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Interaction of palladium(II) coordination compounds with calf thymus DNA and their antibacterial activity

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ABSTRACT

The palladium(II) complexes of the formulations $[Pd(clpbpy)Cl_2]$, $[Pd(clcpbpy)Cl_2]$, $[Pd(brcpbpy)Cl_2]$, $[Pd(clmpbpy)Cl_2]$ {clpbpy=4-(4-chlorophenyl)-6-phenyl-2,2′-bipyridine (L^1), clcpbpy=4,6-bis(4-chlorophenyl)-2,2′-bipyridine (L^2), brcpbpy=4-(4-bromophenyl)-6-(4-chlorophenyl)-2,2′-bipyridine (L^3) and clmpbpy=6-(4-chlorophenyl)-4-*p*-tolyl-2,2′-bipyridine (L^4)} have been synthesized and characterized using elemental analysis, electronic spectra, IR and mass spectra. The study on the interaction of the palladium complexes with calf thymus DNA (CT DNA) has been performed using absorption titration, viscosity measurements and thermal denaturation techniques. The study suggests the intercalative mode of DNA binding. Gel electrophoresis assay demonstrates the ability of the complexes to cleave the pUC19 DNA. The antibacterial activity of complexes has been screened against two Gram$^{(+ve)}$ and three Gram$^{(-ve)}$ microorganisms.

Due to resounding success of cisplatin, as antitumor drug, and closely related platinum complexes, a large number of platinum and palladium complexes containing not only amine based ligands, but also various other ligands have become the subject of intensive research [1]. Palladium(II) complexes have been investigated for developing the new antitumor agents, [2] because palladium(II) has a similar coordination mode and chemical properties to platinum(II). Some palladium complexes with aromatic N-containing ligands, e.g. derivatives of pyridine, quinoline, pyrazole and 1,10-phenanthroline, have shown very promising antitumor characteristics [3].

DNA plays a fundamental role in the storage and expression of genetic information in a cell. Studies on the interaction of transition metal complexes with DNA have been pursued in recent years [4]. Investigations of the interactions of DNA with transition metal complexes are basis to design new types of the pharmaceutical molecules to elucidate the mechanism and principles involved in the site specific recognition of DNA [5]. In general, most components have three distinct modes of non-covalent interaction with DNA, i.e. intercalative association, DNA groove binding and electrostatic attraction [6].

In continuation of our earlier work [7], herein we report the synthesis, characterization and biological behaviours of four Pd(II) complexes (Scheme 1). The DNA binding properties have been studied by absorption titration, viscosity measurement and DNA melting temperature. The cleavage properties of the complexes have been investigated using gel electrophoresis technique. The antibacterial activity of the complexes has been performed against five microorganisms.

The IR spectral data of complexes are shown in Table 1. The Infrared spectral measurement of bipyridines showed the bands at ~1550 cm^{-1} and ~1470 cm^{-1}, correspond to C=C and C=N ring stretching, whereas the bands at ~740 cm^{-1} and ~3050 cm^{-1} are due to aromatic C—H out of plane bending and stretching respectively. Major change that occurs after complexation are the shifting of bands for C=C and C=N ring stretching from ~1550, ~1470 to ~1590, ~1530 cm^{-1}, respectively, which supports the binding of metal via nitrogen atoms of bipyridines skeleton. The data are further supported by appearance of a sharp band at ~550 cm^{-1}, characteristic bands of Pd—N bond. Stretching mode of Pd—Cl is to be expected in the region less than 400 cm^{-1} i.e. ~360 cm^{-1} [8].

In the synthesized Pd(II) complexes, only one *d*—*d* band at ~426 nm was observed, which is assigned to $d_{z2}\ d_{x2-y2}$ transition, whereas other two bands are related to charge transfer bands [9]. The bands observed at ~271 and ~250 nm correspond to the charge transfer transitions. All these bands point toward the low spin complex of d^8 system with square planar geometry.

FAB-mass spectra of all complexes were obtained using *m*–nitro benzyl alcohol as matrix. A mass spectrum of complex $[Pd(clpbpy)Cl_2]$ (1) is shown in Fig. 1. Peaks at 136, 137, 154, 289 and 307 *m/z* values are of matrix. Peak at 519 *m/z* is assigned to molecular ion peak of complex 1. The peaks at 482 and 448 *m/z* correspond to the fragments $[Pd(clpbpy)Cl]^+$ and $[Pd(clpbpy)]^+$, respectively and peak at 342 *m/z* corresponds to [clpbpy]. The fragmentation of *p*-chloro phenyl group from clpbpy molecule gives peak at 231 *m/z*. There exist doublets at 519:521, 482:484 and 448:450 *m/z* values, which correspond to isotopic patterns of chlorine atom. The isotopic pattern due to the presence of chlorine and palladium appeared in the spectrum.

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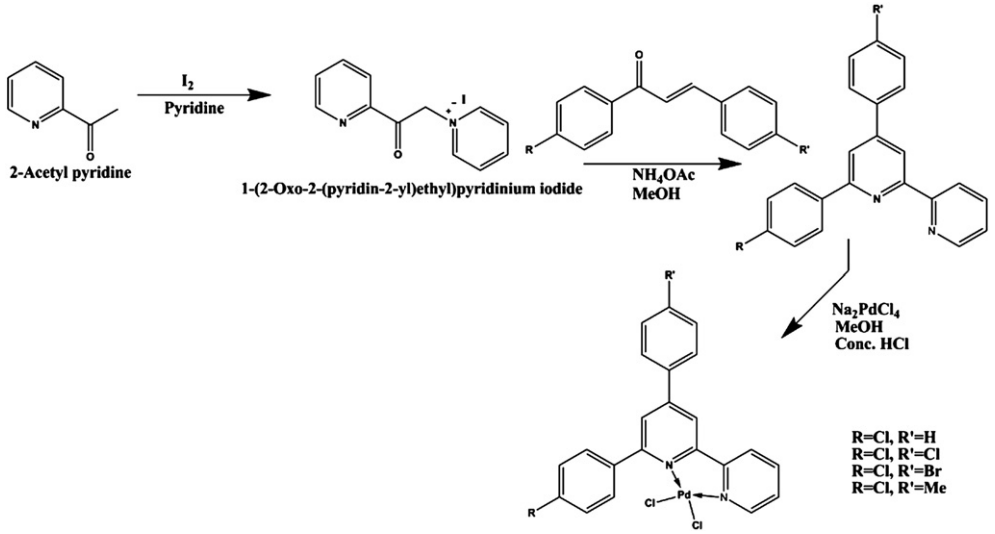

