INTERACTION OF OXALIPLATIN WITH DNA: A THEORETICAL STUDY

Abstract

Recent researches on the kinetics and structure of nucleic acids have shown that salt and solvent can affect the shape of the DNA helix. This adaptability causes DNA to fold either smoothly or by abruptly changing the chain direction and creating kinks. In order to elucidate the behaviour of melting and heat capacity of the platinated and unplatinated DNA, a theoretical analysis involving the interaction of the oxaliplatin and its enantiomeric analogue with the DNA duplex is described in the current study. The modified Zimm and Bragg theory is applied for this aim. The study made use of the experimental models developed by Malinaet. al in 1983. The sensitivity parameter (H/σ) has been used to analyse the transition's sharpness. The many metrics for oxaliplatin binding, such as the transition profile, transition sharpness, curves showing heat capacity variation and half width of the curves both are in good accordance with results of the experiments. For a better perception of bimolecular interaction, this theoretical approach can be used, which has implications for the process of developing new drugs.

Keywords: Heat capacity, nucleation parameter, DNA binding, transitionprofile, intercalation, minor groove

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I. INTRODUCTION

DNA is a common abbreviation for deoxyribonucleic acid. Two polynucleotides compose the polymer, which coils to form a double helix. DNA contains genetic information that is necessary for the substantial growth, operation and replication of every known type of organism as well as a large number of viruses. Nucleic acids include Deoxyribonucleic acid (DNA) and Ribonucleic acid (RNA) both. The knowledge of four main kinds of macromolecules namely proteins,nucleic acids, lipids and complex starch such as polysaccharides forms the basis of all living organisms.Nucleotides are basic monomeric building blocks that comprise up each of the two segments of DNA. These segments or more precisely 'strands' are also known as polynucleotides [1,2].Deoxyribose is a type of pentose (five carbons) sugar, one phosphate group, and one nucleobasecontaining nitrogen (cytosine [C], guanine [G], adenine [A], or thymine [T]) combine with each other to make up a nucleotide.

phosphodiester linkage is formed when nucleotides get attached in between the phosphate of one nucleotide and the sugar of adjacent nucleotide. This linkage results in an interspersedbackbone of sugar-phosphate. Hydrogen bonding takes place between nitrogenous bases of two different DNA strands to form a DNA having double-stranded in accordance with base pairing principles (T with A and G with C). Because they move in directions that are contrary to one another, the two strands are antiparallel.

DNA strands are used as a template to create RNA strands. With the exception of thymine (T), where RNA replaces the comparable base with uracil, DNA nucleotides are substituted for their corresponding bases. Transcription is the name of this technique. The genetic code, that dictates how amino acids are arranged in a sequence in proteins, gets translated by these RNA strands. Chromosomes are the lengthy scaffolds of DNA that make up eukaryotic cells. Prior to the normal cell division, these chromosomes are copied as part of DNA replication, giving each daughter cell a full complement of chromosomes.

In eukaryotic organisms (plants,animals, prostists and fungi), the majority of the DNAexist in cell nucleus as nuclear DNA, however few also exist in chloroplast or mitochondrial DNA[3].DNAis stored in cytoplasm as circular chromosomes prokaryotesas well asarchaea and bacteria. Chromatin proteins like histones compress and organizeDNAinside the eukaryotic chromosomes. Sucharrangements after compressionsupport to control the regions of DNAthat are transcribed by the interaction of DNAwith other proteins.

1. **Base Pairing:** A double helix coil of DNAhas only one link between each type of nucleobase on each of its two strands. We use a technique called complementary base pairing to do this. Adenine (A) and thymine (T) createdouble hydrogen bonds while cytosine (C) and guanine (G) nucleobaseform tripple hydrogen bonds.Purines and pyrimidines form single hydrogen bond. A Watson-Crick base pair is used to describe this form of interaction in two nucleotides through the double helix (from ring of six carbons to another ring having six carbons.). DNAhaving a high degree of GC is comparatively steadier than DNA with a low degree of GC content.

   Hoogsteenmodel of base pairing is a special kind of the base pairing that entails hydrogen attaching a ring of 6-carbon atoms to a ring of 5-carbon atoms [4]. Hydrogen

bonds can be easily broken and reassembled because they are not covalent. Thus, the two DNA strands that make up a double helix get splattedinto two similar to zipper by applyingeither high temperature or mechanical force [5]. Because it ensures that every bit of information in a DNA helix's double-stranded sequence is replicated on every strand, this base pair complementarity is necessary for DNA replication. This specific, reversible connection between base pairs is necessary for all of DNA's functions in all animals [6].

