular Metabolism: CTP is a crucial nucleotide involved in several key metabolic pathways. It is essential for the synthesis of RNA and serves as a high-energy donor for the synthesis of phospholipids (e.g., CDP-choline) and the biosynthesis of isoprenoids through the non-

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mevalonate pathway [6], [38]. In the latter, the enzyme 2-C-methyl-D-erythritol-4-phosphate cytidyltransferase (IspD) utilizes CTP and MEP as substrates, requiring Mg^{2+} for activity. Structural studies of the IspD/CTP-Mg^{2+} complex have shown that the metal ion is critical for orienting the CTP molecule and activating the α-phosphate for nucleophilic attack [6]. The Chemical structure of Cytidine 5'-Triphosphate (5'-CTP) is shown below:

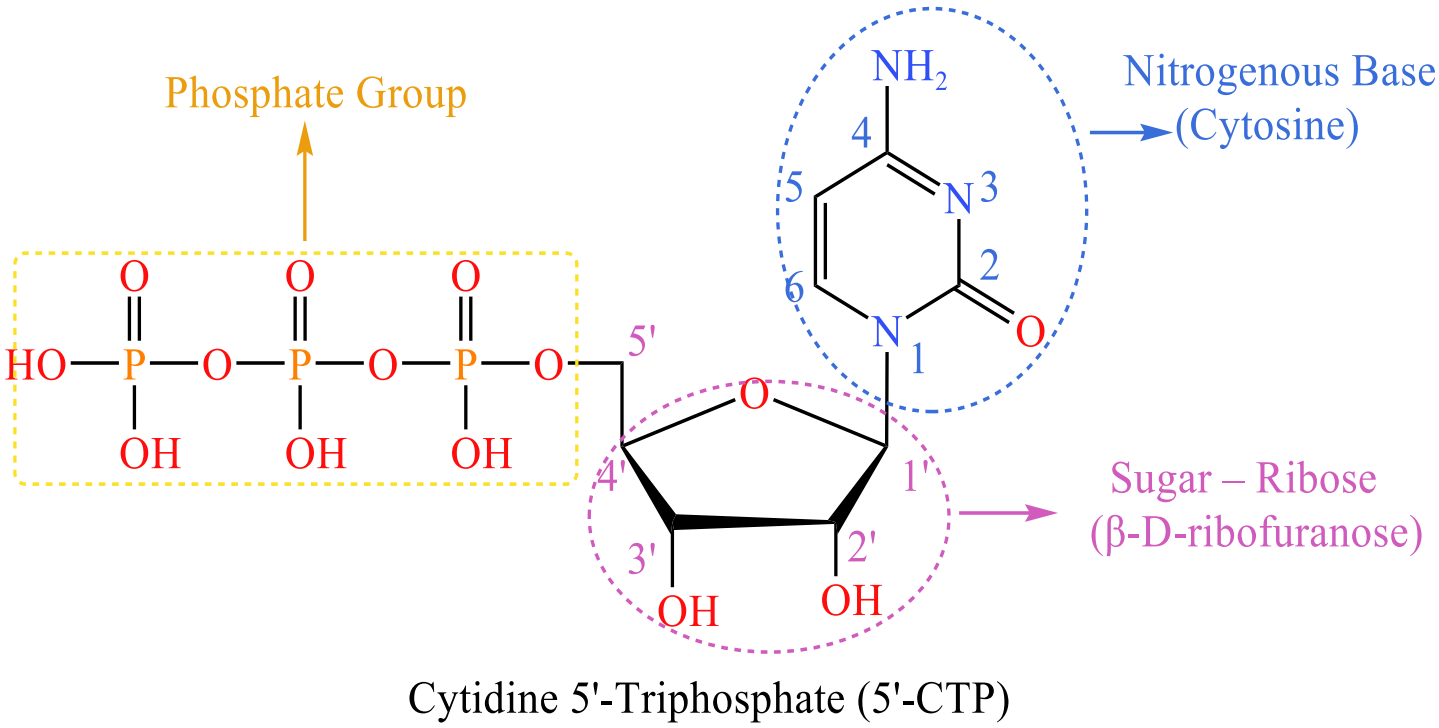

Figure 2. Chemical Structure of Cytidine 5'-triphosphate

Charge Neutralization and Catalytic Activation: Nucleotides like CTP possess a highly negative charge concentrated in the triphosphate tail. In the absence of metal ions, the electrostatic repulsion between the phosphates and incoming nucleophiles would prevent reaction. Mg^{2+} and Ca^{2+} alleviate this by coordinating to the oxygen atoms of the phosphate groups, effectively lowering the activation energy for hydrolysis or group transfer reactions [1], [15]. Recent theoretical studies suggest that the coordination mode (bidentate vs. tridentate) significantly influences the catalytic efficiency, with Mg^{2+} often favouring a tridentate (α, β, γ) arrangement in enzyme active sites [6], [15].

SPECTROSCOPIC TECHNIQUES FOR STUDYING METAL-NUCLEOTIDE INTERACTIONS

The characterization of metal-nucleotide complexes requires a suite of techniques capable of resolving specific binding sites, coordination geometries, and the rapid dynamics of ligand exchange in aqueous environments.

Vibrational Spectroscopy: IR, Raman, and 2D-IR: Vibrational spectroscopy remains one of the most accessible methods for studying the interactions between divalent metals and the phosphate/base moieties of nucleotides [4], [28].

Fourier Transform Infrared (FT-IR) Spectroscopy: Changes in the antisymmetric (ν_{as}) and symmetric (ν_s) stretching frequencies of the $-PO_2^-$ and $-PO_3^{2-}$ groups are indicative of metal binding. For example, a shift to higher frequencies in the $\nu_{as}(PO_2^-)$ band upon the addition of Mg^{2+} or Ca^{2+} typically indicates inner-sphere coordination [11], [28]. Studies on 5'-CMP have shown that different divalent metals induce distinct shifts, allowing for the discrimination of binding affinity [28] which structure is shown below:

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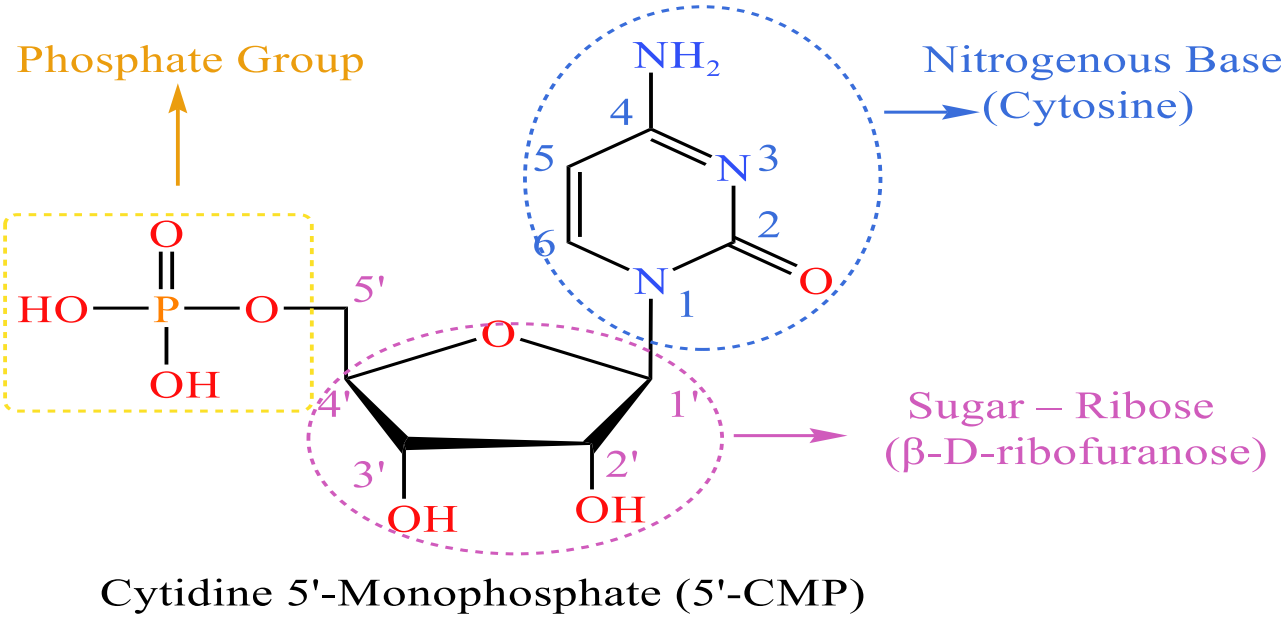
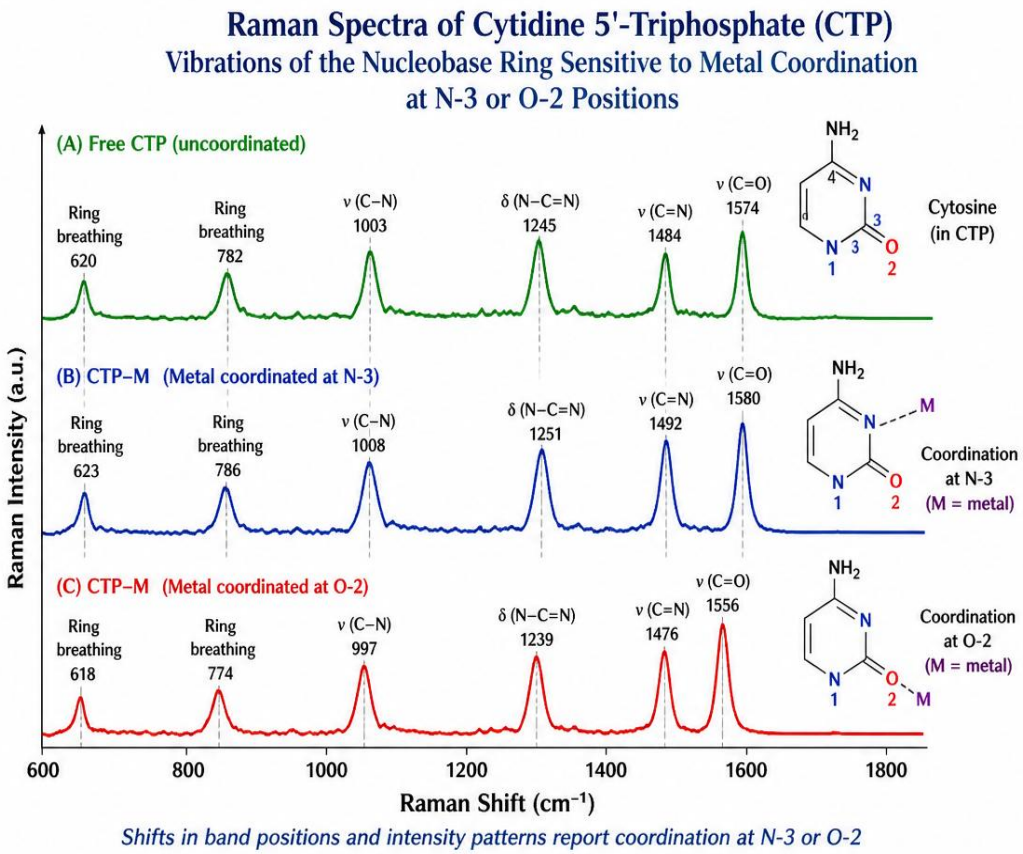


Figure 3. Chemical Structure of Cytidine 5'-monophosphate

Raman Spectroscopy: Raman spectroscopy complements IR by providing information on the polarizability of bonds. It is particularly useful for studying the vibrations of the nucleobase rings, which are sensitive to metal coordination at the N-3 or O-2 positions of cytosine [1], [28].



