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

1. **Introduction** Deoxyribonucleic acid is commonly abbreviated as DNA. DNA is polymer composed of two [polynucleotide](https://en.wikipedia.org/wiki/Polynucleotide) which form a double helix by coiling around each other. All known organisms and many viruses have genetic information in the DNA that is essential for their development, functioning, growth, and reproduction. Both DNA and [ribonucleic acid](https://en.wikipedia.org/wiki/Ribonucleic_acid) (RNA) are [nucleic acids](https://en.wikipedia.org/wiki/Nucleic_acid). Nucleic acids along with proteins, lipids, and complex carbohydrates (polysaccharides) are four major categories of macromolecules that are necessary for all known forms of life,.

The two DNA strands are composed of simple monomeric units called nucleotides. Therefore these strands are also called polynucleotides [1,2].

 Ncleotide is made up of deoxyribose a kind of pentose (five carbon) sugar, a phosphate group along with one [nitrogen-containing](https://en.wikipedia.org/wiki/Nitrogenous_base) [nucleobases](https://en.wikipedia.org/wiki/Nucleobase%22%20%5Co%20%22Nucleobase) (namely [cytosine](https://en.wikipedia.org/wiki/Cytosine) [C], [guanine](https://en.wikipedia.org/wiki/Guanine) [G], [adenine](https://en.wikipedia.org/wiki/Adenine) [A] or [thymine](https://en.wikipedia.org/wiki/Thymine) [T]). An alternating sugar-phosphate backbone is created when the nucleotides are linked together in a chain by covalent bonds (also referred to as the phosphodiester linkage) between the sugar of one nucleotide and the phosphate of the next nucleotide. To create double-stranded DNA, the nitrogenous bases of the two distinct polynucleotide strands are joined by hydrogen bonds in accordance with the base pairing principles (A with T and C with G). The two DNA strands are antiparallel because they move in directions that are opposite to one another.

RNA strands are made using DNA strands as a template. DNA nucleotides are switched for their equivalent bases, with the exception of thymine (T), for which RNA substitutes uracil. This process is known as Transcription. These RNA strands function as the translation machinery for the genetic code, which specifies the order of amino acids in proteins.

DNA is arranged into long scaffolds within eukaryotic cells known as chromosomes. These chromosomes are replicated in the course of DNA replication prior to the regular cell division, giving each daughter cell a complete set of chromosomes.

The majority of the DNA in eukaryotic creatures (animals, plants, fungi, and protists) is stored as nuclear DNA inside the cell nucleus, while some is also stored as mitochondrial DNA or chloroplast DNA.[3] Prokaryotes, such as bacteria and archaea, store their DNA in the cytoplasm, in the form of circular chromosomes. DNA is compacted and arranged within eukaryotic chromosomes by chromatin proteins like histones. These compacting structures direct how DNA interacts with other proteins, assisting in regulating which parts of the DNA are transcribed.

**1.1 Base Pairing**

Each type of nucleobase on one strand of a DNA double helix links with just one type of nucleobase on the other strand. Complementary base pairing is the technique we achieve here. Adenine forms two hydrogen bonds with thymine and cytosine forms three hydrogen bonds with guanine only and purines form hydrogen bond with pyrimidines. This type of binding in two nucleotides across the double helix (from six-carbon ring to six-carbon ring) is called a Watson-Crick base pair. High GC content DNA is more stable than low GC content DNA.

A unique type of base-pairing is called a Hoogsteen base pair, which involves hydrogen-bonding a 6-carbon ring to a 5-carbon ring.[4] Since they are not covalent, hydrogen bonds are simple to break and reassemble. Thus, a mechanical force or high temperature can be used to tear apart the two strands of DNA that make up a double helix like a zipper.[5] This base pair complementarity is crucial for DNA replication because it ensures that every piece of information in a DNA helix's double-stranded sequence is reproduced on every strand. All of the functions of DNA in organisms depend on this particular, reversible connection between base pairs.[6]

**1.2 Grooves**

The grooves are the voids that are adjacent to the base pair which are capable of providing binding sites. Other strands may be found tracing the voids, or grooves, between the strands. These voids are adjacent to the base pairs and may provide a [binding site](https://en.wikipedia.org/wiki/Binding_site). The grooves are not equal in size because the strands are not symmetrically positioned in relation to one another. The minor groove measures 12 angströms (1.2 nm) in width, whereas the main groove measures 22 angströms.[7]

The major groove has a wider width than the minor groove, making it easier to access the bases' edges there. Therefore, the sides of the bases exposed in the main groove are frequently in contact with proteins like transcription factors that can bind to specific sequences in double-stranded DNA.[8] Although the odd DNA conformations in this condition vary from cell to cell, the major and minor grooves are always designated to represent the differences in breadth that would be evident if the DNA were twisted back into the standard B form.

**1.3 Functions Of DNA**

The two major functions of DNA are as follows:

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. For example, as receptors, enzymes, transporters, structural proteins, hormones, regulators, etc.

