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ORIGINAL PAPER

Synthesis of ionic liquid-based Ru(II)–phosphinite complexes and evaluation of their antioxidant, antibacterial, DNA-binding, and DNA cleavage activities

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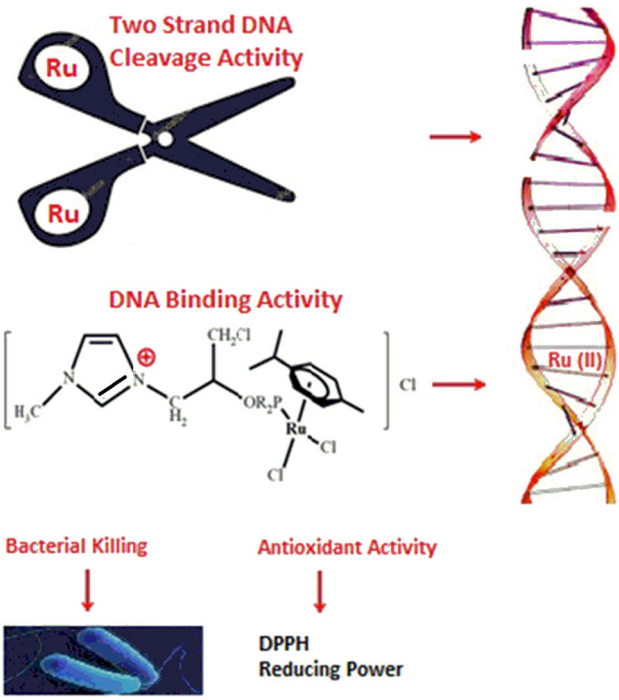
Abstract

Two Ru(II) complexes were synthesized by reaction of phosphinite-functionalized imidazolium salts $[(Ph_2PO)C_7H_{11}N_2Cl]Cl$ **(1)** and $[(Cy_2PO)C_7H_{11}N_2Cl]Cl$ **(2)** with 1/2 equivalent of $[Ru(\eta^6\text{-p-cymene})(\mu\text{-Cl})Cl]_2$ in anhydrous CH_2Cl_2 and under argon atmosphere. The complexes were then isolated as analytically pure substances and characterized using multinuclear NMR and infrared spectroscopies and elemental analysis. The Ru(II) compounds were used to study their biological assay. For this purpose, radical scavenging, reducing power, antibacterial activity, DNA binding, and DNA cleavage activity were fully studied. The maximum 1,1-diphenyl-2-picrylhydrazyl radicals (DPPH) scavenging (78.9%) and reducing power were obtained from compound **4** at the concentration of 200 µg/ml. The compounds were also tested against three Gram-positive and three Gram-negative bacteria, and they were found to be more effective against Gram-positive bacteria. In addition, both compounds showed excellent DNA binding and DNA cleavage activity.

Graphical abstract



Extended author information available on the last page of the article

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Keywords Ionic liquid · Phosphinite · Ruthenium · Antibacterial · DNA binding · DNA cleavage

Introduction

After years of exponential development, the field of ionic liquids (ILs) has attained a substantial degree of maturity in many aspects, such as preparation, purification, and physicochemical characterization (Hallett and Welton 2011; Prediger et al. 2013). It has been known that ionic liquids (ILs) can be functionalized easily by incorporating several functional moieties into the IL structure to design different functionalized ILs (FILs), which dually maintain the characters of the incorporated functionalities as well as those of the ILs (Luska and Moores 2011; Vicente et al. 2012; Andrieu et al. 2010). An important factor for effective use of ILs as solvents in green chemistry is to enable clean and efficient syntheses of the ILs, so that an additional waste is not introduced into the overall process (Bonhote et al. 1996; Holbrey et al. 2002, 2003a, b). Furthermore, ionic liquids including hydroxyl moiety have interesting properties such as high hydrophilicity and a potential for enzyme stabilization (Holbrey et al. 2003a, b). Metal-containing ionic liquids are regarded as promising new materials which combine the properties of ionic liquids with additional intrinsic magnetic, spectroscopic, or catalytic properties, depending on the incorporated metal ion (Chiappe et al. 2012).