2. **Grooves:** The spaces next to the base pair known as the grooves are able to act as binding sites. Tracing the gaps that are known as grooves between the strands may reveal additional strands. These voids close to base pairs, could serve as a site for binding. Because the strands don't getarranged proportionally in relation to one another, the grooves are not all the same size. Themajor groove has widthy 22 Å (2.2 nm), whereas minor groove has width 12 Å (1.2 nm) [7]. It is easier to reach the bases' edges in the main groove since it is wider than the minor groove. The proteinsmay bind to double stranded DNA in a particular sequences like transcription factors. Itusually interacts with base sidewalls exposed in the major groove [8]. The major groove and minor grooves always represent the differences in width that is obvious if the DNAs were perverted back into the typical B form, despite the fact that the peculiar DNA conformations under this situation differ from cell to cell.

3. **DNA Functions:** Two major functions of DNA are as follows:

    - **Transcription:** Ribonucleic acid, or RNA, extracts data from the DNA and uses it to produce proteins in the body. Proteins play a variety of roles in all bodily functions such as receptors, enzymes, transporters, structural proteins, hormones, regulators, etc.

    - **Replication:** DNA can reproduce itself. As was previously mentioned, each strand of DNA's double-helix structure is consist of adenine (A), cytosine (C)thymine (T) andguanine (G) . Phosphodiester connections bind these nucleotides togetherwithin a strand. The two strands are joined to each other mostly by Watson-Crick hydrogen bonds, in which adenineforms double hydrogen bonds with thymineand cytosine form triple hydrogen bonds with guanine. Pairing of the bases AT and G-C Proteins and tiny molecules can specifically recognise DNA sequences by combining the donor or acceptor sites of hydrogen bonds that are present on either the major groove or minor groove.

4. **Interaction Between Drug and DNA:** For cells to survive and grow, as well as for the efficient operation of every biological process, transcription and replication are crucial. DNA doesn't start transcription or replication unless it receives a signal, which is frequently provided by a regulatory protein which binds to a specific region of DNA. Therefore, if a small molecule can match the binding specificity and potency of that regulatory protein, it is possible to control, inhibited, or triggered DNA function artificially by binding the molecule. Therefore, if it is important to cure or manage a condition, this artificial or natural small molecule is able to work as drug by activating or inhibiting DNA function.

Depending on which spot the medicine is targeting, DNA activation may result in DNA replication or a higher production of the essential protein. Cell death would come from DNA inhibition, which would prevent the replication or synthesis of proteins. The majority of the time, DNA inhibition is a process to target to destroy cells of antitumor or antibiotic action.

Drugs are able to bind to DNA through covalent or non-covalent linkages. Cell death is invariably the outcome of DNA covalent binding since it completely limits DNA activity and is irreversible. As an anticancer drug, cis-platin (cisdiamminedichloroplatinum) is a well-known covalent molecule. An intra as well as interstrand cross-link is created when the chloro groups in cis-platin interact with the nitrogens in DNA bases.

The drugs fall into one of the following two categories, which mostly bound non-covalently:

- **Minor Groove Binders:** Drugs having Minor groove binding frequently have forms like crescents, which complement the form of the groove and facilitate van der Waals interactions, which facilitate binding. Adenine and thymine's N_3 and O_2 can be used by these substances to produce hydrogen bonds, which are the most common bases for such bonds to form. A/T rich sequences are the primary binding sites for drugs that bind to minor grooves. Greater Van der Waals interactions between the ligand, groove walls and the steric barrier provided by the C_2 amino group of the guanine base in the A/T groove region explain why it is narrower than the G/C groove region. This preference is in addition to the designed propensity for the electronegative pockets of AT sequences. Lexitropsins and imidazole-pyrrole polyamides, two synthetic polyamides with a focus on the G-C and C-G sections of the grooves, have been developed, though.

  In human genome if a small compounds can bind to some specified DNA sequence in the human genomewith high affinity, they become very useful in molecular biology and possibly in medicine also. Pairing rules are developed to logically regulate the sequence specificity of minor groove-binding polyamides, such as N-methylpyrroleand N-methylimidazoleamino acids [9].

  The dye Hoechst 33258 is probably the minor groove binding chemical that has received the most research to date. Recent studies examined the relationship between this dye and dodecanucleotide [d(CGCAAATTTGCG)2, A3T3] is self complementary[10-12].

  The 3-4-dimethoxybenzylidene-4-aminoantipyrinyl-4-aminoethylphenol(L) Schiff base produced from tyramine and a number of its transition metal complexes of the form, ML_2Cl_2, where M = Cu(II), Zn(II),Co(II), and Ni(II)have been developed and synthesised by Raman *et. al* [13]. The behaviour of these complexes during binding with calf thymus DNA (CT-DNA) were studied using molecular docking analysis, viscosity testing, cyclic voltammetry, and electronic absorption spectroscopy. The results demonstrate that metal (II) complexes interact with DNA

through binding to minor grooves. The antibacterial and antifungal activities were improved as compared to the free ligand.

