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DNA binding activity of a decavanadate cluster complex $[H_2V_{10}O_{28}][LH]_4$ (L = 2-methyl imidazole)

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ABSTRACT

The title complex was obtained from the reaction of $VOSO_4$ with 2-methyl imidazole in presence of benzoic acid. The interaction of DNA with this structurally characterized decavanadate complex has been studied by UV–visible and fluorescence spectroscopy. The complex binds with DNA effectively. The binding constant of the complex with DNA is determined by electronic absorption studies and calculated to be $1.4507x10^4M^{-1}$.

***Keywords**: Binding constant, decavanadate, DNA interaction, polyoxometalates, quenching constant.*

1. INTRODUCTION

Vanadium occurs as an "essential trace" element in diverse living organisms and has wide spread involvement in enzymatic and physiological activities [1-2]. The coordination chemistry of vanadium complexes are of immense interest due to their significance in various biochemical, pharmacological and catalytic activities [3-4]. Vanadium possesses the ability to assume various oxidation states ranges from -1, 0, +1, +2, +3, +4, +5 [5]. Under physiological conditions, *in vivo*, vanadium complexes are usually stable in their +4 and +5 oxidation states. Among various transition metal complexes, the importance of vanadium chemistry is currently receiving considerable recognition owing to its diverse applications in biology, pharmacology and their catalytic activity [6-7]. The polyoxovanadate anions e.g. the dimer ($H_2V_2O_7^{2-}$, $HV_2O_7^{3-}$ or $V_2O_7^{4}$), the tetramer ($V_4O_{12}^{4-}$), the pentamer ($V_5O_{15}^{5-}$) and the decamer ($H_2V_{10}O_{28}^{4-}$, $HV_{10}O_{28}^{5-}$ or $V_{10}O_{28}^{6-}$) [8,9] are known to possess different geometric features in aqueous solutions but exhibit nearly identical biological activities. However, decavanadate, $[H_nV_{10}O_{28}]^{(6-n)-}$ (V_{10}), has recently attracted attention as a potential precursor of therapeutic agents against a number of maladies and much effort has been made to shed light on the pathways through which treatment with V_{10} affects lipidic structures, cell surface proteins and microbial targets [10-12]. The study of interaction of exogenous molecules with DNA has been the subject of intense investigation for decades [13]. The identification of metal compound-DNA interaction is of fundamental importance to the understanding of the molecular basis of therapeutic activities.

2. EXPERIMENTAL

2.1. Materials and methods

Chemicals were of reagent grade and used without further purifcation. Calf thymus DNA (CT-DNA), tris(hydroxymethylaminomethane) hydrochloride (Tris–HCl), ethidium bromide (EB), dimethyl sulfoxide (DMSO), and all other chemicals were of analytical grade and obtained from Sigma–Aldrich. Solvents were purifed by distillation prior to use. The FT-IR spectra were recorded as KBr discs using a Perkin Elmer 100

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FT-IR spectrophotometer. Electronic spectra were recorded on a Shimadzu 1800 spectrophotometer. Fluorescence spectra were measured on a Fluorescence spectrophotometer model Fluorolog- 3, Horiba Scientific.

2.2. Preparation of the complex

To an aqueous solution (5 mL) of $VOSO_4,H_2O$ (1 mmol, 0.181g), methanolic solution (10 mL) of benzoic acid (1 mmol, 0.122g) was added dropwise with constant stirring to obtain a clear solution. To the resulting solution, methanolic solution (5 mL) of 2-methylimidazole (2 mmol, 0.164g) was added dropwise with constant stirring and the resultant mixture was further stirred at room temperature for ca 3 h, giving a light green solution. Solution was filtered and left undisturbed at room temperature, after 2-3 days, the colour of this solution gradually turns into yellow and finally yellow crystals suitable for X-ray diffraction studies were deposited after 5-6 days. Compound was isolated by filtration, washed with a small volume of methanol several times and dried in vacuo over anhydrous $CaCl_2$ to give compound 1. Yield 40%. Anal. Calcd. for $V_{10}O_{28}N_8H_{30}C_{16}$: C, 14.90; H, 2.19; N, 8.69. Found: C, 14.95; H, 3.20; N, 8.75. FTIR (KBr, cm^{-1}): *v*(C-H) 2980; *v*(N-H) 3148; *v*(OH) 3460; *v*(C=N) 1620; *v*(C=C) 1385; *v*(V-OH) 1690; *v*(V=O_t) 960; v_{asym}(V-O-V) 830, 725; v_{sym}(V-O-V) 580, 552, 520. The crystal structure of the complex has been reported [14] earlier (Fig. 2).