Shifts in band positions and intensity patterns report coordination at N-3 or O-2

Assignments of Nucleobase Ring Vibrations (Cytosine moiety in CTP)			
Wavenumber region (cm⁻¹)	Vibrational mode	Wavenumber region (cm⁻¹)	Vibrational mode
600 – 650	Ring breathing mode	1220 – 1260	δ (N–C=N) in–plane bending
770 – 800	Ring breathing mode	1450 – 1500	ν (C=N) stretching
980 – 1020	ν (C–N) stretching	1540 – 1600	ν (C=O) stretching

Metal–induced spectral changes (Δ = shift w.r.t. free CTP)		
Mode (approx. position in free CTP, cm⁻¹)	Δ (cm⁻¹) for N-3 coordination	Δ (cm⁻¹) for O-2 coordination
Ring breathing (620)	+3	−2
Ring breathing (782)	+4	−8
ν (C–N) stretching (1003)	+5	−6
δ (N–C=N) in–plane bend (1245)	+6	−6
ν (C=N) stretching (1484)	+8	−8
ν (C=O) stretching (1574)	+6	−18

Spectroscopic indicators

- Coordination at N-3 generally causes upshifts (blue) due to decreased electron density on the ring N and strengthened C=N and C=O bonds.
- Coordination at O-2 causes downshifts (red), most pronounced for ν(C=O).

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Ultrafast 2D-IR Spectroscopy: A significant technological leap in the last decade has been the application of 2D-IR to probe the structural dynamics of ion pairs. Unlike traditional IR, 2D-IR can resolve the coupling between different phosphate vibrations, providing a "fingerprint" for specific contact ion pair (CIP) geometries [10], [18]. Recent studies using 2D-IR have characterized the ligand exchange mechanisms for Mg^{2+} and Ca^{2+}, revealing that Mg^{2+} exchange is governed by a slow, dissociative process due to its tight hydration shell, whereas Ca^{2+} exchange is more rapid [7].

Nuclear Magnetic Resonance (NMR) of Quadrupolar Nuclei: NMR provides unparalleled site-specific information, but the direct study of Mg^{2+} and Ca^{2+} is hindered by their nuclear properties.

^{31}P NMR: This is the most common NMR technique for studying nucleotide-metal interactions. The ^{31}P chemical shifts and relaxation rates are highly sensitive to the proximity of divalent cations, allowing for the determination of binding constants and the identification of the specific phosphate groups (α, β, or γ) involved in coordination [1], [12].

Direct ^{25}Mg and ^{43}Ca NMR: Both ^{25}Mg and ^{43}Ca are quadrupolar nuclei with low natural abundance and low gyromagnetic ratios, leading to extremely weak and broad signals. However, advances in high-field magnets (up to 21.1 T) and Magic Angle Spinning (MAS) have enabled the resolution of ^{25}Mg sites in solid-state complexes of ATP [12]. More recently, the use of Dynamic Nuclear Polarization (DNP) has significantly boosted the sensitivity of ^{43}Ca NMR, allowing for the investigation of calcium complexation in frozen solutions—a method that provides a snapshot of the species present in the liquid state [14].

Computational Modelling: DFT and MD Simulations: The interpretation of complex spectroscopic data is increasingly dependent on theoretical modelling.

Density Functional Theory (DFT): DFT calculations are used to optimize the geometries of metal-nucleotide-water clusters and predict their vibrational frequencies and chemical shifts [15], [20]. Studies have shown that including the first solvation shell (6-18 water molecules) is crucial for accurate predictions [9], [19].

Molecular Dynamics (MD) Simulations: MD simulations provide insights into the dynamic nature of these complexes, capturing the transition between solvent-separated ion pairs (SSIP) and contact ion pairs (CIP) [18], [32]. Polarizable force fields and ab initio MD (AIMD) have been employed to better describe the electrostatic environment of the highly charged triphosphate tail [16].