By triggering apoptosis, S009-131 which is acoumarin-chalcone hybrid, exhibits anti-proliferative and anti-tumor properties. The role of the DNA damage signalling pathway in the S009-131-induced death of cancer cells was investigated by Sarkar*et. al*[14]. They proved that S009-131 harms DNA by perhaps attaching to the minor groove, which phosphorylates ATM and DNA-PK but not ATR to activate them earlier in the DNA damage process.

- **Intercalators:** These have nearby DNA base pair-stacking planar heterocyclic groups. The complex is believed to be stabilised, among other things, by interactions between drugs and DNA bases known as "stacking." Intercalators significantly alter DNA's structural integrity. Considering the medication metabolism and severe side effects, non-covalent binding is often favoured over covalent adduct formation. However, a significant benefit of covalent binders is their strong binding capacity. With binding constants in the nanomolar range, proteins are big molecules that bind to DNA quite strongly. Using tiny non-covalent binders to attain equivalent specificity and affinity has been challenging and continues to be a significant obstacle in the development of medicines for DNA.

  Although intercalators are a significant class of DNA interacting ligands, there have been very few thorough thermodynamic investigations characterising these interactions. There is still a dearth of comprehensive thermodynamic information on intercalation processes, with the exceptional case of daunomycin-DNA interaction. This has been well researched in all respects. Hopkins and Wilson were some of the first people to document a change in the heat capacity of intercalation process.[15]

  In vivo and in vitro, intercalatorscan be often used as fluorescent probes to observe DNA and interaction of DNA with protein. The stability and structure of DNA are known to be disturbed by them, and this can alter how proteins process DNA. To clarify the perturbation by combining single-dye fluorescence microscopy and force spectroscopy, Wuite*e.t al* analyse the dynamics of DNA intercalation using the mono-intercalating and bis-intercalating cyanine dyes SYTOX Orange, SYBR Gold,SYTOX Green, YOYO-1, YO-PRO-1, and POPO-3 [16]. They demonstrated that a significantly tension-dependent dissociation rate primarily controls their DNA-binding affinity. These amounts can be altered over a range having seven orders of magnitude by varying intercalating species, DNA tension and ionic strength. By maximising these rates, intercalator’s impact on the separation of strands and enzymatic activity is lessened.

  To investigate the intercalation of the anticancer medicine doxorubicin (DOX) and its analogue N-(trifluoroacetyl) doxorubicin (FDOX) with DNA duplex, Riahi*et. al* [17] applied FTIR, CD, fluorescence spectroscopy, and molecular modelling approaches. FDOX interaction did not result in any alterations to the DNA's structural makeup, whereas DOX intercalation coupled with a partial B to A-DNA transition did.

A strong anticancer medication called mitoxantrone (MTX) is used to treat specific cancers. For the first time, Fathi*et. al* [18] use spectral fluorescence spectroscopy and SPR (surface plasmon resonance) based techniques to explore the intercalation of anticancer drugs into DNA. This research demonstrates that the primary binding force for intercalating MTX to DNA is hydrogen bonding.

Barone*et. al* [19] used Density functional theory (DFT) to computationally analyse the intercalation of the anticancer drug daunomycin into six stacks of Watson-Crick DNA base pairs (AT-AT, AT-TA, GC-AT, CG-TA, GC-GC, and GC-CG). According to their research, hydrogen interactions between daunomycin and hetero atoms in the minor groove of AT base pairs are important for both the intercalation complexes' overall stability and the sequence specificity that has been calculated and empirically observed.

5. **Crosslinking in DNA:** When different exogenous or endogenous substances interact with two DNA nucleotides, a covalent bond is created between them. This process is known as crosslinking of DNA. This crosslink can happen within the same strand of double-stranded DNA (intrastrand) or between the opposing strands (interstrand). These adduct cause cell death by interfering with biological processes including DNA replication and transcription. Nevertheless, these crosslinks can be removed by excision or recombination mechanisms.

   Additionally, DNA crosslinking is advantageous for chemotherapy and apoptosis targeting of cancer cells as well as for studying how proteins interact with DNA.

   - **Crosslinking Agents:** Many characterised crosslinking agents have two independently reactive groups that can each bind to a DNA nucleotide residue inside the same molecule. These substances are divided into exogenous and endogenous categories based on where they came from. Chemicals and substances, both natural and manufactured, that come from environmental exposures like drugs, cigarette smoke, or vehicle exhaust are known as exogenous crosslinking agents such as Nitrogen musterd, Cisplatin, Mitomycin C, Psoralen etc.. Compounds and metabolites that enter a cell or organism through cellular or biochemical processes are referred to as endogenous crosslinking agents such as Nitrous acid, Bifunctional Aldehydes etc.