The phosphorus-based FILs have long been investigated to design the ionic organometallic compounds and application to homogeneous catalysis (Luska et al. 2012; Brauer et al. 2001; Abdellah et al. 2010; Canac et al. 2012; Barthes et al. 2013). It has been found that, while the coordinating P(III) atom is vicinal to the positive-charged imidazolium ring, the corresponding phosphine FILs possess π-acceptor character as well as σ-donor (You et al. 2013; Zhou et al. 2012; Wang et al. 2013; Chen et al. 2013). In addition, it has been well known that phosphinites have different chemical, electronic, and structural features in comparison with phosphines. For instance, the metal–phosphorus bond is often stronger for phosphinites than the corresponding phosphine owing to the existence of electron withdrawing P–OR group. Moreover, the empty σ*-orbital of the phosphinite P(OR)R_2 is stabilized, rendering it a better acceptor (Galka and Kraatz 2003; Aydemir et al. 2011; Işık et al. 2013; Meriç et al. 2014a, b; Ak et al. 2015a, b).

Metallo drugs have emerged as an important area of medical chemistry due to their therapeutic use of metal-based pharmaceuticals. Platinum-based drugs used as chemotherapeutic agents show high systemic toxicity and resistance problems (Naveen et al. 2018). It has been reported that Ru(II)-based compounds are important therapeutic agents and less toxic than platinum-based compounds (Devagi et al. 2018). For this reason, the interest in ruthenium compounds as biological agents is constantly increasing. As far as we know, there are not many reports on biological agents using chiral Ru(II) phosphinites, which have been employed successfully tested as anticancer, antibacterial, and antioxidant agents (Appelt et al. 2017). Free radicals can damage lipids, proteins, and DNA, leading to an increase in cancer rates. Fortunately, antioxidants have the ability to scavenge free radicals. Studies on the binding and cleavage of DNA to small molecules and antioxidant activities of new synthesized compounds are very important for the design of new anticancer drugs (Aziz and Elbadawy 2014; Deepika et al. 2016). We report here, for the first time, the synthesis and characterization of two ruthenium(II) compounds based ionic liquids and theirs radical scavenging, reducing power, antibacterial activity, DNA binding, and DNA cleavage activity.

Experimental

Materials and methods

Unless, otherwise, stated, all reactions were carried out under an atmosphere of argon using the conventional Schlenk glassware, solvents were dried using the established procedures and distilled under argon immediately prior to use. Analytical grade and deuterated solvents were purchased from Merck. Epichlorohydrin, 1-methylimidazole, PPh_2Cl, PCy_2Cl, and $[Ru(\eta^6\text{-}p\text{-cymene})(\mu\text{-Cl})Cl]_2$ are purchased from Fluka, and were used as received. The infrared spectra were measured by a Perkin Elmer Lambda 25. ^1H (400.1 MHz), ^{13}C NMR (100.6 MHz), and $^{31}P\text{-}\{^1H\}$ NMR spectra (162.0 MHz) were recorded on a Bruker AV400 spectrometer, with δ referenced to external TMS and 85% H_3PO_4, respectively. Elemental analysis was carried out on a Fisons EA 1108 CHNS-O instrument. Melting points were recorded by a Gallenkamp Model apparatus with open capillaries.

Synthesis and characterization of ligands and their complexes

General procedure for the synthesis of phosphinites (1 and 2)

A dry and degassed CH_2Cl_2 (20 ml) solution of 1-(3-chloro-2-hydroxypropyl)-3-methylimidazolium chloride under argon atmosphere (0.100 g, 0.474 mmol) was cooled to − 78 °C in acetone and dry ice bath. To the cooled solution, was added dropwise a hexane solution of *n*-BuLi (0.296 ml,

0.474 mmol). After the addition, the mixture was stirred at − 78 °C for 1 h and for an additional 30 min at room temperature. The reaction solution was cooled to − 78 °C again, and a solution of chlorodiphenylphosphine for **1** or chlorodicyclohexylphosphine for **2** (0.474 mmol) in CH_2Cl_2 (10 ml) was added dropwise to the reaction medium. Stirring was maintained for further 1 h at − 78 °C. Then, the cooling bath was removed and the mixture was stirred for another 1 h at room temperature. Precipitated lithium chloride was removed by filtration under argon, and then, the volatiles were evaporated in vacuo to leave viscous oily phosphinite ligand **1** or **2**. The experimental details were in given in a reference by Aydemir et al. (2014).

