**Interaction of Oxaliplatin with DNA: A Theoretical Study**

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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 drug oxaliplatin and its enantiomeric analogue with 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 Malina *et. 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, heat capacity curve, and half widths, are in good accordance with the 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, transition profile, intercalation, minor groove

1. **Introduction**

DNA is a common abbreviation for deoxyribonucleic acid. Two polynucleotides compose the polymer, which coils in the form of a double helix. DNA contains genetic information that is necessary for the development, growth, operation and reproduction 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. All known forms of life require four main kinds of macromolecules: nucleic acids, proteins, lipids, and complex starches (polysaccharides).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 which is a type of pentose (five carbon) sugar, one phosphate group, and one nucleobase containing nitrogen (cytosine [C], guanine [G], adenine [A], or thymine [T]) combine with each other to make up a nucleotide.

When the nucleotides are connected to the chain by covalent bonds between the phosphate of the one nucleotide and the sugar of next nucleotide, this is known as the phosphodiester linkage and results in an alternating backbone of sugar-phosphate. The hydrogen bonds are formed between the nitrogenous bases of the two different DNA strands to form double-stranded DNA in accordance with the 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 the sequence of amino acids 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 DNA is exist in the nucleus of cell as nuclear DNA, however few also exist in chloroplast or mitochondrial DNA[3]. Prokaryotes, including archaea and bacteria, store their DNA in the cytoplasm as circular chromosomes. Chromatin proteins like histones compress and arrange DNA inside the eukaryotic chromosomes. These structures after compression help to control the regions of DNA that are transcribed by the interaction of DNA with other proteins.

**1.1 Base Pairing**

A double helix coil of DNA has 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) form two hydrogen bonds, cytosine (C) and guanine (G) form three hydrogen bonds, and purines and pyrimidines form single hydrogen bond. A Watson-Crick base pair is used to describe this form of interaction in two nucleotides across the double helix (from six-carbon ring to six-carbon ring). DNA with a high GC level is more stable than DNA with a low GC content.

Hoogsteen model 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 can be split into two like a zipper by applying mechanical force or high temperature [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].

**1.2 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, which are close to the base pairs, could serve as a binding site. Because the strands are not proportionally arranged in relation to one another, the grooves are not all the same size. The width of major groove is 22 Å (2.2 nm), whereas the width of minor groove is 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 proteins that may bind to particular sequences in double-stranded DNA like transcription factors usually come into contact with the sidewalls of the bases exposed in the major groove [8]. The major groove and minor grooves are always chosen to represent the differences in width that would be obvious if the DNAs were twisted back into the typical B form, despite the fact that the peculiar DNA conformations under this situation differ from cell to cell.

**1.3 DNA Functions**

Two major functions of DNA are as follows:

**1.3.1** **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.

**1.3.2** **Replication:**

DNA can reproduce itself. As was previously mentioned, each strand of DNA's double-helix structure is made up of four nucleotides: thymine (T), adenine (A), guanine (G) and cytosine (C). Phosphodiester connections bind these nucleotides together within a strand. The two strands are held together mostly by Watson-Crick hydrogen bonds, in which A forms two hydrogen bonds with T and C form three hydrogen bonds with G. 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.

**1.4 Interaction of drug with 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 binding to a particular region of the DNA. Therefore, if a small molecule can match the binding specificity and potency of this regulatory protein, DNA function can be artificially controlled, inhibited, or triggered by binding the molecule. Therefore, if it is important to cure or manage a condition, this artificial/natural small molecule can act as a 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 is targeted in an inhibitory manner to destroy cells for antitumor and antibiotic action, despite the possibility of both of these actions.

Drugs bind to DNA through covalent and 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/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:

**1.4.1 Minor groove binders**

Minor groove binding drugs 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 N3 and O2 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 and groove walls and the steric barrier provided by the C2 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 regions of the grooves, have been developed, though.

If small compounds can bind to any specified DNA sequence in the human genome with high affinity, they will be very useful tools in molecular biology and possibly in human medicine. Pairing rules have been developed to logically regulate the sequence specificity of minor groove-binding polyamides, such as N-methylpyrrole and N-methylimidazole amino 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, ML2Cl2, where M = Cu(II), Zn(II), Co(II), and Ni(II) have been developed and synthesised by Raman *et. al* [13]. The binding properties of these complexes with calf thymus DNA (CT-DNA) were investigated 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, a coumarin-chalcone hybrid, has been shown to have 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.

**1.4.2 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, DNA intercalators are 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 rates can be tuned 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 drug 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.

