# Binding interaction of Trivalent Praseodymium with Calf Thymus DNA: A Comparative Study

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## Abstract

The interaction of trivalent praseodymium ion with Calf-Thymus DNA (CT-DNA) has been studied by employing absorption spectroscopy involving 4f-4f transitions. The absorption spectra of Pr(III) exhibits hyperchromism without shifting in wavelength on increasing the amount of CT-DNA thereby inducing the subsequent changes in the oscillator strengths of different 4f-4f bands. The other spectral parameters namely Slator-Condon, nephelauxetic ratio, bonding and covalency parameters were also determined to correlate with the binding of calf-thymus DNA to Pr(III). The binding constant, $K_b$ has been determined and found to be $5.18 \times 10^2$ $M^{-1}$. The viscosity of rod-liked DNA was found to be decreased on addition of Pr(III). The absorption and viscosity measurement result suggest the non-intercalative mode of binding between trivalent praseodymium and Calf-thymus DNA. Thermodynamic parameters determined from relevant absorption data further revealed the appearance of hydrophobic interaction in addition to electrostatic mode of binding on negatively charged DNA phosphate backbone that occurs along external DNA double helix.

## 1. Introduction

Studies on the interaction of metal ions with DNA have resulted useful since it plays a crucial role in the biological activity of nucleotides and nucleic acids changing their properties in ways that depends on the nature of the metal ion [1]. Metal ions are believed to be important cofactors in DNA structures and function, facilitating the double helical structure stabilization and catalysis [2]. Also the extent of hydration of cations bound to DNA is a key parameter in the energies of the binding process as well as a relevant issue in the catalytic roles and structural effects of bound ions. An understanding of the factors involved in metal ion-DNA interaction is thus of considerable importance.

Calf Thymus DNA (CT-DNA) is a polymer. The DNA backbone contains alternating sugar phosphate sequence. CT-DNA has relatively low protein content with a highly polymerised skeleton. Interaction of DNA with small molecules, in general involve the three types of binding modes : (i) electrostatic binding between the negatively charged DNA phosphate backbone that is along the external DNA double helix and the cationic or positive end of the polar molecule, (ii) groove binding involving hydrogen bonding or van der Walls interaction with the nucleic acid bases in the deep major groove or the shallow minor groove of the DNA helix and finally, (iii) intercalative binding where the molecule interacts itself within the nucleic acid base pairs[3,4]. Studies directed toward the design of site – and conformation-specific reagents provide rationale for new drug design as well as a means to develop sensitive chemical probes for nucleic acid structure. Trivalent lanthanide ions, Ln(III) have been known to have attractive, spectroscopic and magnetic properties [5] and have been used as probes for the interaction of metal ions with DNA. Nucleic acid may be considered to be ambidentate ligands, with various potential binding sites, including nitrogen and oxygen donor atoms on the bases, hydroxyl groups on the ribose sugar, and negatively charged oxygen atoms in the phosphate groups. As a consequence of the abundant of negatively charged oxygen donor groups, the DNA molecule readily interact with Ln(III) ions. Pr(III) possess many similarities in their properties to Ca(II) and isomorphous replacement of this cation by Ln(III) ions holds out the promise of exploiting the rich and variety of spectroscopic properties of the lanthanides for obtaining information on the structure of Ca(II) in biological systems [6,7]. In last few years, we have initiated research work on the binding

behaviour of some amino acids and peptides to trivalent lanthanides using 4f-4f transition spectra.[8-10].

Previously, we have studied the binding behaviour of Nd(III) with Calf-thymus DNA in different solvents [11]. In the present study as a continuation of our research work, we have utilized the pseudohypersensitive transitions of Pr(III) to investigate the binding behaviour of trivalent praseodymium, Pr(III) with Calf-thymus DNA. The binding constant has been determined basing on the intensity of pseudohypersensitive transition of Pr(III). Viscosity measurement is further carried out for distinguishing the binding mode of DNA binding agents. Thermodynamic parameters of the DNA binding were determined to further characterise the binding force between Pr(III) and CT-DNA.

