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Original article

Influence of chirality of V(V) Schiff base complexes on DNA, BSA binding and cleavage activity

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ABSTRACT

New chiral V(V) Schiff base complexes (*S*)-[VO(OMe)**L**] and (*R*)-[VO(OMe)**L**] were synthesized and characterized by microanalysis, infrared (IR), UV–Visible, Circular dichroism (CD) spectroscopy and single crystal X-ray studies. The interaction of these complexes with calf thymus (CT) DNA and bovine serum albumin (BSA) protein showed chiral expression DNA/protein binding strength. The influence of chirality was also observed in cytotoxicity assay of Hep 2 cells. (*R*)-[VO(OMe)**L**] enantiomer exhibited higher binding constant ($5 \pm 1 \times 10^5$ M^{-1}) as compared to (*S*)-[VO(OMe)**L**] ($8 \pm 1 \times 10^4$ M^{-1}). The fluorescence quenching, thermal melting and viscosity data suggest DNA surface and/or groove binding nature of the complexes and electrophoresis studies also showed greater activity for (*R*)-[VO(OMe)**L**] in cleaving DNA and protein as against (*S*)-[VO(OMe)**L**].

1. Introduction

One of the life's intrinsic biochemical features is the high selectivity of chiral molecular species. Consequently, many biological responses are greatly influenced by the chirality of the incumbent molecules [1]. It is therefore not surprising to come across incidents where chirality plays decisive role in the area pharmaceuticals, agrochemicals, flavors and fragrances. For instance, in most cases only one optical isomer of the drug molecule selectively interacts with drug-receptor site to show desirable therapeutic activity [2]. A classical example of this behavior was first noticed with thalidomide drug prescribed for morning sickness in pregnant women, where ***R*** enantiomer particularly showed drug action whereas ***S*** enantiomer caused birth defects [3]. Therefore, in medicinal research it has been made mandatory to test the pure steroisomer of the chiral drug molecule. Although pharma sector is dominated by organic molecules, there is a great deal of interest in the biochemical response of inorganic metal complexes [4]. In recent years, interest in the synthesis of chiral metal complexes has increased many folds for variety of applications. Likewise, the interaction of transition metal complexes with DNA has also evoked great interest, due to their importance in designing new and promising drugs, probes for nucleic acids [5–7], DNA-dependent electron transfer reactions, DNA footprinting, sequence-specific cleaving agents and anti-tumor drugs [8–12]. Introduction of chirality in such type of complexes additionally enhances their pharmacological behavior by adopting specific conformation and target selective binding affinity with intrinsically chiral DNA and protein [13–19]. Among the various transition metal ions used in pharmacological studies, vanadium is reported

Abbreviations: CD, circular dichorism; CT-DNA, calf thymus deoxyribonucleic acid; BSA, bovine serum albumin; SC, supercoiled; NC, nicked circular; EB, ethidium bromide; SDS, sodium dodecyl sulphate; ds DNA, double stranded DNA; TLC, thin layer chromatography; T_m, melting temperature.

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to have biological response in lowering of cholesterol, triglycerides, contraction of blood vessels, enhancement of oxygen-affinity of hemoglobin and myoglobin [20]. Vanadium complexes have also been explored for lowering of glucose levels [21–24], diuretic and natriuretic effects, anti-tumor activity against chemical carcinogenesis in animals and malignant cell lines (in vitro). The origin of anticancer activity of vanadium has been attributed to its ability to cleave DNA [25,26]. Further, several V(IV) and V(V) complexes of maltol, ethylmaltol [27,28], 3-hydroxy-4-pyrones [29–31], pyridinones [32–36] have also shown various other promising pharmacological activities. Apparently, many non-chiral vanadium-phenanthroline [37–39], vanadium-Schiff base [40–43] and vanadyl acetylacetonate [25] complexes have been reported for DNA binding and cleavage activity, while the information on the influence of chirality for such complexes is scanty. Our ongoing interest in the synthesis of chiral Schiff base complexes [44–47] for their application in catalysis and biology resulted in recent report on the DNA binding and cleavage activity of chiral Ru(II) salen complexes [14] and DNA binding and antioxidant activity of chiral Mn(III) salen complexes [48]. In view of inquisitive response of vanadium in biology, the present paper reveals for the first time the application of chiral vanadium metal complexes in DNA, BSA binding and cleavage activity. We have also tried to give experimental evidence for the influence of chirality of incumbent metal complexes on cytotoxicity of Hep2 cells.