6. **Oxaliplatin:** In present study the stability of Oxaliplatin-DNA duplex has been examined theoretically which is a cisplatin exogenous cross linking agent. Oxaliplatin is one of the drug in the class of chemotherapy known as alkylating agents. Oxaliplatin functions by binding to a DNA strand within the cancer cell. Oxaliplatin[trans- (R,R)- 1,2-diminocyclohexaneoxaloplatinum] and its enantiomer[trans- (S,S)- 1,2-diminocyclohexaneoxaloplatinum] marketed as Eloxatin is a antineoplastic agent based on platinum. It is very helpful in cancer chemotherapy.

   It is a new platinum compound of the third generation effective in therapy of colorectal and advanced ovarian cancers. With low haematotoxicity and moderate, controllable gastrointestinal toxicity, it has shown to have an excellent safety profile. The peripheral sensory neuropathy brought on by oxaliplatin, characterised by distal and

perioral dysaesthesia, is generally regressive between treatment cycles and is brought on or made worse by the cold. The majority of the time, this cumulative dose-limiting toxicity reverses within a few months of medication cessation[20]. It has a large diaminocyclohexane (DACH) moiety, that destroys cancer cells primarily by causing transcriptional inhibitory (DACH)Pt-GpGintrastrand cross-links [21].

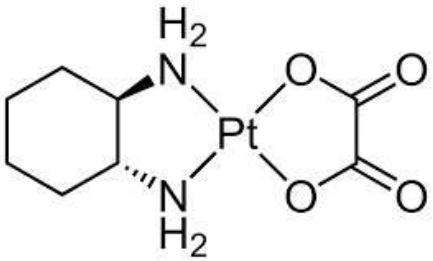

Figure 1: (a) Structural Configuration of Oxaliplatin

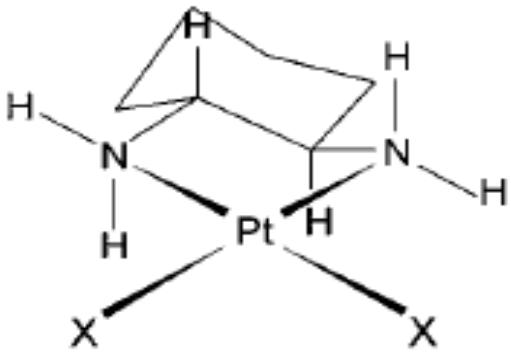

Figure 1: (b) Structural Configurationof Enantiomer $[Pt(R,R\text{-}DACH)]^{2+}$

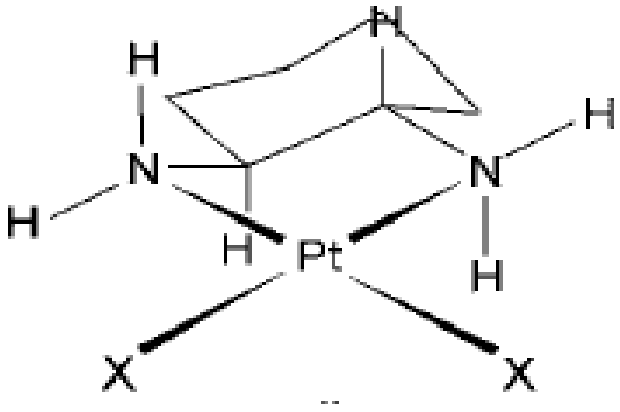

Figure 1: (c) Structural Configurationof Enantiomer $[Pt(s,S\text{-}DACH)]^{2+}$

Only carboplatin (cis-diamminecyclobutanedicarboxylatoplatinum(II)) and oxaliplatin ((1R,2R-diamminocyclohexane)oxalatoplatinum(II)) have achieved universal approval and broad clinical usage since the invention of cisplatin [cis-diamminedichloridoplatinum(II)] [22]. Carboplatin is substantially less harmful than cisplatin. Therefore we are able to use it where much higher doses are required.

Regrettably, carboplatin still only works against tumours that are within the same range as cisplatin [23]. When unite with 5-fluorouracil or folinic acid, oxaliplatin has shown promise in treating some cisplatin-resistant cancers [24]. When employed as a sole agent, it has not yet demonstrated any discernible benefits over carboplatin or cisplatin. Third-generation platinum anticancer drug oxaliplatin and orthodoxcisplatin are expected to have different biological effects because of downstream mechanisms that discriminate between their respective DNA adducts. These diverse biological effects of oxaliplatin are explained by its increased ability to produce DNA adducts in biological processes.

