

# Drug-DNA Interaction: A Theoretical Study of the Stability of CP-DNA Binding with Thionine

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## ABSTRACT

The recent study on binding of small molecules to double stranded DNA suggested that the intercalation of a tricyclic heteroaromatic molecule, thionine, with natural DNA provided thermal stabilization to the complex. In the present study, we reported theoretical analysis of thionine binding with *Clostridium perfringenes* DNA duplex (CP-DNA) by using an amended Zimm and Bragg theory, to explain the melting behaviour and heat capacity of CP-DNA with and without thionine binding. The experimental models of Paul *et al.* (2010) have been used for the study. The sharpness of transition has been examined in terms of half width and sensitivity parameter ( $\Delta H/\sigma$ ). The results of theoretical approach suggested that the various parameters such as transition profile, sharpness of the transition, heat capacity curve and half widths are in good agreement with the experimental measurements for binding of thionine. Therefore, the proposed theoretical analysis may be useful in order to understand interaction of small molecules to DNA that may be applied in the process of drug development and for designing more potential DNA binding therapeutic molecules.

**Keywords:** Thionine; DNA Binding; Transition Profile; Heat Capacity; Drug Design

## 1. Introduction

The study of the interaction of small molecules with DNA is a field of high tropical interest and the number and verity of techniques devoted to evidence drug-DNA interactions is continuously growing. The binding of heterocyclic aromatic molecules to nucleic acids has received considerable attention over the past several years due to their relevance in various biological applications including cancer chemotherapy [1-8]. Accordingly, a number of experimental studies are conducted to understand the nature and thermodynamics of heterocyclic aromatic molecules and nucleic acid interaction [7,9-16]. Thionine (3,7-Diamino-5-phenothiazinium) (**Figure 1**), a tricyclic heteroaromatic molecule, has been studied for its intercalative interaction with duplex DNA [13] and photoinduced mutagenic actions on binding to DNA [11]. On the basis of satellite hole spectroscopy study Chang *et al.* [17] recommended that thionine binds specifically with guanine-cytosine (GC) contents of duplex DNA. However, Tuite and Kelly [13] suggested that (GC) specificity of thionine binding was not very marked. The model proposed by Hecht *et al.* [18,19] suggested that thionine exists in two different tautomeric forms and the amino form is intercalated while the imino form is not. Although these data provide somewhat cont radicting

data on the GC specificity of thionine binding to linear double stranded DNA. A recent study [18] by pressure tuning hole burning spectroscopy has conclusively shown an external stacking mode of binding of thionine to quadruplex structures. Thus, although some structural data is available, the same is not conclusive and the thermodynamics of thionine binding to DNA is not yet elucidated. The calorimetric analysis of thionine binding to a DNA duplex was reported by Paul *et al.* [7]. They also investigated the structural and thermodynamic aspects of thionine binding to natural DNAs of varying base composition. They showed strong binding of thionine with CP-DNA which increases the thermal stability of the duplex, and at saturation the duplex melts with a  $T_m$  some 6.3°C above that of the free duplex [7]. They also concluded that binding of thionine to CP-DNA is an exothermic process and there is involvement of multiplicity of non covalent interactions in the binding process. In the present study, we have attempted to understand the effect of thionine binding on a native DNA duplex using the model of Paul *et al.* [7] who studied the thermal and

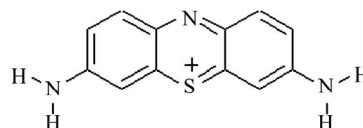


Figure 1. Chemical structure of thionine.

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thermodynamic behaviour of thionine binding to CP-DNA. To elucidate lambda point anomalies in heat capacities and order-disorder transition in thionine bounded and unbounded DNA duplexes, we used amended Zimm and Bragg theory which is considered initially for the helix coil transitions in polypeptides [20-22]. The effect of thionine binding is reflected in the change in nucleation parameter, which is an inverse measure of binding strength.

## 2. Theory

The results of the structural studies proposed by Paul *et al.* [7] for the complex of heterocyclic aromatic molecules with DNA on the basis of spectroscopic and calorimetric study, as mentioned above, suggested that thionine binds strongly with the *Clostridium perfringens* DNA that resulted in thermal stabilization of the complex. The binding of thionine to the AT rich *Clostridium perfringens* DNA was intercalative and favored by higher entropic contribution indicating the stronger perturbation of the water structure associated with the AT sequences [7]. However, the system remains a highly co-operative one therefore the co-operative transition theory could be applied to explain the melting profile and temperature dependence of thermodynamical parameter, such as heat capacity. Therefore, we can use amended Zimm and Bragg theory [20] which is described in our previous publication [23]. Briefly, the above mentioned theory consists of writing an Ising matrix for a two-phase system, the bounded state and unbounded state. As discussed earlier [21,22,24-26] and by Zimm and Bragg [20], the Ising matrix  $M$  can be written as:

$$M = \begin{matrix} & \begin{matrix} f_r & f_k & f_h \end{matrix} \\ \begin{matrix} f_r \\ f_k \\ f_h \end{matrix} & \begin{vmatrix} f_r & f_r^{1/2} f_r^{1/2} & f_r^{1/2} f_k^{1/2} & 0 \\ f_r^{1/2} f_r^{1/2} & 0 & f_k^{1/2} f_h^{1/2} \\ f_h^{1/2} f_r^{1/2} & 0 & f_h^{1/2} f_h^{1/2} \end{vmatrix} \end{matrix} \quad (1)$$

where  $f_r$ ,  $f_h$  and  $f_k$  are corresponding base pair partition functions' contributions in the three states *i.e.* ordered, disordered and boundary or nucleation. The eigen values of  $M$  are given by:

$$\begin{aligned} \lambda_1 &= \left[ (f_r + f_h) + \left\{ (f_r - f_h)^2 + 4f_r f_k \right\}^{1/2} \right] \\ \lambda_2 &= \left[ (f_r + f_h) - \left\{ (f_r - f_h)^2 + 4f_r f_k \right\}^{1/2} \right] \\ \lambda_3 &= 0 \end{aligned} \quad (2)$$

Since we are dealing with a finite system hence the effect of initial and final states becomes important. The contribution of the first segment to the partition function is given by:

$$U = (f_r^{1/2}, 0, 0) \quad (3)$$

where the column vector  $V$  gives the state of the last segment,

$$V = \begin{vmatrix} f_r^{1/2} \\ f_k^{1/2} \\ f_h^{1/2} \end{vmatrix} \quad (4)$$

The partition function for an  $N$ -segment chain is given by;

$$Z = UM^{N-1}V \quad (5)$$

The matrix  $T$  which diagonalizes  $M$  consists of the column vectors given by:

$$MX = \lambda X \quad (6)$$

$$\text{where, } X = \begin{vmatrix} X_1 \\ X_2 \\ X_3 \end{vmatrix}.$$

By substituting the values of  $M$  from Equation (6), we get:

$$T = \begin{vmatrix} 1 & 1 & 1 \\ \frac{(\lambda_1 - f_r)}{(f_r^{1/2} f_k^{1/2})} & \frac{(\lambda_1 - f_r)}{(f_r^{1/2} f_k^{1/2})} & -\left(f_r^{1/2} f_k^{1/2}\right) \\ \frac{(f_h^{1/2} f_r^{1/2})}{(\lambda_1 - f_h)} & \frac{(f_h^{1/2} f_r^{1/2})}{(\lambda_1 - f_h)} & -\left(f_h^{1/2} f_r^{1/2}\right) \end{vmatrix} \quad (7)$$

Similarly, we get  $T^{-1}$  from the matrix equation

$$YM = \lambda Y \quad (8)$$

where,  $Y = [Y_1, Y_2, Y_3]$

Again by substituting the values of  $M$  from Equation (1) in Equation (8), we get:

$$T^{-1} = \begin{vmatrix} C_1 & \frac{c_1(f_r^{1/2} f_k^{1/2})}{\lambda_1} & \frac{c_1(f_k f_r^{1/2} f_h^{1/2})}{\lambda_1(\lambda_1 - f_h)} \\ C_2 & \frac{c_2(f_r^{1/2} f_k^{1/2})}{\lambda_2} & \frac{c_2(f_k f_r^{1/2} f_h^{1/2})}{\lambda_2(\lambda_2 - f_h)} \\ C_3 & \frac{c_3(f_r^{1/2} f_k^{1/2})}{\lambda_3} & \frac{c_3(f_k f_r^{1/2} f_h^{1/2})}{\lambda_3(\lambda_3 - f_h)} \end{vmatrix} \quad (9)$$

The normalization constants are:

$$C_1 = \frac{\lambda_1 - f_h}{\lambda_1 - \lambda_2}, C_2 = \frac{\lambda_2 - f_h}{\lambda_2 - \lambda_1}, C_3 = 0 \quad (10)$$