General procedure for the synthesis of ruthenium complexes (3 and 4) (Chiappe et al. 2012)

$[Ru(\eta^6\text{-}p\text{-cymene})(\mu\text{-}Cl)Cl]_2$ (0.12 mmol) and $[(Ph_2PO)\text{–}C_7H_{11}N_2Cl]Cl$, **1** or $[(Cy_2PO)\text{–}C_7H_{11}N_2Cl]Cl$, **2** (0.24 mmol) were dissolved in 25 ml of dry CH_2Cl_2 under argon atmosphere and stirred for 30 min at room temperature. The volume of the solvent was then reduced to 0.5 ml before addition of petroleum ether (10 ml). The precipitated product was filtered and dried in vacuo yielding **3** or **4** as a clear red solid.

$[(Ph_2PO)C_7H_{11}N_2Cl]Cl$ (1) Yield 0.180 g, 96.3%. ^{1}H NMR (400.1 MHz, $CDCl_3$-d_1, ppm): δ: 10.14 (s, 1H, –(CH_3)NC**H**N–), 7.13–7.78 (m, 12H, P(C_6**H**$_5$)$_2$ + –NC**H**C**H**N–), 4.94 (m, 1H, NC**H**$_2$, (a)), 4.71 (br, 1H, –C**H**OH), 4.57 (m, 1H, NC**H**$_2$, (b)), 3.91 (m, 1H, –C**H**$_2$Cl, (a)), 3.85 (m, 1H, –C**H**$_2$Cl, (b)), 3.80 (s, 3H, NC**H**$_3$); ^{13}C NMR (100.6 MHz, $CDCl_3$-d_1, ppm): δ 36.55 (N**C**H$_3$), 45.14 (–**C**H$_2$Cl), 52.52 (N**C**H$_2$), 78.45 (d, ^2J = 23.1 Hz, (–**C**HOP), 122.59, 122.90 (–N**C**H**C**HN–), 129.53 (d, $^3J_{31P–13C}$ = 10.1 Hz, *m*-P(**C**$_6$H$_5$)$_2$), 131.41 (*p*-P(**C**$_6$H$_5$)$_2$), 135.26 (d, $^2J_{31P–13C}$ = 19.6 Hz, *o*-P(**C**$_6$H$_5$)$_2$)), 140.65 (d, $^1J_{31P–13C}$ = 47.8 Hz, *i*-P(**C**$_6$H$_5$)$_2$), 138.17 (–(CH_3)N**C**HN–); assignment was based on the ^{1}H–^{13}C HETCOR, DEPT, and ^{1}H–^{1}H COSY spectra; ^{31}P-{^{1}H} NMR (162.0 MHz, $CDCl_3$-d_1, ppm): δ 118.46 (s, O**P**Ph$_2$); IR, (KBr): υ 3053 (aromatic C–H), 1434 (P-Ph), 1060 (O-P) cm^{-1}; $C_{19}H_{21}N_2OCl_2P$ (395.27 g/mol): calcd. C 57.74, H 5.35, N 7.09; found C 57.48, H 5.15, N 6.96.