## 2. Materials and Methods

### 2.1. Materials and Reagents

Praseodymium nitrate hexahydrate were purchased from CDH, Mumbai and Calf Thymus DNA from Sigma was used as supplied. All solvents used were of analytically grade. All the experiments involving interaction of the Pr(III) with Calf-Thymus DNA were formed in Tris-HCl (0.01 M, $P^H$-7.4). Double distilled water was used to prepare all stock solutions for DNA binding studies. The absorption spectral data were recorded on temperature controlled Perkin Elmer Lambda -35 UV-Vis Spectrophotometer with attached kinetic assembly.

### 2.2. Absorption titration experiment

Solutions of CT-DNA in buffer gave a ratio of UV absorbance at 260 and 280 nm, $A_{260}/A_{280}$, of 1.8-1.9 indicating that DNA is free from protein [12]. The DNA concentration was measured by its absorbance at 260 nm using the molar extinction coefficient, $6600M^{-1}cm^{-1}$. Absorption titration experiments were carried out in a quartz cell by adding increasing amounts of CT-DNA to a solution of Pr(III) of a fixed concentration, and recording the UV-Vis spectrum after each addition. The intrinsic binding constant ($K_b$) for the interaction of Pr(III) with CT-DNA was determined from a plot of $A_0/{A-A_0}$ Vs $1/[DNA]$ using the following equation [13]:

$$\frac{A_0}{A-A_0} = \frac{\varepsilon_P}{\varepsilon_{P-D}-\varepsilon_P} + \frac{\varepsilon_P}{\varepsilon_{P-D}-\varepsilon_P} \frac{1}{K_b[DNA]} \quad (1)$$

where "$A_0$" and "$A$" are the absorbance of Pr(III) in the absence and presence of DNA, $\varepsilon_P$ and $\varepsilon_{P-D}$ are their absorption coefficients respectively. P and P-D represents Pr(III) and Pr(III)-DNA species. The $K_b$ value is given by the ratio of intercept to the slope.

### 2.3. Viscosity measurements

Viscosity measurements was performed on a Rheometer (BRUKER), immersed in a thermostated water bath maintained at $25^oC$. Titrations are performed by the addition of aliquots of the Pr(III) ($1 \times 10^{-4}$ - $5 \times 10^{-4}$ mM) solution into a constant concentration of DNA in the viscometer. Data are presented as $\left(\eta/\eta_0\right)^{1/3}$ versus the concentration of Pr(III), $\eta$ is the viscosity of DNA in the presence of Pr(III) and $\eta_0$ is the viscosity of DNA alone.

### 2.4. Methods

The experimental oscillator strength has been determined using the known equation [14],

$$P = 4.31x10^{-9}\left[\frac{9\eta}{(\eta^2+2)^2}\right]\int \varepsilon(\upsilon)d\upsilon \quad (2)$$

where $\upsilon$ is the energy of the transition, $\varepsilon$ the molar extinction coefficient and $\eta$ the refractive index of the medium, were calculated [15].

Theoretically, Judd-Ofelt predicts that that the intensity of 4f-4f transitions arises principally from forced electric dipole mechanism. Thus the electric dipole oscillator strength (P) is expressed as the product of $T_\lambda$ parameters and appropriate transition matrix element $U^{(\lambda)}$ at frequency of transition $J \to J'$, i.e.,

$$P_{cal} = \sum_{\lambda=2,4,6}T_\lambda\upsilon\left(f^n\psi_J\left\|U^\lambda\right\|f^n\psi_{J'}\right)^2 \quad (3)$$

The Judd-Ofelt intensity parameters are empirical, yet these show high sensitivity towards even minor changes in the coordination environment and symmetry of the molecule [16]. These parameters have been widely used in the structure elucidation of lanthanoid coordination compounds in solution.

The energy of 4f-4f transitions comprises of two main components: coulombic (represented by inter-electronic repulsion ($F_k$, Slater Condon) and spin-orbit (Lande-$\xi_{4f}$) components. The complexation of lanthanoids bring about lowering of nephelauxetic effect represented by nephelauxetic ratio ($\overline{\beta}$) :

$$\beta_1 = \frac{F_k{}^c}{F_k{}^f} ; \quad \beta_2 = \frac{\xi_{4f}{}^c}{\xi_{4f}{}^f} ; \quad \overline{\beta} = \frac{\beta_1+\beta_2}{2} \quad (4)$$

$$b^{1/2} = \left[\frac{1-\beta}{2}\right]^{1/2} \qquad \delta = \left(\frac{1-\beta}{\beta}\right)\times100 \quad (5)$$