2. Results and discussion

2.1. Synthesis and general properties

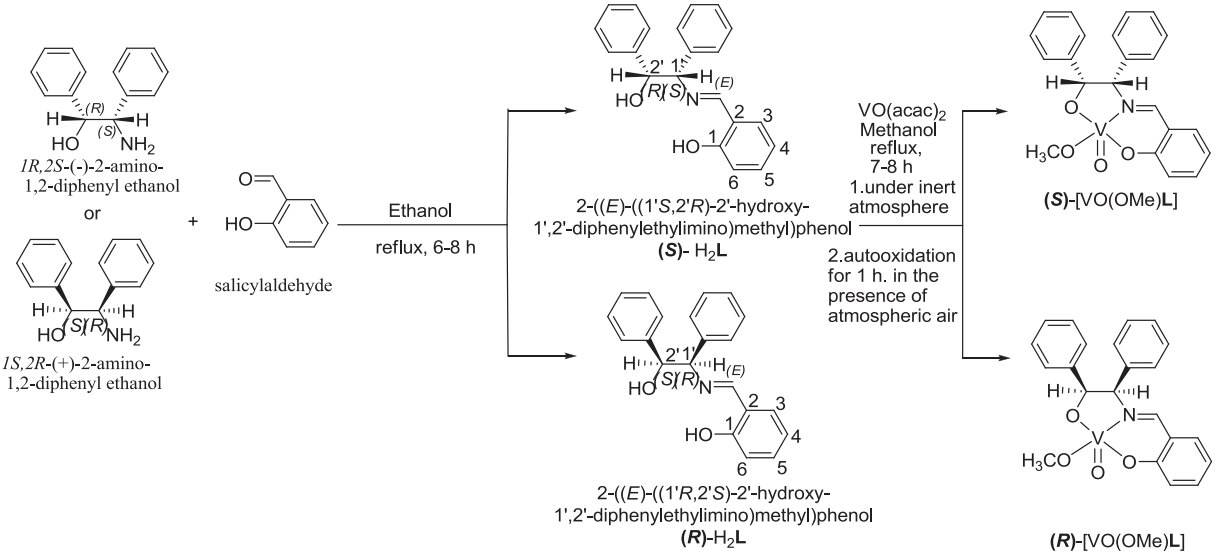
Chiral Schiff base complexes (*S*)-[VO(OMe)**L**] and (*R*)-[VO(OMe)**L**] were synthesized by the reaction of respective chiral Schiff base ligands viz., 2-((*E*)–((*1′S,2′R*)-2′-hydroxy-1′,2′-diphenylethylimino)methyl)phenol/2-((*E*)–((*1′R,2′S*)-2′-hydroxy-1′,2′-diphenylethylimino)methyl)phenol with $VO(acac)_2$ in methanol under nitrogen atmosphere, followed by auto-oxidation in atmospheric oxygen (Scheme 1). These complexes were characterized by micro analysis, IR-, UV–visible, mass spectrometry and single crystal X-ray analysis (data given in the experimental section). These complexes are fairly soluble in MeOH, EtOH, CH_2Cl_2, MeCN, DMF, and DMSO. The UV–visible spectra of these complexes in the above mentioned solvents and in mixed solvent (DMSO/deionized water) showed no sign of free ligand or metal salt hence remained unchanged over 48 h. Metal-ligand titrations and thermodynamic studies also concluded that these complexes are fairly stable in these solvents. The UV–visible spectra for DMSO/water mixture are given in Supporting Information, Fig. S1. All the biochemical experiments conducted with these metal complexes were done in DMSO/water mixture.

2.2. Crystal structure

The single crystal X-ray structure of chiral Schiff base complex (*S*)-[VO(OMe)**L**] is shown in Fig. 1. Crystallographic data and refinement statistics are given in Table 1. The π descriptor (0.366) [49] indicated that the structure is distorted square pyramidal with vanadium atom situated slightly out of the square plane. The fifth co-ordination site is occupied by a methoxy group originated from the solvent used during the synthesis of the complex. The selected bond lengths and bond angles are listed in (Table 2). The V–O's and V–N bond lengths are similar with the other known pentacoordinated oxovanadium(V) complexes [41,50]. The two phenyl moieties of the ligand are oriented on the same side of the complex. No classical hydrogen bonds are present in the complex. However, C–H···O hydrogen bonds played an important role in the crystal packing (Fig. 2). Only the O(1) (oxido) and O(4) (methoxido) atoms are involved in the C–H···O hydrogen bond formation.

2.3. Absorption spectral study of (R)-H_2L with VO(acac)$_2$ metal salts

To have better understanding for the affinity of (*R*)-H_2**L** with $VO(acac)_2$ metal salt, absorption titration studies were performed by the addition of $VO(acac)_2$ solution to a solution of (*R*)-H_2**L** and the results are shown in Fig. 3. The electronic absorption spectrum of the (*R*)-H_2**L** displayed intense bands at 400 nm and hump at 280 nm. With addition of $VO(acac)_2$ metal salt, this absorption band diminished with 17 nm blue shift. Moreover, the 280 nm hump was completely disappeared with an emergence of a new band at 344 nm. The conditional stability constant of the complexes was determined by the Benesi–Hildebrand method using absorption spectral data [51,52]. The Benesi–Hildebrand plots were examined to reconfirm the stoichiometry of the metal and Schiff base in the



Scheme 1. Synthesis of chiral Schiff base complexes.