**1.5 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.

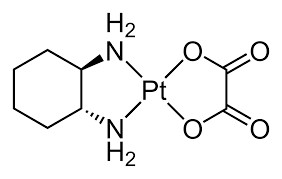
* + 1. **Crosslinking agents**

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.

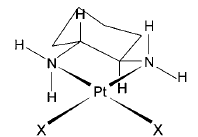
**1.5 Oxaliplatin**

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 platinum based antineoplastic agent used in cancer chemotherapy.

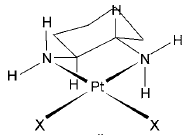
It is a new platinum compound of the third generation which is effective in therapy of colorectal and advanced ovarian cancers. With low haematotoxicity and moderate, controllable gastrointestinal toxicity, it has shown to have an excellent safety profile. The peripheral sensory neuropathy brought on 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-GpG intrastrand cross-links [21].



**Figure 1 (a) Structural Configuration of Oxaliplatin**



**Figure 1 (b) Structural Configuration of Enantiomer [Pt(R,R-DACH)]2+**



**Figure 1 (c) Structural Configuration of Enantiomer [Pt(s,S-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 and can be used at much higher doses. Regrettably, carboplatin still only works against tumours that are within the same range as cisplatin [23]. When combined 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 advantages over carboplatin or cis platin. Third-generation platinum anticancer drug oxaliplatin and conventional cisplatin 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 Enantiomeric analog ([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.

1. **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 melting 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 =

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

λ3=0 …..(1)

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

U = (fr1/2,0,0) .....(2)

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

…..(3)

N-segment chain's partition function is provided by

Z = UMN-1V …..(4) The matrix T consists of the column vectors only. It diagnolizes M and is given by

…..(5)

Where: …..(6)

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

T =

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

…..(7)

Where,

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

…..(8)

These are the normalisation constants:

And C3 = 0 …..(9)

  If Λ = T-1MT be the diagonalized form of M, one can write the partition function as:

Z = UTΛN-1T-1V …..(10)

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

…..(11) In disoedered form, the fraction of the segments is given by

The solution to the aforementioned equation is:

…..(12)

Where

, , ,

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 Ar and Ah indicate absorbance in the disordered and ordered states, respectively, the total absorption can be represented as follows:

…..(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 and respectively. We obtain the specific heat by differentiating internal energy with respect to temperature.

.....(14)

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

.....(15)

Where Tm is the transition temperature, and

With

Where, and 

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 Cv has been transformed into the constant pressure heat capacity Cp.

( …..(16)

Where Tm is the melting temperature and A0 is a constant with a common universal value of [3.910-9 (Kmol)/J-1].

1. **Discussion**

**3.1 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 depend on the strength of all hydrogen bonds 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 fall 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-DACH)]2+ and [Pt(S,S-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 Enantiomeric Analog. To determine how acute the transition is, we use a sensitivity parameter with the symbol ΔH/ σ and half width. It can be seen that the transition is sharpest 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-DACH)]2+ and [Pt(S,S-DACH)]2+ respectively. Solid curve represents experimental values taken by Malina *et. al* [24] while the ӾӾӾӾ 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 expected, the sharpness is better 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.

**Table1.Transition parameters for drugs binding to DNA**

|  |  |  |  |
| --- | --- | --- | --- |
| **Parameter** | **DNA** | **[Pt(R,R-DACH)]2+ -DNA** | **[Pt(S,S-DACH)]2+ -DNA** |
| Tm(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  (ΔH/σ) | 8.06×103 | 63.05×103 | 6.30×103 |
| 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-DACH)]2+**

**Figure 4 Heat capacity and transition profile of DNA bounded with oxaliplatin enantiomer [Pt(S,S-DACH)]2+**

**3.2 Heat Capacity**

The second 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-DACH)]2+ or [Pt(S,S-DACH)] 2+ reduced the thermal stability of duplex. [Pt(S,S-DACH)] 2+ s crosslinker reduced DNA melting temperature more effectivelt than [Pt(R,R-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 intrastrand Crosslinker of these platinum complexes. It's interesting to note that compared to its R,R counterpart, the intrastrand crosslinker of [Pt(S,S-DACH)]2+ produced in this latter sequence thermodynamically destabilised the duplex much more.

1. **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 a deeply effective instrument for delivering knowledge that can direct such initiatives.