Mg^{2+} & Ca^{2+} INTERACTIONS WITH CTP

Mg^{2+}-CTP Coordination and Enzymatic Activity: One of the most significant recent findings involves the role of Mg^{2+} in CTP-dependent enzymes. In the structure of Bacillus subtilis IspD (BsIspD), Mg^{2+} is found at the heart of the catalytic site, coordinating to the α, β, and γ phosphates of CTP [6]. This tridentate binding mode is not merely structural; it serves to position the α-phosphate for nucleophilic attack by the MEP substrate. The presence of Mg^{2+} also stabilizes the accumulation of negative charge in the transition state. Interestingly, while Mg^{2+} is the preferred cofactor, its absence or substitution with other metals can significantly inhibit enzyme activity, demonstrating the high specificity of the Mg^{2+}-CTP interaction in biological systems [6], [38]. Theoretical investigations into Mg^{2+} binding modes with ATP and CTP suggest that the tridentate (α, β, γ) mode is the most thermodynamically stable in a low-dielectric environment, such as a protein interior [15]. In water, however, Mg^{2+} may exist in an equilibrium between bidentate (β, γ) and tridentate modes, with the hydration state of the metal ion playing a decisive role in the switching between these configurations [15], [16].

Ca^{2+} Reactivity and Alternative Binding Sites in CMP: While Mg^{2+} has a clear preference for the phosphate backbone, Ca^{2+} exhibits a more promiscuous binding behaviour. In a comprehensive study of Ca^{2+} adducts with cytosine and CMP, researchers identified six new structural motifs [11]. In one complex, $[Ca_2(CMP)_2(H_2O)_{11}]$, the Ca^{2+} ions were found to coordinate to the ribose O2' and O3' hydroxyl groups and the O2 of the cytosine base, while the phosphate groups remained uncoordinated to the metal in that specific arrangement [11]. This

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suggests that Ca^{2+} can bridge different parts of the nucleotide molecule, potentially inducing larger conformational changes than Mg^{2+}, which is shown in below:

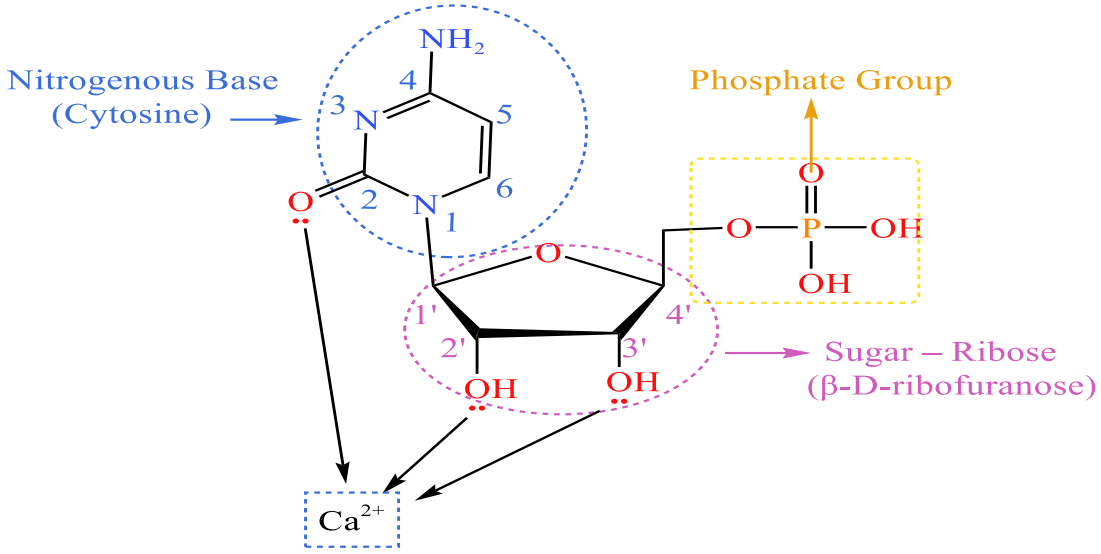

Figure 4. Chemical Structure of expected Complex

Furthermore, comparative studies on phosphor-tyrosine (pTyr) demonstrated that while both Mg^{2+} and Ca^{2+} can form "cation-binding pocket" structures involving the phosphate group and the aromatic ring (cation-π interaction), Mg^{2+} forms a more rigid and stable pocket [8]. The selectivity for Mg^{2+} in these pockets is attributed to its smaller size, which allows for a more compact and energetically favourable arrangement of the side groups [8].