Bonding (b) and percent covalency parameter ($\delta$) which are related to nephelauxetic ratio ($\beta$) are also used to describe the structural features of a lanthanoid complexes. The significance and evaluation of these ($F_k$, $\overline{\beta}$, $\delta$, $\xi_{4f}$ and $b^{1/2}$) parameters have been discussed in our earlier papers [17,18]. Peacock[19] has shown that the inclusion of covalency can affect the angular part of the 4f wave function. Writing metal wave function as the sum of the original 4f wave function and ligand wave function weighted by mixing coefficient (b) also known as bonding parameter and related to nephelauxetic effect.

$$<\varphi_{4f} = (1-b)^{1/2} <4f\,|-b^{1/2}<\varphi_{ligand}| \quad (6)$$

## 3. Results and Discussions

The sensitivity of hypersensitive bands in lanthanides towards the coordination environment has been recognised since long. A few, however, are very sensitive to the environment and are usually more intense when a lanthanide ion gets complexed than it is in the corresponding aquo ion. Such transitions are called hypersensitive transition [20]. But the transitions $^3H_4 \to ^3P_2$, $^3P_1$, $^3P_0$ and $^1D_2$ of Pr(III) do not obey the selection rules for hypersensitive transition, but have been found to exhibit substantial sensitivity with even minor coordination changes in the immediate coordination environment around

it and they are termed as Ligand Mediated Pseudo hypersensitive or Pseudo hypersensitive transition.

The introduction of DNA in to Pr(III) leads to changes in the energies of 4f-4f bands which causes the degree of lowering in the energy interaction parameters namely Slator-Condon interelectronic repulsion causing expansion of electron cloud of 4f orbital leading to M-L bond covalency. This phenomenon of nephelauxetic effect has long been regard as a measure of covalency. The introduction of covalency to Pr(III)-L bonding causes the intensification of 4f-4f bands. This is clearly shown in Table 1 and Table 2. The significant lowering of these parameters takes place in complexes as compared to the values for aquo ions indicating the expansion of the central metal ion orbital on interaction.

The intensity parameters are reflected in the form of oscillator strengths ($P$) and determined under different experimental conditions for Pr(III)-DNA interaction (Table 2). A noticeable enhancement in the oscillator strengths of 4f-4f bands on addition of DNA suggest the binding of CT-DNA to Pr(III) in solution. The intensifications of bands can be interpreted in terms of extent of interaction of 4f-orbitals with ligand. We observed significant variation in the magnitude of oscillator strength on varying the composition of solvent. That is, immediate changes in the coordination environment around metal ion contribute to the intensification of 4f-4f bands. Out of the four observed transitions, $^3H_4 \rightarrow ^3P_2$ is the most intense indicated by the large value of oscillator strength followed by $^3H_4 \rightarrow ^3P_1$ and then $^3H_4 \rightarrow ^1D_2$. $^3H_4 \rightarrow ^3P_0$ band has lower oscillator strength as compared to other transitions [21, 22]. $^3P_2$ is most sensitive to the environment as indicated by the appreciable variation of oscillator strength with solvent but cannot be considered as hypersensitive as it does not obey electric quadrupolar selection rule. Although there are appreciable changes in the values of oscillator strength, the band shape of this transition does not show any marked difference in different solvents.

Another transition $^3H_4 \rightarrow ^1D_2$ also show increase in the magnitude of oscillator strength in all solvents on comparing to Pr(III) aqua ion. This transition is also sensitive in terms of intensity. We also see that there is a well agreement between the calculated and experimental values of oscillator strengths of $^3P_2$ and $^1D_2$ levels but a large difference in the corresponding values of $^3P_1$ and $^3P_0$ levels. This shows that the former transitions are affected considerably by the coordination number and geometry of the complex. So, the sensitivities of the four bands can be drawn as $^3P_2 > ^1D_2 > ^3P_0 > ^3P_1$. Absorption spectra of Pr(III) complex in different aquated organic solvents (Fig. 1) clearly shows the affinity of solvents towards the Pr(III) coordination environment. The small differences in the 4f-4f band shape in the different solvents may be related to differences in how the donor groups interact with f-electrons of the lanthanide ion. DMF appears to have strongest influence on Pr(III) : CT-DNA followed by dioxane and least in acetonitrile. This means that DMF has larger impact in promoting 4f-4f electric dipole intensity, which is in accordance with our previous studies [23,11]. Invasion of the hydration sphere about the praseodymium ion by DMF could be expected to cause alternation in strength and symmetry of field about Pr(III). Distortion of geometry around Pr(III) relaxing the selection rule for Laported