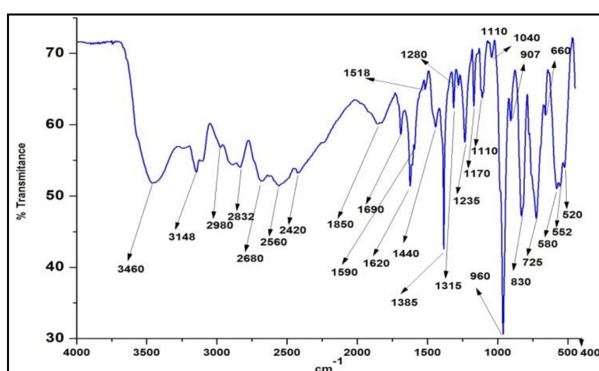

Fig. 1. Infrared spectra of the complex $[H_2V_{10}O_{28}][C_4N_2H_7]_4$

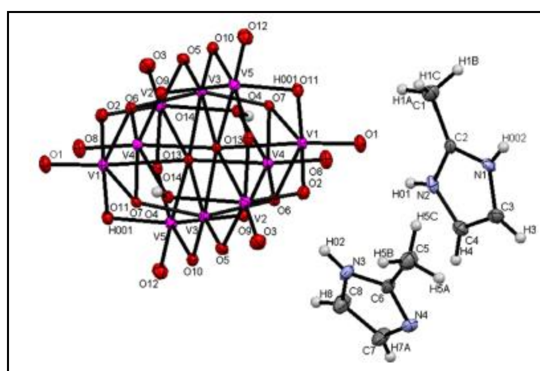

Fig. 2. Ortep view of the structural representation of the complex

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2.3. DNA binding experiments

2.3.1. Preparation of stock solution

The CT-DNA stock solution was prepared by dissolving an appropriate amount of CT-DNA in tris(hydroxymethylaminomethane)hydrochloride (Tris–HCl) buffer (0.01 M, pH 7.4) at ambient temperature. A stock solution of ethidium bromide (1×10^{-5} M) was prepared by dissolving it in deionized double-distilled water. The solution of complex (10^{-3} M) was prepared by dissolving in DMSO.

2.3.2. Absorbance spectroscopy

UV–visible spectroscopic study was performed using a Shimadzu1800 spectrophotometer. For DNA binding experiment, a fixed amount of CT-DNA (1×10^{-5} M) was titrated with increasing amounts of the solution of the complex (10^{-3} M), and absorbances were measured in the wavelength range of 225–300 nm.

2.3.3. Emission spectroscopy

The excitation wavelength was set at 512 nm. The fluorescence measurements were monitored in the wavelength range of 517–520 nm by keeping the concentration of CT-DNA and EB (ethidium bromide) constant, [CT-DNA] = [EB] = 1×10^{-5} M, while varying the concentration of the decavanadate complex.

3. RESULT AND DISCUSSION

3.1. Spectrophotometric studies on DNA binding by the complex

Electronic absorption titration is one of the most common techniques to investigate the interaction between CT-DNA (calf thymus DNA) and metal complexes [15]. Generally, hypochromic (or hyperchromic) effect and red (or blue) shift are observed in the absorption spectra of small molecules if they intercalate with CT-DNA [16]. The DNA binding study with the complex unveils its potentiality to interact with CT-DNA. Addition of decavanadate complex to a solution of CT-DNA probably results in a ground state complex denoted as DNA-drug; herein, "drug" refers to decavanadate complex. The absorption characteristics of the interaction of CT-DNA with the complex at different concentrations, including blank tests in the absence of the complex, are depicted in Fig. 3. A hyperchromic effect is observed upon addition of decavanadate complex to CT-DNA. The changes in the absorption pattern for CT-DNA observed during addition of the complexes with no change in the location of peak (258 nm), suggest that the interaction probably occurs via non-intercalating binding mode, on the periphery of the double helix [17,18]. The extent of the hyperchromism is indicative of the non-intercalative binding mode, suggesting that the binding of the synthesized compounds with CT-DNA is probably supported by electrostatic, Vander Walls and hydrogen bonding interactions [19].