The differential scanning calorimetry (DSC) of oxaliplatin and its enantiomericanalog ([Pt(R,R-DACH)]2+ and [Pt(s,S-DACH)]2+) has been published by Malina et. al[25]. The chemical structures are shown in figure 1(a), 1 (b) and 1 (c). Their study discussed DNA polymerization across the large 1,2-GG intrastrand cross-link caused by cisplatin and oxaliplatin as well as recognition by the HMG domain protein.Since the system remains cooperative after the binding therefore modified Zimm and Bragg theory[26] have been used to study the effect of binding of oxaliplatin and its enantiomer with DNA in the present study.

II. THEORETICAL APPROACH TO STUDY THE BINDING OF OXALIPLATIN WITH DNA

According to calorimetric analysis of Malina*et. Al*, the complex formed between oxaliplatin and DNA, the transition behaviour of both the platinated and unplatinated duplexes are completely reversible. Each transition exhibits hardly any differences in the heat capacities between the final and initial states. The duplex, however, continues to be very cooperative, allowing the co-operative transition theory to be used to clarify the melting profile and temperature dependence of thermodynamical characteristics, including heat capacity. The modified Zimm and Bragg theory had been thus adopted. The Ising-Model, which was initially developed to study the ferromagnetic transition of linear spin chains, serves as the basis for all hypotheses. A residue in a long polymer chain can exist in either an ordered or disordered form; similar to how a spin can be in both a spin up and spin down position. Due to the finite nature of interactions, a one-dimensional system is unable to demonstrate any sort of phase transition; consequently the Ising model has been modified by incorporating the boundary state. This boundary state is the initial ordered state in a sequence of ordered states. Once the residue transitions, maintaining it in the second state is simpler. Now, different states U can each have a different partition function assigned to them.

One can create an Ising matrix for an ordered and disordered state of a two-phase system using the theory. The Ising matrix, as was previously addressed [27–33] and by Zimm and Bragg [26] can be represented mathematically as follows;

$$M = \begin{array}{c} \\ f_r \\ f_k \\ f_h \end{array} \begin{array}{c} \begin{array}{ccc} f_r & f_k & f_h \end{array} \\ \begin{vmatrix} f_r^{1/2} f_r^{1/2} & f_r^{1/2} f_k^{1/2} & 0 \\ f_r^{1/2} f_k^{1/2} & 0 & f_k^{1/2} f_h^{1/2} \\ f_h^{1/2} f_r^{1/2} & 0 & f_h^{1/2} f_h^{1/2} \end{vmatrix} \end{array}$$

Where contributions from the comparable base pair partition functions in the three states, such as ordered, disordered, boundary or nucleation, are f_r, f_h, and f_k. The values of M's eigenvalues are provided by:

$$\lambda_1 = \frac{(f_r + f_h) + \{(f_r - f_h)^2 + 4f_r f_k\}^{1/2}}{2}$$

$$\lambda_2 = \frac{(f_r + f_h) - \{(f_r - f_h)^2 + 4f_r f_k\}^{1/2}}{2}$$

$\lambda_3 = 0$ .....(1)

The effects of the starting and end states become extremely important because we are dealing with a finite system. The impact of the first segment to the partition function can be found by the following:

$U = (f_r^{1/2}, 0, 0)$ .....(2)

When the last segment's state is represented by column vector V,

$$V = \begin{vmatrix} f_r^{\frac{1}{2}} \\ f_k^{\frac{1}{2}} \\ f_h^{\frac{1}{2}} \end{vmatrix}$$ .....(3)

N-segment chain's partition function is provided by

$Z = UM^{N-1}V$ .....(4)

The matrix T consists of the column vectors only. It diagnolizes M and is given by

$XM = \lambda X$ .....(5)

Where: $X = \begin{vmatrix} X_1 \\ X_2 \\ X_3 \end{vmatrix}$ .....(6)

When the values of M from Equation 5 are substituted, we obtain:

$$T = \begin{vmatrix} 1 & 1 & 1 \\ \frac{\lambda_1 - f_r}{f_r^{1/2} f_k^{1/2}} & \frac{\lambda_2 - f_r}{f_r^{1/2} f_k^{1/2}} & -f_r^{1/2} f_k^{1/2} \\ \frac{f_r^{1/2} f_h^{1/2}}{\lambda_1 - f_h} & \frac{f_r^{1/2} f_h^{1/2}}{\lambda_2 - f_h} & -f_r^{1/2} f_h^{1/2} \end{vmatrix}$$

Similarly, the matrix equation yields T^{-1} as follows:

$YM = \lambda Y$ .....(7)