forbidden transition contribute to intensification of 4f-4f bands. The difference in oscillator strength in different solvents may be associated to ligand (solvent) structure and their coordination behaviours. The DMF has two coordination sites but it generally binds via oxygen when it coordinates to hard acids like lanthanides. The red shift is observed in the energies of all the pseudohypersensitive bands which are considered as marker for quantitative analysis in Pr(III) ion i.e. $^3H_4 \rightarrow ^3P_2$, $^3H_4 \rightarrow ^3P_1$, $^3H_4 \rightarrow ^3P_0$ and $^3H_4 \rightarrow ^1D_2$. Although we have found red shift in energies of all transitions, the effect is more pronounced in DMF. The red shift is due to the expansion of the metal orbital radius which leads to nephelauxetic effect. At the same time, the nephelauxetic effect brings about a shortening of the metal-ligand bond length thereby increasing the probability of interaction between metal and ligand orbital. This clearly shows without doubt that the interaction of Pr(III)-DNA is effected significantly by the nature of solvents. All results obtained clearly show the sensitivities of pseudohypersensitive transitions of Pr(III) on minor coordination changes, being caused by different coordinating sites of DNA, solvent nature, coordination number, nature of Pr(III):CT-DNA band which do induce significant variation in the intensity of pseudohypersensitive transitions.

## 3.1. CT-DNA binding studies

### 3.1.1. Electronic absorption titration

The absorption titration was carried out to investigate the binding affinity of Pr(III) with CT- DNA. Binding through intercalation generally results in hypochromism and a red shift (bethochromism) of the absorption band due to a strong stacking between the base pairs of the DNA [24]. Fig. 2, on the other hand, shows that the absorption intensity of Pr(III) is increased (hyperchromism) without shifting upon increasing the concentrations of CT-DNA [25]. The extend of hyperchromism is indicative of partial or non-intercalative binding modes which would possibly be (i) hydrogen bonding and (ii) electrostatic interaction between Pr(III) and the negatively charged phosphate groups on the DNA backbones. To determine qualitatively, the DNA binding strength of Pr(III), the intrinsic binding constant ($K_b$) was calculated by E1 (Fig. 3), basing on the variation of absorbance of the most intense band, $^3H_4 \rightarrow ^3P_2$, resulting $5.18 \times 10^2$ L mol$^{-1}$ at 25°C. Their $K_b$ value is lower than that of classical intercalator ethidium bromide ($1.4 \times 10^6$ M$^{-1}$) [26] suggesting that Pr(III) may bind externally along the side of the DNA without entering the core. This binding constant is a little bit smaller than that of Nd(III) [11].