The apparent association constant or binding constant, K_{app} for the formation of compound (DNA-drug) between CT-DNA and the decavanadate complex is represented by equation 2.

$$\text{CT - DNA} + \text{drug} \rightleftarrows \text{DNA} - \text{drug} \quad (1)$$

$$K_{app} = [\text{DNA - drug}] / [\text{CT- DNA}] \times [\text{drug}] \quad (2)$$

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The K_{app} is obtained based on Benesi and Hildebrand's method [20]

$$A_{obs} = (1 - \alpha)C_0\varepsilon_{DNA}l + \alpha C_0\varepsilon_c l \quad (3)$$

Herein, A_{obs} is the observed absorbance of the solution, containing various concentrations of decavanadate complex (drug) at 258 nm, α is the degree of association between CT-DNA and drug, ε_{DNA} and ε_c are the molar extinction coefficients at the defned wavelength (λ=258 nm) for CT-DNA and the formed compound respectively, 'l' is the optical path length, and C_0 is the primary concentration of CT-DNA. Equation (3) can be expressed as follows:

$$A_{obs} = (1 - \alpha)A_0 + \alpha A_c \quad (4)$$

Where, A_0 and A_c are the absorbance of CT-DNA and the compound at 258 nm, respectively, having a concentration of C_0. Further, α can be equated to (K_{app}[drug])/(1+K_{app}[drug]). Thus, Equation (2) is changed to:

$$1/A_{obs} - A_0 = 1/A_c - A_0 + 1/K_{app}(A_c - A_0) \times 1/[drug] \quad (5)$$

On enhancement of the absorbance at 258 nm due to absorption of the DNA-drug complex, a linear relationship between the reciprocal concentration of drug $1/(A_{obs} - A_0)$, slope $1/K_{app}(A_c - A_0)$ and an intercept $1/(A_c - A_0)$ is expected (Fig.4). The determined value of the binding constant or apparent association constant (K_{app}) for the decavanadate complex is 1.4507×10^4 M^{-1}.

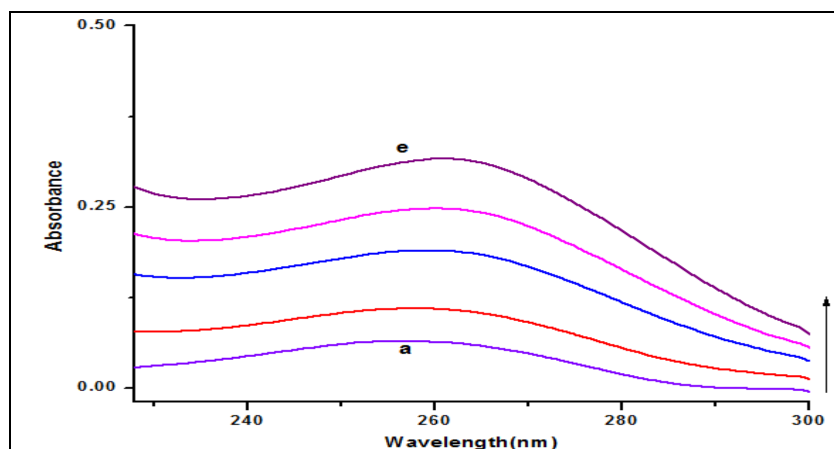

Fig.3. Absorption spectra of CT-DNA (1×10^{-5} M) in the presence of increasing amounts of the complex (0, 5, 10, 15 and 20) $\times 10^{-6}$ M for curves a–e, respectively.

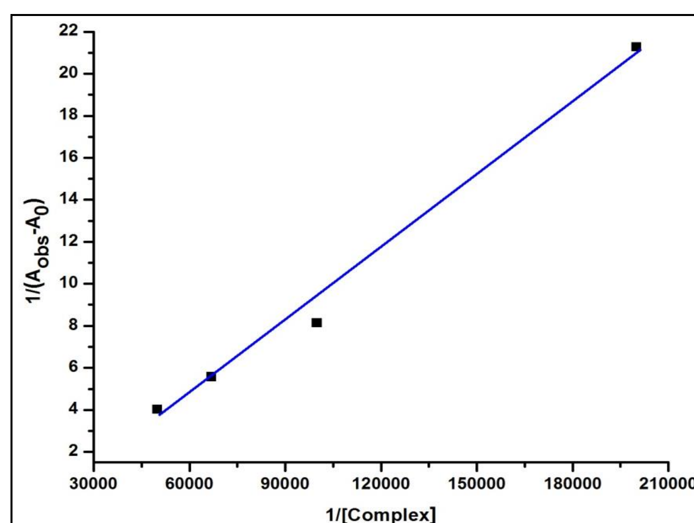

Fig. 4. Plot of $1/(A_{obs}-A_0)$ vs 1/[Complex] for absorption titration of CT-DNA with complexes.