Where, $Y = |Y_1 \quad Y_2 \quad Y_3|$

When we again use the values of M from equation 1 in equation 7, we obtain;

$$T^{-1} = \begin{vmatrix} C_1 & \frac{(C_1 f_r^{1/2} f_k^{1/2})}{\lambda_1} & \frac{(C_1 f_k f_r^{1/2} f_h^{1/2})}{\lambda_1(\lambda_1 - f_h)} \\ C_2 & \frac{(C_2 f_r^{1/2} f_k^{1/2})}{\lambda_2} & \frac{(C_2 f_k f_r^{1/2} f_h^{1/2})}{\lambda_1(\lambda_2 - f_h)} \\ C_3 & \frac{(C_3 f_r^{1/2} f_k^{1/2})}{\lambda_3} & \frac{(C_3 f_k f_r^{1/2} f_h^{1/2})}{\lambda_3(\lambda_3 - f_h)} \end{vmatrix} \quad \text{…..(8)}$$

These are the normalisation constants:

$$C_1 = \frac{(\lambda_1 - f_h)}{(\lambda_1 - \lambda_2)}$$

$$C_2 = \frac{(\lambda_2 - f_h)}{(\lambda_2 - \lambda_1)}$$

And $C_3 = 0$ …..(9)

If $\Lambda = T^{-1}MT$ be the diagonalized form of M, one can write the partition function as:

$Z = UT\Lambda^{N-1}T^{-1}V Z = UT\Lambda N^{-1}T^{-1}V$ …..(10)

The partition function is as follows once the values from equations 1, 2, 3, 6, 8, and 9 are substituted in equation 10:

$$Z = C_1\lambda_1^N + C_2\lambda_2^N \quad \text{…..(11)}$$

In disoedered form, the fraction of the segments is given by

$$Q_r = \frac{\delta lnZ / \delta lnf_r}{N}$$

The solution to the aforementioned equation is:

$$Q_r = \frac{1}{2} + \frac{(1-s)(2A-1)}{2P} + \frac{(1+s)\{(2A-1)P-1+s\}}{2P^2N} \quad \text{…..(12)}$$

Where

$$P = \frac{\lambda_1 - \lambda_2}{f_r}, \quad S = \frac{f_h}{f_r}, \quad \sigma = \frac{f_k}{f_r}, \quad A = [(f_r - f_h)^2 + (4f_k f_r)]^{-2}$$

Here, s is the propagation parameter in this case, and it is considered to be one for simplicity. In reality, it is discovered to be very close to unity in the majority of systems.

If A_r and A_h indicate absorbance in the disordered and ordered states, respectively, the total absorption can be represented as follows:

$$A = Q_r A_r + (1 - Q_r)A_h \quad \text{…..(13)}$$

It is simple to extend this formalisation to specific heat. The changes in molar enthalpy and entropy during the transition from first state to second state are related to the specific heat. Free energy and internal energy are derived from well-known thermodynamic relations such as $F = -KTlnZ$ and $U = -T^2\left(\frac{\delta}{\delta T}\right)\left(\frac{F}{T}\right)$ respectively. We obtain the specific heat by differentiating internal energy with respect to temperature.

$$C_v = \frac{\delta U}{\delta t} = Nk\left(\Delta H/_{RT_m}\right)^2\left(S\delta Q_r/_{\delta S}\right) \quad .....(14)$$

Where ΔH is the molar change in enthalpy about the transition point and S represents entropy, which is equal to

$$S = exp^{\left[\left(\frac{\Delta H}{R}\right)\left\{\left(\frac{1}{T}\right)-\left(\frac{1}{T_m}\right)\right\}\right]} \quad .....(15)$$

Where T_m is the transition temperature, and

$$\frac{\delta Q_r}{\delta S} = \left(\frac{1}{2P^2}\right)\left[2P(1-S)\frac{\delta A}{\delta S} - P(2A-1) - (1-S)(2A-1)\frac{\delta P}{\delta S}\right] + (1/2P^3N)[P\{(S+1)\{(2A-1)\frac{\delta P}{\delta S} + 2P\frac{\delta A}{\delta S} + 1\} + \{(2A-1)P - 1 + S\}\} - \{(2A-1)P - 1 + S\}2(S+1)]$$

With

$$\frac{\delta A}{\delta S} = \left[\frac{(S-\sigma)^N}{Z/_{f_r^N}^2}\right]\left[\frac{\sigma}{P^3}\right]\left[-2 + \left\{\frac{N(S-2\sigma-1)}{S-\sigma}\right\}\right]$$

Where, $\frac{\delta P}{\delta S} = \frac{S-1}{P}$ and $\sigma = \frac{f_k}{f_r}$

The nucleation parameter σ measures the energy released or expanded at the formation of the initial state of ordered/disordered state. It's got related to do the lengths of uninterrupted sequences. Using Nernst-Lindemann approximation [19], the volume heat capacity $C_v$has been transformed into the constant pressure heat capacity C_p.

$$(C_p - C_v = 3RA_{0(}\frac{C_P^2 T}{C_v T_m}) \quad .....(16)$$

Where T_m is the melting temperature and A_0 is a constant with a common universal value of [3.910-9 (Kmol)/J-1].