Scheme 1. General reaction scheme for synthesis of ligand and complex $[Pd(L^n)Cl_2]$.

Table 1
IR spectra of complexes (cm^{-1}).

Compounds	ν(C—H)	ν(C C)	ν(C N)	ν(C—Cl)	ν(C—Br)	δ(C—H)	ν(M—N)
$[Pd(L^1)Cl_2]$ [**1**]	3063	1597	1545	1042	–	733	555
$[Pd(L^2)Cl_2]$ [**2**]	3101	1592	1525	1042	–	748	555
$[Pd(L^3)Cl_2]$ [**3**]	3055	1597	1535	1045	1022	741	545
$[Pd(L^4)Cl_2]$ [**4**]	3055	1589	1553	1044	–	710	532

The complexes were screened for *in-vitro* antibacterial activity against three Gram$^{(-ve)}$ i.e. *E. coli, P. aeruginosa, S. marcescens* and two Gram$^{(+ve)}$ i.e. *S. aureus, B. subtilis,* microorganisms using MIC method. The antimicrobial activity data reveals that all the complexes are more active against all the species compared to metal salt and bipyridine derivatives (Table 2). The complexes show better antibacterial activity than Pd(II) complexes reported by Guerra et al. [10] and Juribašić et al. [11], while they have similar antibacterial with Pd(II) complexes

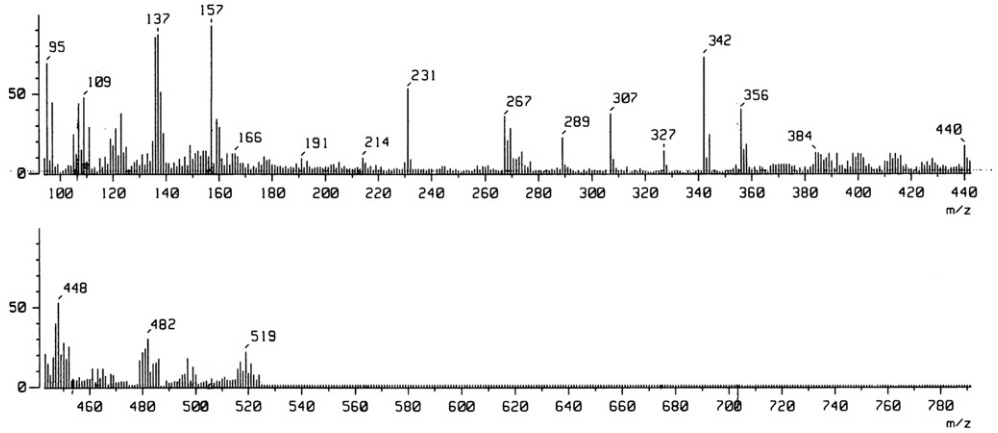

Fig. 1. FAB-mass spectrum of complex **1**, i.e. $[Pd(clpbpy)Cl_2]$, obtained using *m*–nitro benzyl alcohol.

Table 2
Antibacterial activities of metal salt, ligands and palladium complexes in terms of minimum inhibitory concentration (MIC in μM).

Compounds	*S. aureus*	*B. subtilis*	*S. marcescens*	*P. aeruginosa*	*E. coli*
Na_2PdCl_4	2238.00	2490.00	2145.00	1940.00	2820.00
Ligand 1 $[L^1]$	610	705	670	645	675
Ligand 2 $[L^2]$	540	510	585	490	535
Ligand 3 $[L^3]$	610	595	650	625	635
Ligand 4 $[L^4]$	690	715	720	720	725
$[Pd(L^1)Cl_2]$ [**1**]	71	72	81	75	79
$[Pd(L^2)Cl_2]$ [**2**]	47	42	49	43	46
$[Pd(L^3)Cl_2]$ [**3**]	57	55	66	58	59
$[Pd(L^4)Cl_2]$ [**4**]	82	81	93	88	89

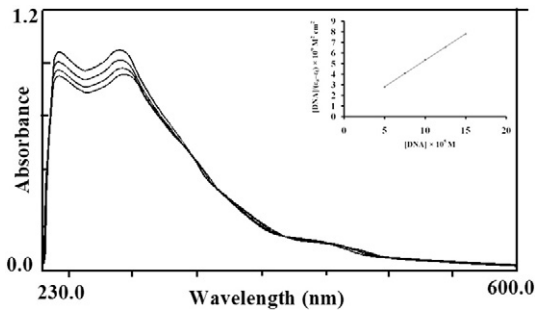

Fig. 2. Absorption titration curve of $[Pd(clpbpy)Cl_2]$ [1] in absence and in presence of increasing amount of DNA; 50–150 μM in Tris–HCl buffer (50 mM Tris–HCl, pH 7.2), [complex] = 15 μM, with incubation period of 30 min. at 37 °C, Inset: Plot of [DNA]/$(\varepsilon_a - \varepsilon_f)$ *versus* [DNA].