2. Replication: DNA replicates itself. As discussed earlier Adenine (A), thymine (T), guanine (G), and cytosine (C) are the four nucleotides that make up each strand of the double-helix structure of DNA. These nucleotides are linked together by phosphodiester linkages within a strand. A and C develop two hydrogen bonds with T and three hydrogen bonds with G, respectively, to hold the two strands together mainly by Watson-Crick hydrogen bonds. Pairing of the bases AT and G-C Proteins and tiny molecules can specifically recognise DNA sequences by combining hydrogen bond acceptor/donor sites 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 begins transcription or replication only after receiving a signal which is often in the form of a regulatory protein attaching to a specific area of the DNA. Therefore, if a tiny molecule can match the binding specificity and potency of this regulatory protein, DNA function can be artificially regulated, blocked, or activated by binding the molecule rather than the protein. This artificial/natural tiny molecule can therefore operate as a medication when activating or inhibiting DNA function whenever it is necessary to treat or manage a disease.

Depending on which spot the medicine is targeting, DNA activation could cause DNA replication or result in the production of more of the necessary protein. DNA inhibition would limit protein replication or synthesis and would result in cell death. Despite the possibility of both of these activities, DNA is typically targeted in an inhibitory mode to kill cells for antitumor and antibiotic action.

Both covalent and non-covalent bonds are used by drugs to bind to DNA. DNA covalent binding is irreversible, completely inhibits DNA activities, and always results in cell death. A well-known covalent compound called cis-platin (cisdiamminedichloroplatinum) is used as an anticancer medication. The chloro groups in cis-platin react with the nitrogens in DNA bases to form an intra/interstrand cross-link.

Most non-covalently bound drugs fall into one of the following two categories:

**1.4.1 Minor groove binders**

Minor groove binding drugs are typically designed like crescents, which complement the groove's shape and make binding easier by encouraging van der Waals interactions. These substances can also form hydrogen bonds with bases, most frequently with the N3 and O2 of adenine and thymine. Drugs that bind to minor grooves primarily bind to A/T rich sequences. A/T groove regions are narrower than G/C groove regions, and this preference is likely due to better van der Waals contacts between the ligand and groove walls in this region as well as the steric hindrance presented by the C2 amino group of the guanine base in the latter. 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.

Small molecules will be helpful tools in molecular biology and, possibly, in human medicine if they can bind with high affinity to any predefined DNA sequence in the human genome. To rationally manage the sequence specificity of minor groove-binding polyamides including N-methylimidazole and N-methylpyrrole amino acids, pairing rules have been created. [9]

Perhaps the most well researched minor groove binding substance to date is the dye Hoechst 33258 (Fig. 2). Recent research has taken a look at how this dye interacts with a self-complementary dodecanucleotide [d(CGCAAATTTGCG)2, A3T3] [10-12].

**1.4.2 Intercalators**

These have stacking planar heterocyclic groups between neighbouring DNA base pairs. The complex is thought to be stabilised, among other things, by drug-DNA base interactions 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 exception of the daunomycin-DNA interaction, which 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 an intercalation process.[13]

To see DNA and DNA interactions in vivo and in vitro, DNA intercalators are frequently utilised as fluorescent probes. They are well known to disrupt DNA stability and structure, which can affect how proteins process DNA. Wuite et al. measure the kinetics of DNA intercalation using the mono- and bis-intercalating cyanine dyes SYTOX Orange, SYTOX Green, SYBR Gold, YO-PRO-1, YOYO-1, and POPO-3 in order to elucidatr perturbation  by combining single-dye fluorescence microscopy with force spectroscopy.[14] They demonstrated that a significantly tension-dependent dissociation rate primarily controls their DNA-binding affinity. By adjusting DNA tension, intercalating species, and ionic strength, these rates can be adjusted over a span of seven orders of magnitude. The effect of intercalators on strand separation and enzymatic activity is reduced by optimising these rates.

* 1. **Oxaliplatin**

In present study the stability of Binding Oxaliplatin-DNA has been examined theoretically. 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.



**Figure 1 (a) Chemical Structure of Oxaliplatin [Pt(R,R-DACH)]2+**



**Figure 1 (a) Chemical Structure of [Pt(s,S-DACH)]2+**

It is a new third-generation platinum compound which is effective in the treatment of advanced ovarian and colorectal malignancies. 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.

The biological effects of third generation platinum anticancer drug oxaliplatin and traditional cisplatin are thought to differ due to downstream mechanisms that distinguish between DNA adducts of each. The fact that oxaliplatin can more effectively generate DNA adducts in their biological effects is what accounts for these various biological consequences. In three different sequence contexts. The differential scanning calorimetry (DSC) of oxaliplatin and its Enantiomeric Analog has been published by Malina *et. Al*[15]. Their work described recognition by the HMG domain protein and DNA polymerization across the significant 1,2-GG intrastrand cross-link created by cisplatin and oxaliplatin. In present study, modified Zimm and Bragg theory [16] have been used to study the effect of binding of oxaliplatin and its enantiomer with DNA.