### 3.1.2. Viscosity measurements

Viscosity measurement can be considered as a simple method for distinguishing the binding mode of DNA binding agents [27]. Viscosity measurements may be used to monitor such DNA structural changes of rode-like DNA [28]. Intercalation agents are expected to increase in separation of base pairs at intercalation sites causing elongation of the double helix resulting in an increase in the viscosity of DNA. In contrast, a partial nonclassical intercalation of ligand could bend the DNA helix, and reduce its effective length, concomitantly [28].
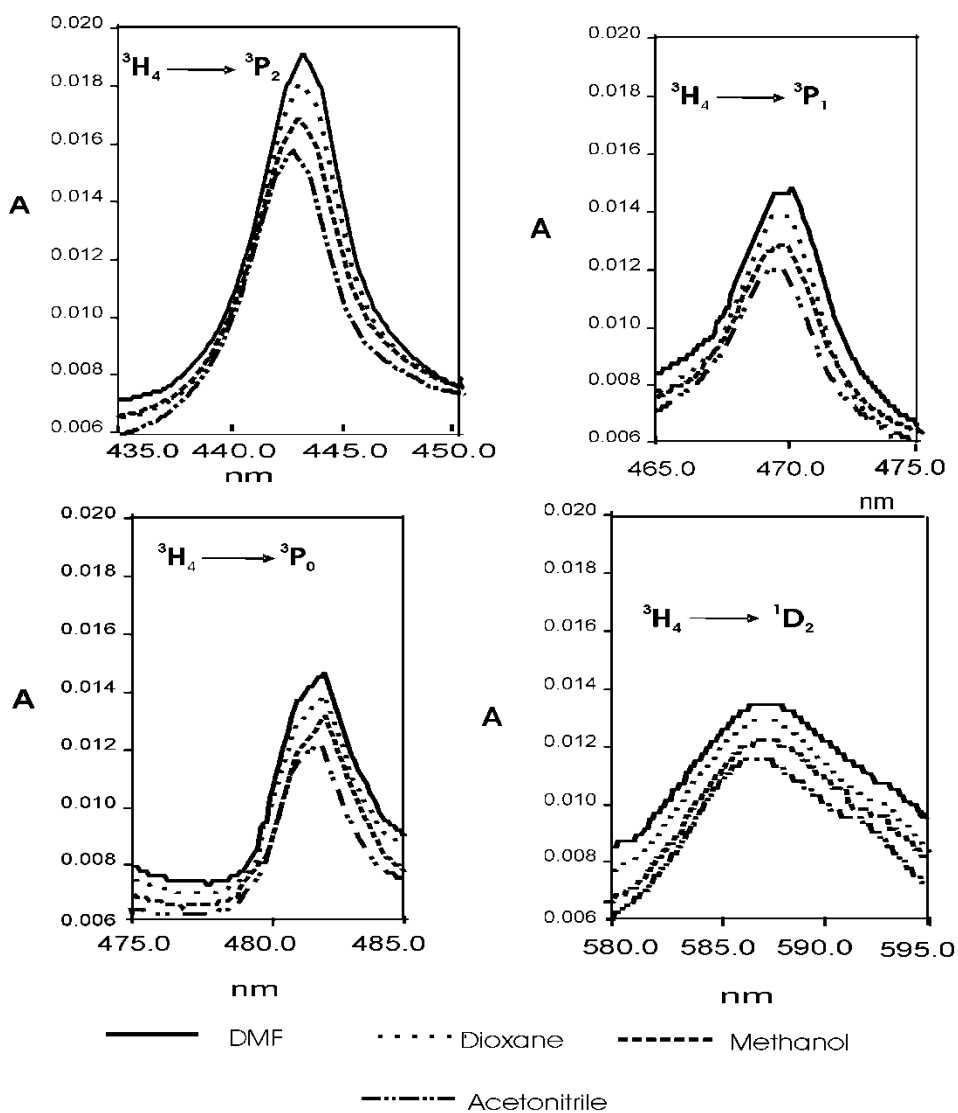
Fig. 1 Comparative absorption spectra of Pr(III):CT- DNA (1:1) in different solvents.
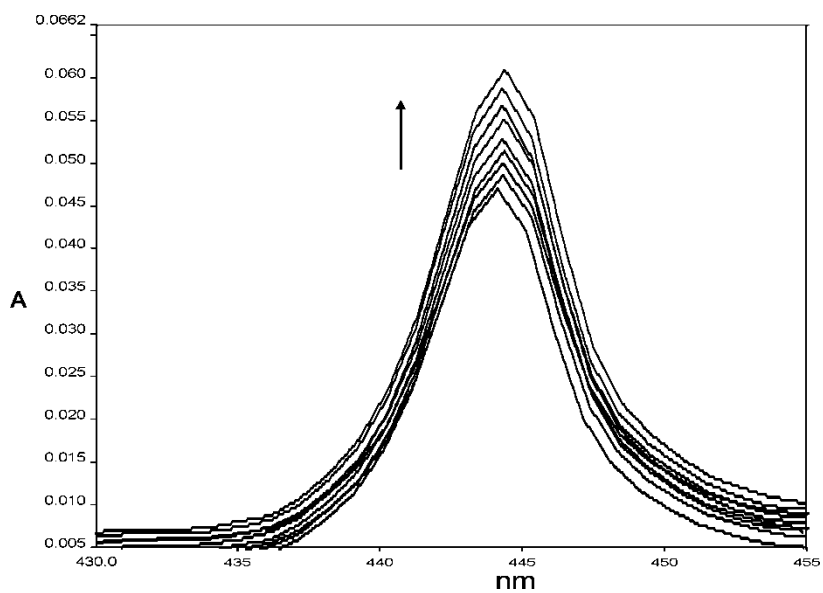