III. DISCUSSION

1. **Transition Profile:** Since DNA's structure is still quite cooperative after oxaliplatin binds to it, the two-state theory of order-disorder transition holds true. In order to account for the ordered (bound-ed/unbounded) and disordered states that coexist at the transition point, the Zimm and Bragg theory is modified. The nucleation parameter and total change in enthalpy/entropy, which together define the transition, are the main thermodynamic forces that propel it. Base pairs in the context sequence may also influence the transition. Assuming that intrastand crosslinking does not significantly affect the surrounding base pair stacking, the kinetics of transformation will be governed by the strength of all hydrogen bonded and non-bonded interactions with altering context sequences. The distortion at the crosslink location spans at least four pairs of guanine residues, which are not connected to their equivalent cytosin residues by hydrogen bonds. The transition is more abrupt the lower the nucleation parameter's value. All of this is considered when calculating the change in enthalpy using the differential scanning calorimeter (DSC) [23].

Along with the drug-induced reduction in the thermal stability of the duplex, a reduction in the overall transition enthalpy of the duplexin also takes place. Enthalpy changes more when [Pt(S,S-DACH)]2+ -DNA duplex is present. At 332.109 K, unmodified DNA melts. The DNA saturated with the medicines $[Pt(R,R\text{-}DACH)]^{2+}$ and $[Pt(S,S\text{-}DACH)]^{2+}$ reaches its melting point at 321.477 K and 318.493 K, respectively.

Table 1 lists the various variables giving transition profiles that best match experimental findings in GG Intrastrand crosslink of antitumor Oxaliplatin and Its EnantiomericAnalog. To determine how acute the transition is, we use a sensitivity parameter with the symbol $\Delta H/\sigma$ and half width. It can be seen that the sharpness of transition is highest in the case of an unbounded state.

The variation in heat capacity with temperature is calculated and plotted in Figures 2, 3 and 4. Figure 2 gives transition profile for unmodified DNA while figure 3 and 4 gives transition Profile for binding of DNA with $[Pt(R,R\text{-}DACH)]^{2+}$ and $[Pt(S,S\text{-}DACH)]^{2+}$ respectively.Solid curve represents experimental values taken by Malina*et. al* [24] while the XXXX represents calculated values. Because there are numerous disordered states present that cannot be specifically identified, there are slight alterations at the tail ends. A variation can also be brought on by the presence of tiny helical segments in the random coil state. As estimated, the sharpness is improved in the unmodified condition for the transition than the changed state.The Transition Profiles and half widths express that the uunplatinated DNA profile is sharper than platinated DNA profiles.

Table 1: Transition Parameters for Drugs Binding to DNA

Parameter	**DNA**	**$[Pt(R,R\text{-}DACH)]^{2+}$ -DNA**	**$[Pt(S,S\text{-}DACH)]^{2+}$ -DNA**
T_m(K)	332.109	321.477	318.493
ΔH(Kcal/mol)	96.8	59.9	56.7
σ	0.012	.00095	.009
No. of segments N	66	66	66
Sensitivity parameter ($\Delta H/\sigma$)	8.06×10^3	63.05×10^3	6.30×10^3
Half Width	287.812	284.479	284.849