Drug binding, thus, impacts the characteristics of the transition in addition to the transition enthalpy and melting temperature, as demonstrated by the change in transition breadth in both experimental and computational data. 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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**References**

1. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P (2014) “[Molecular Biology of the Cell](http://www.garlandscience.com/product/isbn/9780815344322)” (6th ed.). Garland Science
2. Purcell A. ["DNA"](http://basicbiology.net/micro/genetics/dna). Basic Biology. [Archived](https://web.archive.org/web/20170105045651/http:/basicbiology.net/micro/genetics/dna/) from the original 2017.
3. Russell P (2001). iGenetics. New York: Benjamin Cummings.
4. Nikolova EN, Zhou H, Gottardo FL, Alvey HS, Kimsey IJ, Al-Hashimi HM (2013). ["A historical account of Hoogsteen base-pairs in duplex DNA"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3844552). Biopolymers. **99** (12): 955–68. [doi](https://en.wikipedia.org/wiki/Doi_(identifier)):[10.1002/bip.22334](https://doi.org/10.1002%2Fbip.22334). [PMC](https://en.wikipedia.org/wiki/PMC_(identifier)) [3844552](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3844552). [PMID](https://en.wikipedia.org/wiki/PMID_(identifier)) [23818176](https://pubmed.ncbi.nlm.nih.gov/23818176).
5. Clausen-Schaumann H, Rief M, Tolksdorf C, Gaub HE (April 2000). ["Mechanical stability of single DNA molecules"](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1300792). Biophysical Journal. **78** (4) https://doi.org/10.1016/S0006-3495(00)76747-6
6. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Peter W (2002). [Molecular Biology of the Cell](https://www.ncbi.nlm.nih.gov/books/NBK21054/) (Fourth ed.). New York and London: Garland Science
7. Wing R, Drew H, Takano T, Broka C, Tanaka S, Itakura K, Dickerson RE (October 1980). "Crystal structure analysis of a complete turn of B-DNA". Nature. **287** (5784): 75558. [Bibcode](https://en.wikipedia.org/wiki/Bibcode_(identifier)):[1980Natur.287..755W](https://ui.adsabs.harvard.edu/abs/1980Natur.287..755W). [doi](https://en.wikipedia.org/wiki/Doi_(identifier)):[10.1038/287755a0](https://doi.org/10.1038%2F287755a0). [PMID](https://en.wikipedia.org/wiki/PMID_(identifier)) [7432492](https://pubmed.ncbi.nlm.nih.gov/7432492). [S2CID](https://en.wikipedia.org/wiki/S2CID_(identifier)) [4315465](https://api.semanticscholar.org/CorpusID:4315465).
8. Pabo CO, Sauer RT (1984). "Protein-DNA recognition". Annual Review of Biochemistry. **53**: 293–321. [doi](https://en.wikipedia.org/wiki/Doi_(identifier)):[10.1146/annurev.bi.53.070184.001453](https://doi.org/10.1146%2Fannurev.bi.53.070184.001453). [PMID](https://en.wikipedia.org/wiki/PMID_(identifier)) [6236744](https://pubmed.ncbi.nlm.nih.gov/6236744)
9. Wemmer D E, Dervan P B (1997). “Targeting the minor groove of DNA”. Current opinion in Structural Biology. 7(3) 355-361. https://doi.org/10.1016/S0959-440X(97)80051-6
10. Vega M C, Saez I G, Aymami J, Eritija R, Marel V D, Boom J V, Rich A, Coll M. (1994) “Three-dimensional crystal structure of the A-tract DNA dodecamer d(CGCAAATTTGCG) complexed with the minor-groove-binding drug Hoechst 33258”. Europian Journal of Biochemistry. 222(23). 721-726. https://doi.org/10.1111/j.1432-1033.1994.tb18917.x
11. Fornande L H, Wu L, Billeter M, Lincoln P, Norden B. (2013). “Minor-Groove Binding Drugs: Where Is the Second Hoechst 33258 Molecule?”. The Journal of Physical Chemistry B. 117 (19), 5820–5830. https://pubs.acs.org/doi/abs/10.1021/jp400418w
12. Zhang X, Brantley S L, Corcelli S A, Tokmakoff A. (2020) “DNA minor-groove binder Hoechst 33258 destabilizes base-pairing adjacent to its binding site” Communications Biology. 3, 1-9. https://doi.org/10.1038/s42003-020-01241-4