Fig. 2. Enhancement in the absorption bands of Pr(III), $^3H_4 \longrightarrow {}^3P_2$ upon increasing CT-DNA concentration. [Pr(III)]– 20μM and [DNA]–0 - 80μM in aqeous medium.
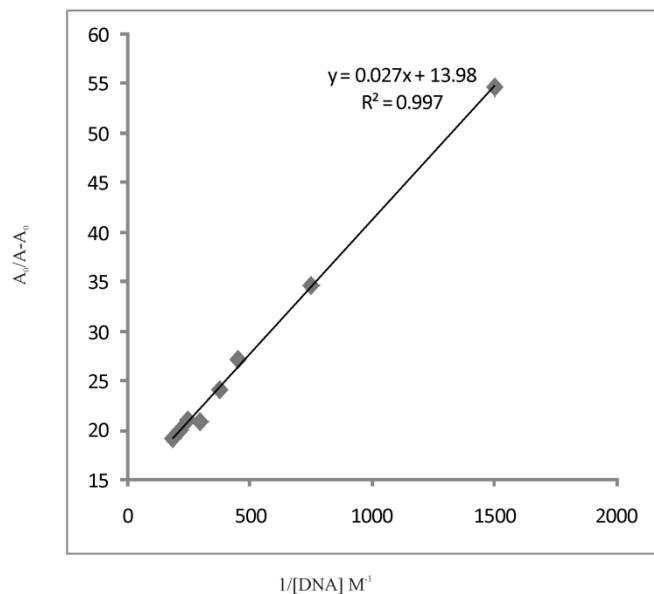
Fig. 3  The plot of $(A_0/A-A_0)$ versus $(1/[DNA])$
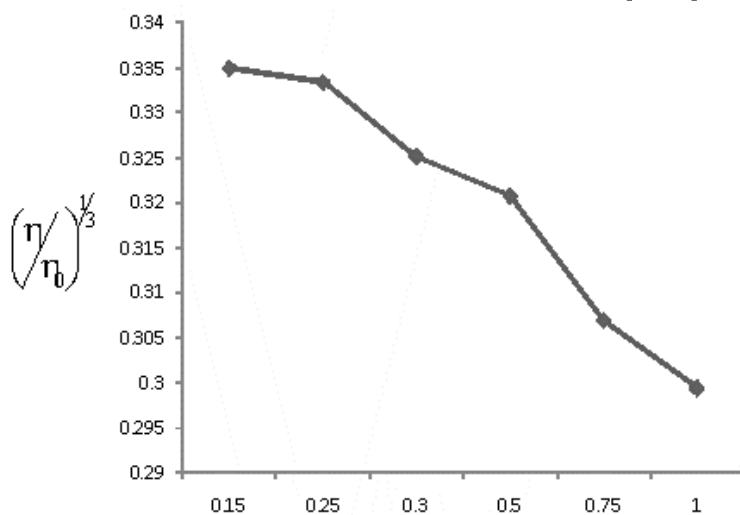    Conditions : Tris-HCl Buffer (0.01 mol L$^{-1}$, P$^H$ 7.4), [DNA]=2x10$^{-4}$ mol L$^{-1}$