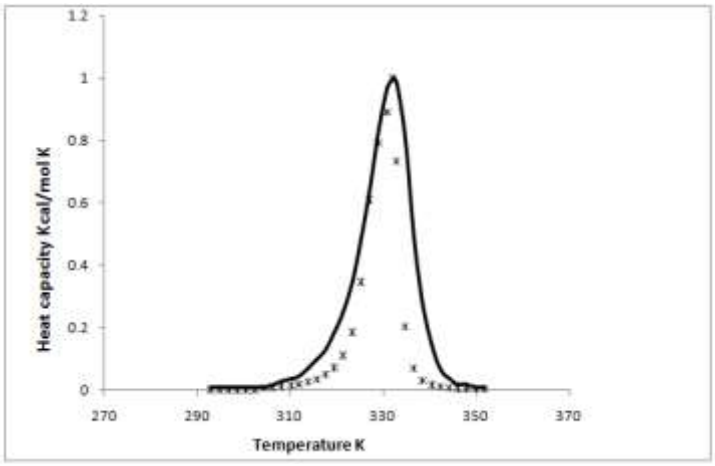

Figure 2: Heat capacity and transition profile of unmodified DNA

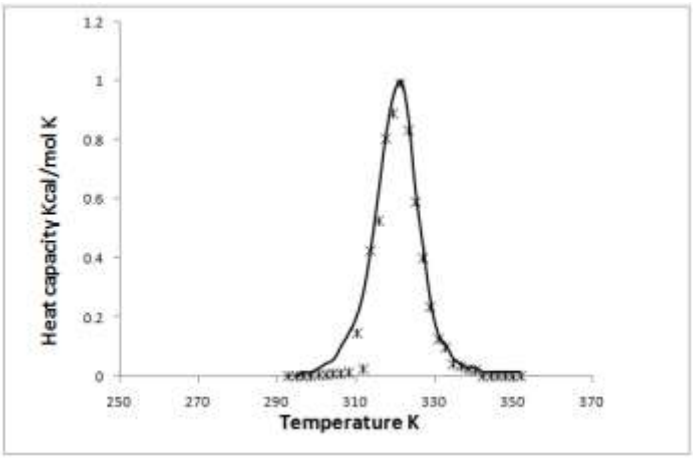

Figure 3: Heat Capacity and Transition Profile of DNA Bounded with Oxaliplatin Enantiomer $[Pt(R,R\text{-}DACH)]^{2+}$.The Concentrations of the Duplex is 30 μM.

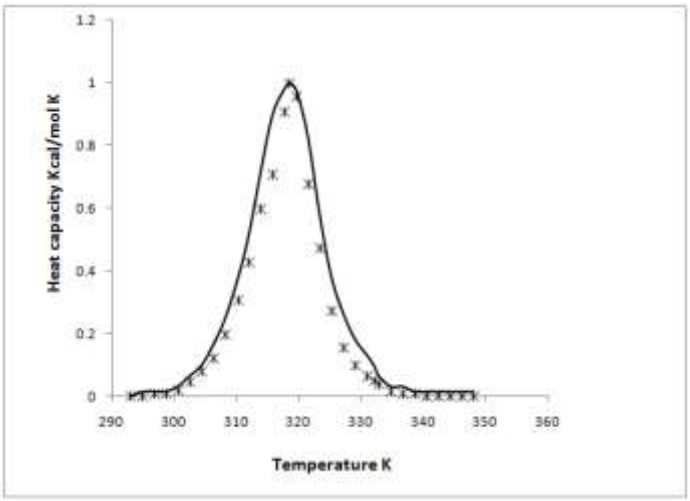

Figure 4: Heat Capacity and Transition Profile of DNA Bounded with Oxaliplatin Enantiomer $[Pt(S,S\text{-}DACH)]^{2}$+.The Concentrations of the Duplex is 30 μM.

2. **Heat Capacity:** The 2nd order derivative of the free energy is used to describe the macromolecular system's structural and dynamical states [32]. By employing scaling factors, which are very close to unity (and only slightly more than one in the case of heat capacity curves) it was almost possible to make the theoretically and experimentally determined heat capacity profiles coincide. The slight variation in experimental and calculated data may arise due to the fact that only one dimensional linear chain has been considered. The three dimensional structure is even more complicated which results in much more complex calculations.

A closer look at these thermodynamic parameters reveals several intriguing characteristics: First, crosslinking formation of $[Pt(R,R\text{-}DACH)]^{2+}$ or $[Pt(S,S\text{-}DACH)]^{2+}$ decreases the thermal stability of duplex. $[Pt(S,S\text{-}DACH)]^{2+}$s crosslinker reduced DNA melting temperature more effectivelt than $[Pt(R,R\text{-}DACH)]^{2+}$'s crosslinker.

Second, the enthalpy of duplex dissociation significantly decreased as a result of crosslinker creation by DACH complexes. In contrast to its unmodified cousin, the duplex is enthalpically destabilised by the intrastrandCrosslinker of these complexes having platinum. It's interesting to note that compared to its R,R counterpart, the intrastrandcrosslinker of $[Pt(S,S\text{-}DACH)]^{2+}$ produced in this latter sequence thermodynamically destabilised the duplex much more.

IV. CONCLUSION

One of the goals of conducting biophysical studies of interaction of DNA with drug is to develop design techniques for novel compounds with therapeutic or biotechnological applications is. In this article, we have made an effort to demonstrate that thermodynamic studies might be adeeply effective instrument for delivering knowledge that can direct such initiatives.

Drug binding, thus, impacts the characteristics of the transition along with the enthalpy of transition and melting temperature, as demonstrated by the change in transition breadth in both experimental and computational facts. Dynamical and thermodynamic behaviour are directly influenced by the kind and strength of interactions. This technique can be used to investigate a polymer's biodegradability. The biomedical sector can use the findings of the current work to better understand the stability of drug interactions with nucleic acids as well as drug-DNA interactions at the bimolecular level.

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