$[(Cy_2PO)\text{–}C_7H_{11}N_2Cl]Cl$ (2) Yield 0.183 g, 94.8%. ^{1}H NMR (400.1 MHz, $CDCl_3$-d_1, ppm): δ 10.48 (s, 1H, –(CH_3)NC**H**N–), 7.64, 7.45 (2xs, 2H, –NC**H**C**H**N–), 4.84 (m, 1H, NC**H**$_2$, (a)), 4.53 (m, 1H, NC**H**$_2$, (b)), 4.16 (br, 1H, –C**H**OP), 4.10 (s, 3H, NC**H**$_3$), 3.83 (m, 1H, –C**H**$_2$Cl, (a)), 3.68 (m, 1H, –C**H**$_2$Cl, (b)), 1.00–1.95 (m, 22H, protons of P(C_6**H**$_{11}$)$_2$; ^{13}C NMR (100.6 MHz, $CDCl_3$-d_1,ppm): δ 26.20, 26.27, 26.64, 26.85, 26.98, 27.21 (**C**H$_2$ of P(C_6H_{11})$_2$), 37.20 (d, ^1J = 15.1 Hz, **C**H of P(C_6H_{11})$_2$), 36.77 (N**C**H$_3$), 44.05 (–**C**H$_2$Cl), 52.34 (N**C**H$_2$), 77.32 (d, ^2J = 22.7 Hz, –**C**HOP), 123.05, 123.43 (–N**C**H**C**HN–), 138.67 (–(CH_3)N**C**HN–); assignment was based on the ^{1}H–^{13}C HETCOR, DEPT, and ^{1}H–^{1}H COSY spectra; ^{31}P-{^{1}H} NMR (162.0 MHz, $CDCl_3$-d_1, ppm): δ 148.76 (s, O**P**Cy$_2$); IR, (KBr): υ 2923, 2850 (aliphatic C–H), 1446 (P-Cy), 1059 (O-P) cm^{-1}; $C_{19}H_{33}N_2OCl_2P$ (407.36 g/mol): calcd. C 56.02, H 8.16, N 6.88; found C 55.83, H 8.01, N 6.70.

Synthesis of $[Ru((Ph_2PO)\text{–}C_7H_{11}N_2Cl)(\eta^6\text{-}p\text{-cymene})Cl_2]Cl$, (3) Yield 0.154 g, 86.5%. M.p.: 110–112 °C ^{31}P-{^{1}H} NMR (162.0 MHz, $CDCl_3$-d_1, ppm): δ 124.23 (s, Ru-O**P**Ph$_2$); IR, (KBr): υ 3053 (aromatic C–H), 1435 (P-Ph), 1047 (O-P), 532 (Ru–P) cm^{-1}; $C_{29}H_{35}N_2OCl_4PRu$ (701.46 g/mol): calcd. C 49.66, H 5.03, N 3.99; found C 49.34, H 4.96, N 3.89. ^{1}H NMR (400.1 MHz, $CDCl_3$-d_1, ppm): δ 9.53 (s, 1H, –(CH_3)NC**H**N–), 7.14–7.93 (m, 12H, P(C_6**H**$_5$)$_2$ + –NC**H**C**H**N–), 5.43 (br, 2H, aromatic protons of *p*-cymene), 5.23 (br, 2H, aromatic protons of *p*-cymene), 4.81 (br, 1H, –C**H**OP), 4.61 (br, 1H, NC**H**$_2$, (a)), 4.48 (br, 1H, NC**H**$_2$, (b)), 3.94 (s, 3H, NC**H**$_3$), 3.42 (br, 2H, –C**H**$_2$Cl), 2.46 (m, 1H, C**H** of *p*-cymene), 1.83 (s, 3H, C**H**$_3$Ph of *p*-cymene), 0.99 (d, 6H, ^3J = 6.8 Hz, (C**H**$_3$)$_2$CHPh of *p*-cymene); ^{13}C NMR (100.6 MHz, $CDCl_3$-d_1, ppm): δ 17.22 (**C**H$_3$Ph of *p*-cymene), 22.16, 22.23 ((**C**H$_3$)$_2$CHPh of *p*-cymene), 30.01 (**C**H of *p*-cymene), 37.36 (N**C**H$_3$), 44.57 (**C**H$_2$Cl), 50.92 (N**C**H$_2$), 75.11 (d, ^2J = 22.9 Hz, –**C**HOP), 86.77 (d, $^2J_{31P–13C}$ = 5.0 Hz, aromatic carbons of *p*-cymene), 88.89 (d, $^2J_{31P–13C}$ = 7.0 Hz, aromatic carbons of *p*-cymene), 89.35 (d, $^2J_{31P–13C}$ = 4.0 Hz, aromatic carbons of *p*-cymene), 92.56 (d, $^2J_{31P–13C}$ = 6.0 Hz, aromatic carbons of *p*-cymene), 96.31, 111.15 (quaternary carbons of *p*-cymene), 122.60, 123.17 (–N**C**H**C**HN–), 128.34 (d, $^3J_{31P–13C}$ = 10.1 Hz, *m*-P(**C**$_6$H$_5$)$_2$)), 131.91 (d, $^4J_{31P–13C}$ = 6.1 Hz, *p*-P(**C**$_6$H$_5$)$_2$), 133.84 (d, $^2J_{31P–13C}$ = 12.6 Hz, *o*-P(**C**$_6$H$_5$)$_2$), 137.87 (d, $^1J_{31P–13C}$ = 52.3 Hz, *i*-P(**C**$_6$H$_5$)$_2$), 139.70 (–(CH_3)N**C**HN–); assignment was based on the ^{1}H–^{13}C HETCOR, DEPT, and ^{1}H–^{1}H COSY spectra.