Fig. 4.  Effect of increasing concentrations of metal ion on the relative viscosity of
    CT- DNA in aqueous medium . [Pr(III)]=1x10$^{-4}$- 5 x10$^{-4}$ mmol. L$^{-1}$
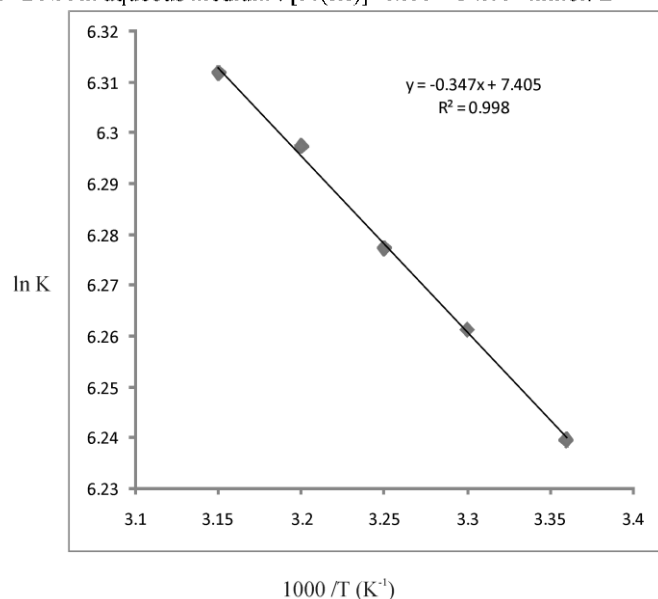


Fig. 5  Van't Hoff plot for the interaction of Pr(III) with CT-DNA in aqueous medium.

**Table 1:** Computed values of energy interaction parameters, Slator-Condon($F_k$), spin-orbit coupling constant ($\xi_{4f}$), nephelauxetic ratio (β), bonding parameters ($b^{1/2}$) and covalency parameters(δ) for the interaction of Pr(III) with Calf Thymus DNA in different solvents at 25°C

| Parameters | Pr(III) aqua-ion | Pr(III):DNA (1:1) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Methanol | Acetonitrile | DMF | Dioxane | DMF:Methanol | DMF: Dioxane | DMF:Acetonitrile |
| $F_2$ | 309.331 | 309.266 | 309.286 | 309.301 | 309.294 | 309.269 | 309.264 | 309.331 |
| $F_4$ | 42.703 | 42.671 | 42.696 | 42.700 | 42.698 | 42.684 | 42.693 | 42.703 |
| $F_6$ | 4.678 | 4.675 | 4.673 | 4.671 | 4.670 | 4.660 | 4.669 | 4.670 |
| $\xi_{4f}$ | 722.60 | 722.53 | 722.43 | 722.230 | 722.520 | 722.51 | 722.40 | 722.60 |
| β | 0.9471 | 0.9472 | 0.9469 | 0.9470 | 0.9470 | 0.9470 | 0.9469 | 0.9471 |
| $b^{1/2}$ | 0.1626 | 0.1625 | 0.1629 | 0.1627 | 0.1628 | 0.1628 | 0.1629 | 0.1626 |
| δ | 5.5833 | 5.5919 | 5.6040 | 5.5931 | 5.5953 | 5.6004 | 5.6037 | 5.5833 |

**Table 2:** Experimental (and calculated) values of ocillator strength ($P \times 10^6$) for Pr(III) : CT- DNA species in different solvents at 25C

| S'L'J' (ground state $^3H_4$) | Pr(III) aquo ion | Pr(III):DNA (1:1)  ($P \times 10^6$) | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | Methanol | Acetonitrile | DMF | Dioxane | DMF:Methanol | DMF:Dioxane | DMF:Acetonitrile |
| $^1D_2$ | 0.490 | 0.359 | 0.585 | 0.616 | 0.604 | 0.405 | 0.303 | 1.156 |
| | (0.490) | (0.359) | (0.585) | (0.616) | (0.604) | (0.405) | (0.303) | (1.156) |
| $^3P_0$ | 0.288 | 0.558 | 0.283 | 0.356 | 0.286 | 0.287 | 0.209 | 0.362 |
| | (0.951) | (0.546) | (0.390) | (0.445) | (0.379) | (0.375) | (0.286) | (0.568) |
| $^3P_1$ | 1.639 | 0.595 | 0.507 | 1.692 | 0.506 | 0.470 | 0.368 | 0.786 |
| | (0.966) | (0.555) | (0.397) | (0.452) | (0.385) | (0.381) | (0.390) | (0.576) |
| $^3P_2$ | 2.068 | 2.115 | 2.025 | 2.508 | 2.285 | 2.014 | 1.795 | 2.232 |
| | (2.068) | (2.115) | (2.025) | (2.508) | (2.285) | (2.014) | (1.795) | (2.232) |