The Role of the Solvation Shell and Hydration Dynamics: The hydration of divalent cations is the primary determinant of their interaction kinetics. Mg^{2+} has a very high dehydration energy (~450 kcal/mol), which results in a rigid first solvation shell of six octahedrally coordinated water molecules [9], [15]. This makes the transition from an outer-sphere to an inner-sphere complex slow. In contrast, Ca^{2+} has a lower dehydration energy and a more flexible coordination shell (typically 6-8 water molecules), allowing for faster ligand exchange [7], [30].

Recent 2D-IR studies on phosphate-Mg^{2+}/Ca^{2+} interactions have provided direct evidence of these dynamics. It was found that for Mg^{2+}, the formation of contact ion pairs (CIP) is a rare event in dilute aqueous solutions, whereas for Ca^{2+}, CIP formation is more frequent and involves a diverse range of geometries [10], [18]. This highlights why Mg^{2+} is often found as a stable part of enzymatic complexes, while Ca^{2+} is better suited for dynamic signalling roles where rapid binding and release are required [16], [30].

COMPARATIVE ANALYSIS OF SPECTROSCOPIC METHODS

A comparative assessment of the major spectroscopic techniques reveals their complementary nature in mapping the landscape of metal-nucleotide interactions.

Sensitivity to Binding Geometry: Vibrational techniques (IR and Raman) are exceptionally sensitive to the immediate coordination environment of the phosphate groups. Shifts in the P-O stretching frequencies can distinguish between monodentate, bidentate, and tridentate binding modes [28]. For example, the splitting of the degenerate antisymmetric stretching mode of the phosphate group is a clear indicator of symmetry breaking upon metal coordination [11], [28].

NMR, particularly ^{31}P and $^{25}Mg/^{43}Ca$, provides a broader structural context. While ^{31}P NMR can indicate which phosphate is coordinated, $^{25}Mg/^{43}Ca$ NMR can directly report on the symmetry and electronic environment of the metal ion itself. The quadrupolar coupling constant (C_Q) derived from metal NMR is a direct probe of the

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deviation from octahedral symmetry, which occurs when water molecules are replaced by nucleotide ligands [12], [14].

Temporal Resolution and Dynamics: The time-scales of these techniques vary by several orders of magnitude. 2D-IR operates on the femtosecond to picosecond time-scale, allowing researchers to observe the ultrafast dynamics of water movement and the short-lived structural fluctuations of ion pairs [10], [18]. In contrast, NMR provides information on the microsecond to second time-scale, which is more relevant for slow ligand exchange processes and the overall stability of complexes in solution [1].

Feature	FT-IR / Raman	2D-IR	NMR (^{31}P, ^{25}Mg, ^{43}Ca)	DFT / MD
Sensitivity	High (Phosphate/Base)	High (Dynamics)	Low to Medium	N/A
Site Specificity	Good	Excellent	Superior	Atomistic
Time Scale	Static/Slow	Ultrafast (fs-ps)	Slow (μs-s)	Variable
Solvent Effects	Indirect	Direct	Indirect	Direct (if modelled)
Primary Limitation	Peak overlap	Technical complexity	Low sensitivity (Mg/Ca)	Model accuracy

The integration of these techniques, as seen in recent studies combining 2D-IR with MD simulations [18] or DNP-NMR with DFT calculations [14], is the most effective strategy for resolving the complexities of these systems.

CURRENT CHALLENGES AND FUTURE DIRECTIONS

Technical Barriers in Metal-Direct NMR: The primary challenge in the field remains the low sensitivity of the metal nuclei themselves. While ^{43}Ca MAS-DNP is a major advance, the requirement for cryogenic temperatures and specialized polarization agents limits its application to specific types of samples [14]. Developing room-temperature sensitivity enhancement methods or more efficient isotope labelling strategies is a priority for future research.