Synthesis of $[Ru((Cy_2PO)\text{–}C_7H_{11}N_2Cl)(\eta^6\text{-}p\text{-cymene})Cl_2]Cl$, (4) Yield 0.163 g, 93.1%. M.p.: 106–108 °C ^{31}P-{^{1}H} NMR (162.0 MHz, $CDCl_3$-d_1, ppm): δ 154.25 (s, Ru-O**P**Cy$_2$); IR, (KBr): υ 2926, 2852 (aliphatic C–H), 1446 (P-Cy), 1057 (O-P), 528 (Ru–P)cm^{-1}; $C_{29}H_{47}N_2OCl_4PRu$ (713.56 g/mol): calcd. C 48.81, H 6.64, N 3.93; found C 48.53, H 6.51, N 3.83. ^{1}H NMR (400.1 MHz, $CDCl_3$-d_1, ppm): δ 9.81 (s, 1H, –(CH_3)NC**H**N–), 7.66, 7.08 (2xs, 2H, –NC**H**C**H**N–), 5.64 (d, 2H, ^3J = 3.8 Hz, aromatic protons of *p*-cymene), 5.61 (d, 2H, ^3J = 3.8 Hz, aromatic protons of *p*-cymene), 5.34–5.36 (m, 1H, –C**H**OP), 4.72 (m, 1H, NC**H**$_2$, (a)), 4.43 (m, 1H, NC**H**$_2$, (b)), 4.02 (s, 3H, NC**H**$_3$), 3.83 (m, 1H, –C**H**$_2$Cl, (a)), 3.26 (m, 1H, –C**H**$_2$Cl, (b)), 2.81 (m, 1H, –C**H** of *p*-cymene), 2.12 (s, 3H,

C**H**$_3$Ph of *p*-cymene), 1.28–1.36 (m, 22H, P(C_6**H**$_{11}$)$_2$), 0.87 (d, 6H, ^3J = 6.5 Hz, (C**H**$_3$)$_2$CHPh of *p*-cymene); ^{13}C NMR (100.6 MHz, $CDCl_3$-d_1, ppm): δ 18.77 (**C**H$_3$Ph of *p*-cymene), 22.33, 22.48 ((**C**H$_3$)$_2$CHPh of *p*-cymene), 26.25, 26.94, 27.21, 27.85, 28.48, 29.06 (**C**H$_2$ of P(C_6H$_{11}$)$_2$), 30.83 (**C**H of *p*-cymene), 37.38 (N**C**H$_3$), 46.00 (–**C**H$_2$Cl), 46.35 (d, ^1J = 29.7 Hz, **C**H of P(C_6H$_{11}$)$_2$), 49.79 (N**C**H$_2$), 74.50 (d, ^2J = 24.2 Hz, –**C**HOP), 84.86, 90.33 (aromatic carbons of *p*-cymene), 96.28, 110.99 (quaternary carbons of *p*-cymene), 122.40, 122.42 (–N**C**H**C**HN–), 139.09 (–(CH$_3$)N**C**HN–); assignment was based on the ^{1}H–^{13}C HETCOR, DEPT, and ^{1}H–^{1}H COSY spectra.