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

$$Z = UT\Lambda^{N-1}T^{-1}V \quad (11)$$

On substituting the values from Equations (1), (3), (4), (7), (9) and (10) in Equation (11), the partition function becomes:

$$Z = C_1 \lambda_1^N + C_2 \lambda_2^N \quad (12)$$

The fraction of the segments in the disordered form is given by

$$Q_r = [\delta \ln Z / \delta \ln f_r] / N$$

Solving the above equation, we get:

$$Q_r = \frac{1}{2} + \frac{(1-s)(2A-1)}{2P} + \frac{(1+s)\{(2A-1)P-1+s\}}{2P^2N} \quad (13)$$

where  $P = \frac{\lambda_1 - \lambda_2}{f_r}$

$$s = \frac{f_h}{f_r}$$

$$\sigma = \frac{f_k}{f_r}$$

$$A = \left[ (f_r - f_h)^2 + 4f_k f_r \right]^{-2}$$

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

with

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

$\delta P / \delta S = (S-1)/P$  and  $\sigma = f_k / f_r$ ;  $\sigma$  is the nucleation parameter and is a measure of the energy expanded/released in the formation (uncoiling) of first turn of the ordered/disordered state. It is related to the uninterrupted sequence lengths [20]. The volume heat capacity  $C_v$  has been converted into constant pressure heat capacity  $C_p$  by using the Nernst-Lindemann approximation [26]:

$$C_p - C_v = 3RA_0 (C_p^2 T / C_v T_m) \quad (16)$$

where  $A_0$  is a constant often of a universal value [ $3.9 \times 10^{-9}$  (Kmol) $^{J^{-1}}$ ] and  $T_m$  is the melting temperature.

### 3. Results

#### 3.1. Transition Profiles

The binding affinity of thionine with C-DNA has been studied by spectroscopic, fluorescence and dialysis methods which showed strong intercalative binding and enabled the assumption of two state systems consisting of

here  $s$  is propagation parameter, which for simplicity is assumed to be 1. In fact, in most of the systems, it is found to be close to unity. If  $A_r$  and  $A_h$  are the absorbance in disordered and ordered states, respectively, the total absorption can be written as:

$$A = Q_r A_r + (1 - Q_r) A_h \quad (14)$$

The extension of this formalism to specific heat ( $C_v$ ) is straight forward. The specific heat is related to the molar enthalpy and entropy changes in the transition from state I to II. From the well known thermodynamic relations, free energy and internal energy are  $F = -KT \ln Z$  and  $U = -T^2 (\delta / \delta T)(F/T)$ , respectively. Differentiating internal energy with respect to temperature we get the specific heat:

$$C_v = \delta U / \delta T = N_k (\Delta H / RT_m)^2 (S \delta Q_r / \delta S) \quad (15)$$

where  $\Delta H$  is the molar change in enthalpy about the transition point,  $S$  is entropy which is equal to

$$S = \exp \left[ (\Delta H / R) \left\{ (1/T) - (1/T_m) \right\} \right],$$

$T_m$  is the transition temperature, and

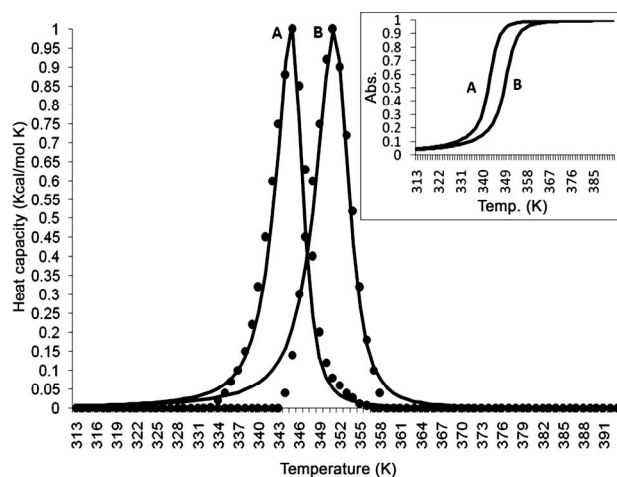
bound and free thionine [7]. When tricyclic heteroaromatic thionine binds with natural *Clostridium perfringenes* DNA duplex, the structure of DNA duplex still remains a very much co-operative and thus two-state theory of order-disorder transition is applicable. The Zimm and Bragg theory [7] is amended so as to consider ordered (bounded/unbounded) and disordered states as the two states which co-exist at the transition point. The transition is characterized mainly by the nucleation parameter and overall change of enthalpy/entropy, which are also the main thermodynamic forces driving the transition. The change in enthalpy obtained from differential scanning calorimetric measurements takes all this into account. This is evident from the enthalpy change and changes in other transition parameters, such as nucleation parameter ( $\sigma$ ) and melting point (**Table 1**). The melting temperature of the duplex was increased after binding with thionine at saturation. At saturation, the duplex melts with a  $T_m$  some 6.5°C above that of the free duplex. The sharpness of the transition can be looked at in terms of half width and a sensitivity parameter defined as  $(\Delta H / \sigma)$ . The variation of these parameters systematically reflects that the transition is sharp in case of unbounded state and goes blunt with thionine saturation. In case of

$\lambda$ -transition, the same trend in the sharpness of transition is seen between the thionine bounded as well as unbounded curves. As expected, the sharpness is better in unbounded, as compared to bounded state. The various parameters, which give transition profiles in best agreement with the experimental measurements for binding of thionine to CP-DNA, are given in **Table 1**.