13. Raman P, Shobha S, Thamaraichelvan (2011) “A novel bioactive tyramine derived Schiff base and its transition metal complexes as selective DNA binding agents” Spectrocimiaca Acta Part A: Molecular and Biomolecular Spectroscopy. 78(2). 888-898. https://doi.org/10.1016/j.saa.2010.12.056
14. Ashraf R, Hamidullah, Hasnain M, Pandey P, Maheshwari M, Singh L R, Siddiqui M Q, Konwar R, Sashidhara K V, Sarkar J. (2017) “Coumarin-chalcone hybrid instigates DNA damage by minor groove binding and stabilizes p53 through post translational modifications” Scientific Reports. 7. https://www.nature.com/articles/s41419-019-1317-7
15. Hopkins H P, Wilson W D. (1987) Enthalpy and entropy changes for the intercalation of small molecules to DNA. II. Ethidium and propidium fluoride. 26 (8) 1347-1355. Biopolymer. https://doi.org/10.1002/bip.360260810
16. Biebricher A S, Heller I, Roijmans R F H, Hoekstra T P, Peterman E J G, Wuite G J L. (2015) “The impact of DNA intercalators on DNA and DNA-processing enzymes elucidated through force-dependent binding kinetics” Nature Comminications. 6. 1-12. https://www.nature.com/articles/ncomms8304
17. Riahi H A, Agudelo D, Bourassa P, Berube G (2014) “Intercalation of antitumor drug doxorubicin and its analogue by DNA duplex: Structural features and biological implications” International journal of Biological Macromolecules. 66. 144-150. https://doi.org/10.1016/j.ijbiomac.2014.02.028
18. Fathi F, Abdin M, Maleki S, Abbasgolizadeh (2023) “Intercalation of anticancer drug mitoxantrone into DNA: Studied by spectral and surface plasmon resonance methods” Journal of Molecular structure 1274 (1). 134509. https://doi.org/10.1016/j.molstruc.2022.134509
19. Barone G, Guerra C F, Gambino N, Silvestri A, Lauria A, Almerico A M, [Bickelhaupt](https://www.tandfonline.com/author/Bickelhaupt%2C+F+Matthias) F M. (2008)“Intercalation of Daunomycin into Stacked DNA Base Pairs. DFT Study of an Anticancer Drug” Journal of Biomolecular Structure and Dynamics 26(1). 115-129. https://doi.org/10.1080/07391102.2008.10507229
20. Lokich, J. (2001) “What is the ‘‘best’’ platinum: cisplatin, carboplatin, or oxaliplatin? Cancer Invest. 19:756–760
21. Shubeita H O, Baker M, Koaq M, Lee S, (2019) “Structural basis for the bypass of the major oxaliplatin-DNA adducts by human DNA polymerase η” Biochem J. 476(4) 747-758. https://doi.org/10.1042%2FBCJ20180848
22. Boulikas, T., and M. Vougiouka. 2003. Cisplatin and platinum drugs at the molecular level. Oncol. Rep. 10:1663–1682 [review].
23. Di Francesco, A. M., A. Ruggiero, and R. Riccardi. 2002. Cellular and molecular aspects of drugs of the future: oxaliplatin. Cell. Mol. Life Sci. 59:1914–1927.
24. Malina A j, Novakova O, Vojtiskova M, Natile G, Brabec V (2007) “Conformation of DNA GG Intrastrand Cross-Link of Antitumor Oxaliplatin and Its Enantiomeric” Biophysical Journal. 93. 3950–3962. https://doi.org/10.1529/biophysj.107.116996
25. Misset J L. (1998) “Oxaliplatin in Practice” British journal of Cancer 77. 4-7. https://www.nature.com/articles/bjc1998428
26. Zimm B H and Bragg J K 1959 *J. of Chemical Physics* **31** https://doi.org/10.1063/1.1730390
27. Srivastava S, Gupta V D, Tandon P, Singh S and Katti S B 1999 *J. of Macromol Science Phy*. **38** doi:10.1080/00222349908212437
28. Srivastava S, Srivastava S, Singh S and Gupta V D 2001 *J. of Macromolecular Sci Phy*. **40** doi:10.1081/MB-100000050
29. Roles K A and Wunderlich B 1991 *Biopoly.* **31** doi:10.1002/bip.360310503
30. Poklar N, PilchD S, Lippard S J, Redding E A, Dunham S U and Breslauer K J 1996 *Proc. of National Academy of Sci USA* **93** DOI: 10.2307/40081
31. Srivastava S, Khan I A, Srivastava S and Gupta V D 2004 *J. of Biochem. and Biophy.* **41** http://nopr.niscpr.res.in/handle/123456789/3727
32. Yunus G, Srivastava S, Kuddus M and Gupta V D 2013 *Current Applied Physics* 13 https://doi.org/10.1016/j.cap.2012.05.020
33. Yunus G, Srivastava S and Gupta V D 2012 A *Int. J of Biophy.* **2** doi:10.5923/j.biophysics.20120201.02