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Synthesis, Kinetics, Reaction Mechanism, and Bioactivity Assays of a Dimeric Palladium Complex

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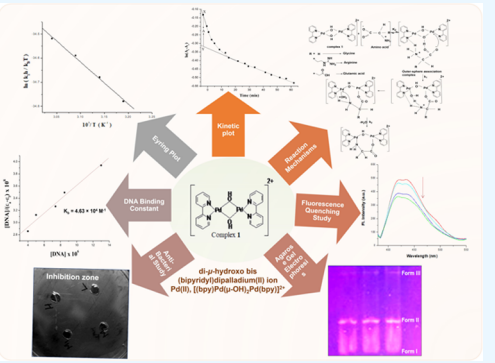
ABSTRACT: A dimer of Pd(II), $[(bpy)Pd(\mu\text{-}OH)_2Pd(bpy)]^{2+}$, (complex **1**) (where bpy = 2,2′-bipyridyl) has been synthesized at physiological pH (7.4) and characterized by electronic spectroscopy, electrospray ionization mass spectrometry (ESI-MS) spectroscopy, and Fourier transform infrared (FT-IR) analysis. Reaction kinetics of **1** with glycine (L^1H), L-glutamic acid (L^2H), and L-arginine (L^3H) were investigated in an aqueous medium at pH of 7.4 and constant ionic strength via a spectrophotometer as a function of temperature and different concentrations of substrate-complex and ligand. The interactions were supported by two discrete successive steps, i.e., ligand-dependent and ligand-independent steps. The equilibrium constant of complex formation (outer-sphere association) and the rate constant during complex-substrate−ligand interaction were calculated. The Eyring equation was applied to evaluate activation factors ($\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$), and associative mechanisms of all reactions were proposed. Thermodynamic parameters ($\Delta H°$ and $\Delta S°$) were also estimated from the standard plot of ln K_E against $10^3/T$. Spectroscopic titration of **1** at pH 7.4 in Tris−HCl buffer with calf thymus DNA, electronic emission titration with ethidium bromide (EtBr), antimicrobial activities, and an agarose gel electrophoresis run of **1** on pBR322 plasmid DNA have shown strong evidence of anticancer activity. Moreover, it has nontoxic water molecules as leaving groups.



1. INTRODUCTION

Metal-based anticancer chemotherapeutic drugs that are less toxic to normal cells and more effective to cancerous cells have been in search ever since the successful clinical application of cisplatin, *cis*-diamminedichloroplatinum(II) (*cis*-DDP) in cancer therapy.[1,2] However, various types of side effects, such as vomiting, nausea as well as nephrotoxicity, neurotoxicity, hemolytic anemia, and ototoxicity, have limited the wide application of cisplatin as an anticancerous drug.[3] Other newly synthesized Pt(II)-based anticancer drugs viz. carboplatin, nedaplatin, lobaplatin, and oxaliplatin are not as successful as cisplatin due to severe side effects and no longer have the clinical advantages.[4,5] Moreover, inherent and acquired resistances have marred the success of cisplatin and limited its efficacy during chemotherapy.[6] The adverse effect of Pt(II)-based anticancer drugs leads the attention toward the less toxic[7] but similar efficacy of Pd(II) complexes showing isostructural pattern (square planar) and analogues with Pt(II) complexes.[8,9] Moreover, Pd(II) complexes could attain rapid equilibrium in comparison to Pt(II) (10^5 times faster)[10,11] analogues which might be applied as a model complex for studying the mechanism of interaction of Pt-analogues with DNA.[12]