The transition profiles and heat capacity for unbounded DNA duplex and bounded with thionine are shown in **Figure 2**. Minor insignificant deviation at the tail ends is primarily due to the presence of various disordered states and presence of short helical segments found in the random coil states. **Figure 2 A** shows experimental and calculated transition curves for the duplex in the absence of thionine and **B** shows the transition when the duplex is saturated with thionine (thionine/DNA = 0.4). As expected, a cooperative transition profile is observed with calculated data. The conclusion deduced from the theoretical data is consistent with the directly measured binding enthalpy by Paul *et al.* [7] determined through DSC.

**Table 1. Transition parameters for thionine binding to CP-DNA.**

Parameters	Unbounded CP-DNA	CP-DNA saturated with thionine
$T_m$ (K)	345	351.5
$\Delta H$ Kcal/M bp	$3.06 \times 10^3$	$3.24 \times 10^3$
$\sigma$	$3 \times 10^{-4}$	$5 \times 10^{-4}$
$N$	98	90
$A_h$	0	0
$A_r$	1	1
Half width (Exp.)	5	6.5
Half width (Theo.)	5	6.5
Sensitivity parameter ( $\Delta H/\sigma$ )	$102 \times 10^5$	$648 \times 10^4$



**Figure 2. Heat capacity and transition profiles (inset) for thionine bounded and unbounded CP-DNA. A: Unbounded state; B: Bounded state at saturation. [(—) calculated and (•••) experimental values].**

### 3.2. Heat Capacity

The conformational and dynamical states of a macromolecular system are characterized by heat capacity which is second derivative of the free energy and has been calculated by using Equation (14). These heat capacity curves with  $\lambda$ -point anomaly are shown in **Figure 2** along with their transition profile. The theoretically obtained heat capacity profiles agreed with the experimentally reported ones and could be brought almost into coincidence with the use of scaling factors, which is very close to one in transition profiles and slightly higher for the heat capacity curves. The sharpness of the transition can be characterized by the half widths of the heat capacity curves that are in good agreement in both experimental and theoretical graphs.

### 4. Discussion

The present study concluded that the natural CP-DNA molecule is an extremely co-operative structure and when thionine bind to it the co-operativity is not so much disturbed. Therefore, the amended Zimm and Bragg theory (phase transitions theory) can be effectively applied to it. It generates the experimental transition profile and  $\lambda$ -point heat capacity anomaly successfully. These results will allow us to assess the thermodynamic profile of the binding process. Our theoretical studies of heterocyclic aromatic molecules binding are being extended to other synthetic and natural nucleic acids. The theoretical data obtained also demonstrated that the binding of thionine to CP-DN is an endothermic process and that this binding increases the melting temperature of the duplex as supported by calorimetric measurement. The specific binding and intercalation of thionine with DNA have been studied by using spectroscopic methods [13,17]. However, Paul and her coworkers used optical melting and DSC techniques to understand the interaction of small molecule, thionine, with double stranded deoxyribonucleic acid, native CP-DNA [7]. The binding of thionine stabilized CP-DNA and  $\Delta T_m$  value of about 6.3°C was obtained under saturating condition. Accordingly, we can interpret our theoretical results in the context of the specific structural features of the complex as deduced from their spectroscopic/DSC data. Inspection of **Figures 2 A** and **B** reveals that the transition of the thionine-saturated CP-DNA duplex is significantly broader than the transition of the thionine-free duplex. Thus, in addition to affecting the transition enthalpy and the melting temperature, binding of heterocyclic aromatic molecules also alters the nature of the transition as reflected by the increase in transition width in experimental and calculated (theoretical) both data. In recent years, an increased understanding of the role played by nucleic acids in biological systems made DNA an alternative candidate for

the development of new drugs. The successful applications of molecular modeling in virtual ligand screening and structure-based design of organic and inorganic molecules that target DNA are highlighted by Ma *et al.* [27]. The interactions of drugs and calf thymus DNA were also investigated by using non-linear fit analysis [28]. Other recent literatures also reviewed that the study of DNA interaction with a small molecules is of high interest [7,29-32]. Thus, the present theoretical analysis can be applied to understand bimolecular interaction and may also be implicated to the process of drug development in biomedical industries.

## 5. Acknowledgements

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