Gaps in Solvation Modelling: Computational chemistry still struggles to accurately model the complex solvation environment of highly charged nucleotides. The use of continuum solvation models often fails to capture the specific hydrogen-bonding networks that stabilize metal-nucleotide complexes [15], [24]. While explicitly including water molecules in the first and second solvation shells helps, the computational cost grows exponentially. There is a need for more efficient multi-scale models that can bridge the gap between quantum mechanical accuracy and molecular dynamics time-scales.

Future Outlook: Toward Real-Time Biocatalysis: The ultimate goal of this research is to understand how metal-nucleotide interactions drive biological function in real-time. Future directions include:

Time-Resolved Crystallography and Spectroscopy: Combining ultrafast spectroscopy with time-resolved X-ray diffraction to "film" the coordination changes during an enzymatic reaction [7].

Single-Molecule Studies: Using fluorescence or force spectroscopy to observe the binding and release of single metal ions from nucleotide complexes, providing insights into the heterogeneity of these processes.

Base-Specific Targeting: Exploiting the subtle differences in metal binding between CTP, ATP, and GTP to design more specific inhibitors for nucleotide-dependent enzymes.

CONCLUSION

The spectroscopic investigation of interactions between cytidine 5′-triphosphate (CTP) and the biologically important divalent metal ions Mg^{2+} and Ca^{2+} demonstrates that both cations strongly influence the structural, electronic, and conformational properties of the nucleotide through coordination with phosphate oxygen atoms.

The study confirms that the triphosphate chain serves as the principal binding region, with preferential coordination occurring predominantly at the β- and γ-phosphate groups.

Mg^{2+}: Slow Ligand Exchange and Time-Integrated Catalysis

Mg^{2+} possesses: a small ionic radius, high charge density, and a very strongly bound first hydration shell.
As a result, water molecules and ligands around Mg^{2+} exchange relatively slowly. This kinetic inertness allows Mg^{2+} to form stable and long-lived coordination complexes with phosphate-containing biomolecules such as ATP, CTP, DNA, and RNA.
Because of this stability, Mg^{2+} is highly suited for: sustained enzymatic catalysis, controlled phosphoryl-transfer reactions, stabilization of transition states, precise substrate orientation in enzyme active sites.
In many enzymes, Mg^{2+} acts as a "molecular anchor," maintaining the correct geometry throughout the catalytic cycle. Its slow ligand exchange prevents random dissociation and ensures accurate time-integrated biochemical processing.
For example: kinases, polymerases, ATPases and ribozymes all rely on Mg^{2+} to stabilize negatively charged phosphate groups during catalysis. The strong Mg^{2+}–phosphate interaction can be represented schematically as:

$$Mg^{2+} + CTP^{4-} \rightleftharpoons [Mg\text{-}CTP]^{2-}$$

This comparatively stable equilibrium reflects slower exchange kinetics and tighter coordination.

Ca^{2+}: Fast Dynamics and Rapid Cellular Signalling

Ca^{2+}, in contrast, has: a larger ionic radius, lower charge density, weaker hydration energy and faster water-exchange kinetics. Therefore, Ca^{2+} complexes are more labile and dynamically reversible. Ligands bind and dissociate rapidly, allowing Ca^{2+} concentrations to change quickly inside cells.
This fast coordination dynamics makes Ca^{2+} ideal for: transient signalling events, rapid conformational switching, neuronal communication, muscle contraction, hormone secretion, and intracellular signal transduction.
Instead of acting as a permanent catalytic anchor, Ca^{2+} behaves as a reversible "signal trigger." Its weakly held coordination sphere enables proteins to rapidly detect changes in Ca^{2+} concentration and convert them into biological responses.
Typical signalling proteins such as: calmodulin, troponin and protein kinase C depend on this rapid Ca^{2+} binding and release behaviour. The dynamic nature of Ca^{2+} coordination may be represented as:

$$Ca^{2+} + L \rightleftharpoons [CaL]^{2+}$$

where rapid forward and reverse exchange support fast signalling cycles.

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