3.2. Fluorescence emission titrations for DNA interaction of the complex

Fluorimetric measurements using ethidium bromide (EB) as a probe is usually carried out to establish the binding mode of small molecule to the target molecule, the double-helical DNA. Ethidium bromide (EB) emits intense fluorescence in the presence of DNA due to its strong intercalation between the adjacent DNA base pairs. This enhanced fluorescence can be quenched by the addition of a third molecule which can bind DNA by intercalative mode by displacing EB [21]. The emission spectra of EB bound to DNA in the absence and presence of the complex are presented in Fig. 5. The addition of the complex to DNA pretreated with EB causes a gradual quenching in emission intensity, indicating that the complex competes with EB in binding DNA, which leads to a quenching in the fluorescence intensity of EB–DNA complex system. In fact, as expected for a displacement effect, the increase in the concentration of complex gradually quenches the fluorescence intensity of EB–DNA complex system. This significant decrease in fluorescence intensity lends strong support in favor of intercalation of the complex into the DNA double helix by displacing EB. Fluorescence quenching study in the presence of the complex was analyzed further by Stern–Volmer equation: $F_0/F = 1 + K_{SV}$ [Q] [22]; where F_0 and F are the fluorescence intensities in the absence and presence of quencher (complex) respectively; [Q] is the concentration of the quencher, K_{SV} is the Stern–Volmer quenching constant, which is obtained from the slope of plot of F_0/F vs. [Q]. A plot of F_0/F vs. [complex] appears linear (Fig. 6) and the Stern–Volmer quenching constant (K_{SV}) was found to be 0.0938×10^4 M^{-1} at 37 °C. This data are also in agreement with the value obtained by electronic spectral studies [23].

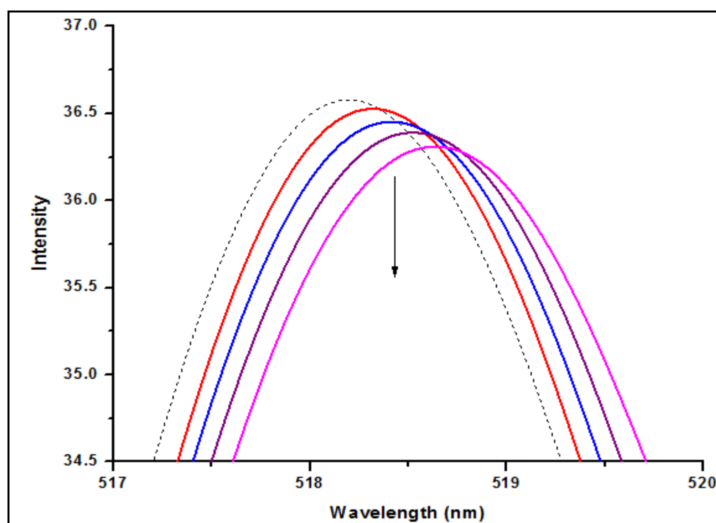

Fig.5. Emission spectrum of EB bound to DNA in the absence (doted line) and presence of increasing complex (5, 10, 15 and 20)×10^{-6} M ([EB] = 1x10^{-5} mol, [CT-DNA] = 1x10^{-5} mol, λ_{ex} = 512 nm).

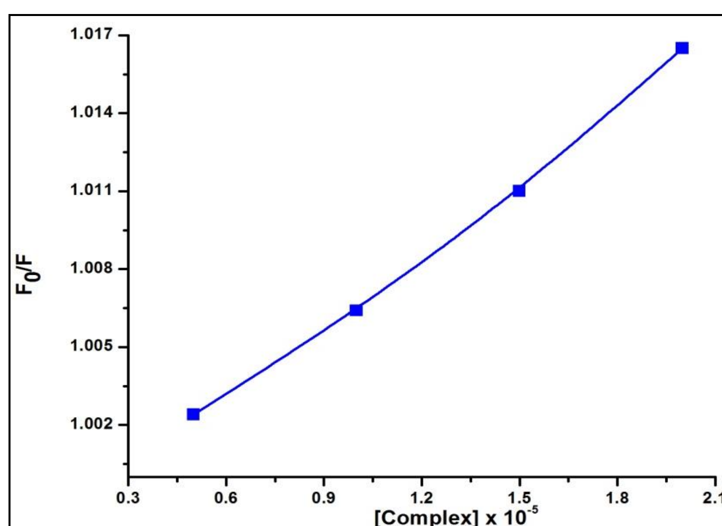

Fig.6. Plot of F_0/F vs. [Complex] for the emission titration of the complex to CTDNA-EB system.

4. CONCLUSSIONS

The DNA binding of decavanadate complex $[H_2V_{10}O_{28}][C_4N_2H_7]_4$ has been established. Absorption titration studies indicate that the complex binds CT-DNA by intercalative mode. Fluorimetric studies also support the proposition of intercalative binding.

5. ACKNOWLEDGEMENTS

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