**Table 3:** Binding constant and thermodynamic parameters for the interaction of Pr(III) and CT-DNA at different temperatures

| T (K) | $K_b$ ($M^{-1}$) | R | ΔH° ($KJmol^{-1}$) | ΔS° ($Jmol^{-1} K^{-1}$) | ΔG° ($KJmol^{-1}$) |
|---|---|---|---|---|---|
| 298 | $5.17 \times 10^2$ | 0.9984 | | | -15.52 |
| 303 | $5.18 \times 10^2$ | 0.9987 | | | -15.83 |
| 308 | $5.32 \times 10^2$ | 0.9990 | 2.82 | 61.57 | -16.13 |
| 313 | $5.38 \times 10^2$ | 0.9993 | | | -16.44 |
| 318 | $5.50 \times 10^2$ | 0.9997 | | | -16.75 |

R is correlation coefficient.

In our experiment, viscosity measurement were carried out on CT-DNA by varying the concentration of Pr(III) and results show that on addition of Pr(III), the viscosity of rod-like DNA decreases as illustrated in Fig. 4. It proved from another aspect that the interaction mode between Pr(III) and CT-DNA were of non-intercalative binding mode i.e. electrostatic interaction with the phosphate group of the DNA backbone.

### 3.1.3. Analysis of thermodynamic parameters

The thermodynamic parameters namely, enthalpy change (ΔH), entropy change (ΔS) and free energy change (ΔG⁰) of reaction are important for confirming binding mode.

Therefore, in order to further characterise the acting forces between Pr(III) and CT- DNA, the thermodynamic parameters dependant on temperature were analysed. The thermodynamic parameters can be evaluated using the following equation [29].

$$\ln K = -\frac{\Delta G}{RT} = -\frac{\Delta H°}{R}\left(\frac{1}{T}\right) + \frac{\Delta S°}{R} \qquad (7)$$

where $K_b$ is the binding constant at the corresponding temperature and R is the gas constant. The binding studies were carried out at 298 K, 303 K, 308 K, 313 K and 318 K. The binding constants for the interaction of Pr(III) with DNA were calculated according to E1 at different temperatures and were listed in Table 3.

The experimental result shows that the $K_b$ values of Pr(III) increases with increasing temperature. This approach provides a good means to determine indirectly the thermodynamic parameters of DNA binding of Pr(III) by using the plots of 1/T versus ln $K_b$ in the temperature ranges. The enthalpy change (ΔH°) and entropy change (ΔS°) were obtained from the slope and intercept of the linear Van't Hoff plot basing on ln $K_b$ versus $1/T$ (Fig. 5) by assuming that H is independent of temperature over the range of employed temperatures [30].

The free energy change (ΔG°) is estimated from the following relationship:

$$\Delta G° = \Delta H° - T\Delta S° \qquad (8)$$

The values of ΔH°, ΔS° and ΔG° are listed in Table 3. The positive enthalpy and entropy values indicates that the mode of binding is an endothermic and entropy increasing process. Because TΔS° > ΔH° and the entropy

increasing effect result in $\Delta G° < 0$, that is consistent with spontaneous reaction. Positive $\Delta H$ and $\Delta S$ values are frequently taken as typically evidence of hydrophobic interactions [31, 32]. Therefore, from these data the binding of trivalent praseodymium to Calf-thymus DNA appears to involve hydrophobic interaction as shown by positive value of $\Delta S$ in addition to electrostatic interaction. Overall speaking, the negatively changes of standard Gibbs energy indicates that the mode of binding process is spontaneous processes and CT-DNA can bind to Pr(III) in solution state.

## 4. Conclusions

The DNA-binding properties of Pr(III) was investigated by absorption and viscosity measurements. According to absorption titration data, the intrinsic binding at 298 K is obtained i.e. 5.18 x$10^2$ M$^{-1}$. The small value of binding constant and viscosity data indicate that Pr(III) bind to DNA along external DNA double-helix without entering the internal core. Thermodynamic parameters further revealed that the mode of binding is an entropically favourable process. All the experimental result taken together suggests that trivalent praseodymium bind predominantly to Calf-thymus DNA by hydrophobic and electrostatic effect. The result obtained should be valuable in understanding the mode of interaction of the trivalent lanthanide ions with DNA as well as laying a foundation for the rational design of novel powerful agents for probing and targeting nucleic acids.

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