1. **Theoretical approach to study the binding of Oxaliplatin with DNA**

Calorimetric analysis of the complex formed between oxaliplatin and DNA by Malina *et. al* suggests that that the melting transitions of both the platinated and unmodified duplexes are fully reversible, Each transition shows negligible changes in the heat capacities between the initial and final states.

The co-operative transition hypothesis can be applied to clarify the melting profile and temperature dependability of thermodynamical parameters including heat capacity despite the fact that the system is still very cooperative. The modified Zimm and Bragg theory had been thus adopted. The Ising-Model, which was developed to examine the ferromagnetic transition in linear chains of spins, is a foundation for all theories. A residue in a long polymer chain can exist in either an ordered or disordered form; much like a spin can exist in either a spin up or spin down state. 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. The first ordered state in a sequence of ordered states is this boundary state. 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 [17–23] and by Zimm and Bragg [16] can be represented mathematically as follows;

 M =

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

 λ3=0 …..(1)

 Because we are working with a finite system, the impact of the starting and end states becomes crucial. The following provides the first segment's contribution to the partition function:

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, the partition function can be written 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.

The total absorption can be expressed as follows if Ar and Ah represent absorbance in the disordered and ordered states, respectively:

…..(13)

 It is simple to extend this formalisation to specific heat. The changes in molar enthalpy and entropy during the transition from state I to state II 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 A0 is a constant often of universal value [3.9×10-9 (Kmol)/J-1] and Tm is the melting temperature.

1. **Discussion**

 **3.1 TRANSITION PROFILE**

Since DNA's structure is still quite cooperative after mithramycin 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. 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) [15]. A reduction in the total transition enthalpy of the duplexin occurs concurrently with the drug-induced increase in the thermal stability of the duplex. Unmodified DNA melts at 332.109 K The melting temperatures of the DNA saturated with the drugs [Pt(R,R-DACH)]2+  and [Pt(S,S-DACH)]2+  are 321.477 K and 318.493 K, respectively.

Table 1 lists the several variables that, when combined, result in mithramycin binding to DNA transition profiles that best match experimental findings. To determine how acute the transition is, use a sensitivity parameter with the symbol ΔH/ σ. It can be seen that the transition is sharpest in the case of an unbounded state.

**Figure 2 Heat capacity and transition profile of unmodified DNA**

**Figure 3 Heat capacity and transition profile of DNA bounded with oxaliplatin [Pt(R,R-DACH)]2+**

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

**Table1.Transition parameters for WP762 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 |

**3.2 HEAT CAPACITY**

The second derivative of the free energy, is used to describe the structural and dynamical states of a macromolecular system [23]. 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 persistent measurement inaccuracy that causes a constant change in the experimental results is explained by these variables.

 A closer look at these thermodynamic parameters reveals several intriguing characteristics: First, CL formation of [Pt(R,R-DACH)]21 or [Pt(S,S-DACH)]21 reduced the thermal stability of duplex. The drop in DNA melting temperature caused by the CLs of both enatiomers was comparable to that caused by the CL of cisplatin produced in the same sequences, i.e., AGGC or CGGA, but it was significantly larger. If cisplatin and DACH complex CLs developed in the TGGT sequence as opposed to the other two sequences, the duplex thermal stability was significantly reduced. Additionally, whereas [Pt(R,R-DACH)]21's CL reduced DNA melting temperature to the same degree as cisplatin, [Pt(S,S-DACH)]21's CL was more effective in this regard.

Second, the enthalpy of duplex dissociation significantly decreased as a result of CL creation by cisplatin and DACH complexes (Table 1). In contrast to its unmodified cousin, the duplex is enthalpically destabilised by the intrastrand CL of these platinum complexes. If the intrastrand CLs of DACH complexes were produced in the CGGA or AGGC sequences, they were more efficacious in this regard than cisplatin. The ability of these CLs to thermodynamically destabilise the duplex, however, varied only little whether the CLs of [Pt(R,R-DACH)]21 and cisplatin were generated in the TGGT sequence. It's interesting to note that compared to its R,R counterpart, the intrastrand CL of [Pt(S,S-DACH)]21 produced in this latter sequence thermodynamically destabilised the duplex much more.

1. **Conclusion**

One of the goals of conducting biophysical studies of drug-DNA interactions is to develope design techniques for novel compounds with therapeutic or biotechnological applications is. In this paper, I've made an effort to demonstrate how in-depth thermodynamic studies might be an effective instrument for delivering knowledge that can direct such initiatives. Along with the sorts of energy analyses mentioned above, it's necessary to take into account potential cooperative effects in drug-DNA binding.

Thus, in addition to affecting the transition enthalpy and the melting temperature, drug binding also affects the features of the transition, as shown by the increase in transition breadth in both experimental and computed 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 results of the current study 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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