From this background, we have chosen Pd(II)[13] as the metal center and an aromatic ligand having an N,N donor center (2,2′-bipyridine)[14,15] as a building block considering the donor center of cis-DDP to explore its kinetic and mechanistic behavior for in vitro studies using three selected amino acids: glycine, L-arginine, and L-glutamic acids. In addition, such metal complexes interrelate noncovalently with DNA due to their planar aromatic rings, which have the potential of powerful anticancerous drugs.[16,17] The calf thymus (ctDNA) has been used primarily for DNA binding studies during the development of metallodrugs for chemotherapeutic applications using different metal-based complexes such as Pd, Cu, Zn, and Ru.[14,18] In vitro studies, such as evaluation of the linear Stern−Volmer quenching constant (K_{sv}), ability to cleave plasmid DNA (pBR 322), and antimicrobial activity of the complex and ligand, are beneficial to understand the

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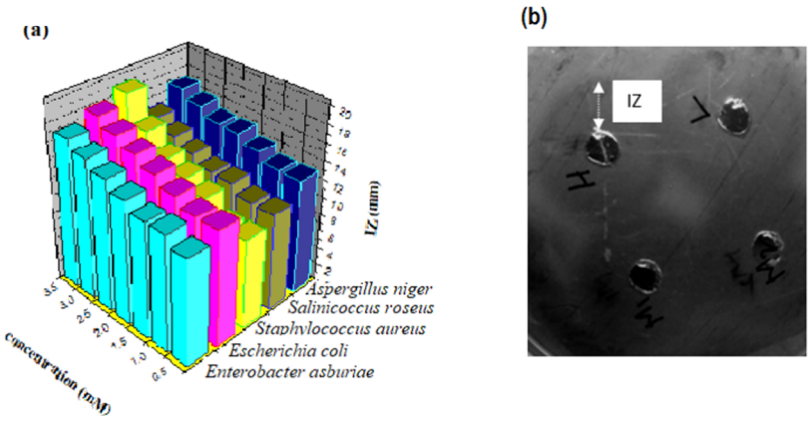

Figure 15. (a) Plot of inhibition zone versus concentration of antimicrobial study of **1** and (b) inhibition zone of bacterial agar Petri dish.

4. CONCLUSIONS

The dimer of the Pd(II) complex was synthesized at pH 7.4 and characterized by electronic spectroscopy, FT-IR, and ESI-MS spectroscopy. Reaction kinetics of **1**'s substitution reactions with the three selected amino acids containing N and O donor centers at 7.4 pH in the aqueous solution have been studied to optimize reactivity and selectivity. Low positive values of enthalpy of activation ($\Delta H_1^{\neq}$ and $\Delta H_2^{\ddagger}$) and high negative values of entropy of activation ($\Delta S \neq 1$ and $\Delta S \neq 2$) for the three reactions suggest a reasonable degree of ligand participation in the associative mode of the transition state, which implies ligand-dependent step I. In contrast, step II is ligand-independent ring closure. The high nucleophilicity of glycine among the three amino acids leads to greater stabilization of the transition state with the Pd(II) dimer and requires the lowest activation enthalpy. In vitro DNA binding studies suggest a strong interaction of **1** with ctDNA. The antimicrobial and antifungal activities reveal that **1** can be active against selected bacterial and fungal strains. Comparing the K_b and K_{SV} values (Table 6), it is found that **1** has a higher value than **2** but a lower value than the other (Pd 1, Pd 2, Pd 3, and Pd 4). So, dimerization from **2** to **1** increases DNA binding capacity. In the case of Pd 2, Pd 3, Pd 4, and Pd 5, though they are dimers having a higher DNA binding value than **1**, each of the four has toxic chloride (Cl^-) as a leaving group, while **1** has a nontoxic water molecule as a leaving group.

Further studies can be carried out to evaluate its pharmacological properties in vivo and the definite mechanism of its bioactivity. However, the results of this study can be beneficial in understanding the reaction kinetics and the interaction of the Pd(II) complex with amino acids, DNA, and selected microbes. It can encourage the development and production of superior anticancer therapeutic reagents. The following points summarize the novelty of this study, such as a correlation between kinetic study and bioactivity assay in an aqueous medium at physiological pH, optimization between reactivity and selectivity, optimum rate, nontoxic side product (H_2O), and antimicrobial activity.

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Notes

The authors declare no competing financial interest.

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