Biological assays

Chemicals

All the materials (DPPH, Calf Thymus (CT) DNA, supercoiled plasmid DNA pBR322, dimethyl sulfoxide (DMSO), methanol, α-tocopherol, and trolox) used in the biological test work were supplied from Sigma (Sigma-Aldrich GmbH, Steinheim, Germany).

DPPH radical scavenging activity

The free radical scavenging activities of the Ruthenium (**3** and **4**) compounds were studied through the DPPH assay method (Ağırtaş et al. 2014). The compounds stock solution was diluted to final concentrations of 25, 50, 100, 150, and 200 µg/ml in DMSO. 2.0 ml methanol solution of DPPH was added to 0.5 ml of different concentrations of compounds and solution mixture incubated at 25 ºC in the dark for an hour. The absorbance was then measured at 517 nm using the spectrophotometer. Trolox was utilized as a positive control.

Reducing power

The reducing power activity of ruthenium compounds was evaluated as reported by Oyaizu (1986). All the compounds were prepared (25–200 µg/ml) in DMSO (0.5 ml). 0.5 ml of 200 mM sodium phosphate buffer (pH 6.6) and 0.5 ml of potassium ferricyanide (1%) were added, and the mixed solution was incubated for 20 min at 50 °C. Then, 0.5 ml of trichloroacetic acid (10%) was mixed, and the mixed solution was centrifuged at 1000 rpm for 10 min. 1.0 ml sterilized water and 0.4 ml ferric chloride (0.1%) were mixed with the upper part of the solution (1.0 ml). Finally, at 700 nm, the absorbance was evaluated against the blank. As positive control, α-tocopherol was used.

Antibacterial activity

Antibacterial activities of the compounds were assessed through disc diffusion method making use of nutrient agar medium (Khan and Asiri 2012). *Escherichia coli* (ATCC 10536), *Legionella pneumophila* subsp. *pneumophiia* (ATCC 33152), and *Pseudomonas aeruginosa* (ATCC 9027) were used as Gram-negative bacteria, and *Staphylococcus aureus* (ATCC 6538), *Bacillus cereus,* and *Enterococcus hirae* (ATCC 10541) were used as Gram-positive bacteria for antibacterial activity of compounds. Blank antibiotic discs were spread by 15 µL of the compounds (500 µg/ml) and discs were placed on the solidified medium inoculated with the bacteria in petri dishes. Streptomycin (10 µg) and tetracycline (30 µg) were used as positive control, and blank disc impregnated with DMSO was used as negative control. The petri dishes were incubated with bacterial cultures for 24 h at 37 °C. After incubation time, the antibacterial activity of the compounds was evaluated using zone inhibition technique.

DNA binding and DNA cleavage activity

Binding and cleavage of DNA with compounds were studied through agarose gel electrophoresis. For DNA-binding activity, stock solution of CT-DNA (conc: 20 µg/ml) diluted 1:10 ratio with sterile distilled water and 5 µl diluted DNA was treated with the 8 µl Ru (II) compounds in DMSO (50, 100, and 200 µg/ml). For DNA cleavage activity, stock solution of supercoiled pBR322 DNA (conc: 1.0 µg/ml) diluted 1:10 ratio with sterile distilled water and 5 µl diluted DNA was treated with the 8 µl Ru (II) compounds in DMSO (100 µg/ml). To determine both activities, the mixture of solutions was incubated at 37 °C for 4 h in the dark, and then, 3 µl DNA loading dye was added. The samples were loaded separately on 0.8% agarose gel containing 7 µl ethidium bromide (0.05%). Electrophoresis was applied for 60 min at 80 V in TAE buffer (50 mM Tris base, 50 mM acetic acid, 2 mM EDTA, and pH:7.8). The gel was visualized under UV light and photographed (Ağırtaş et al. 2017; Keypour et al. 2015).

Results and discussion

Synthesis of the ligands and complexes

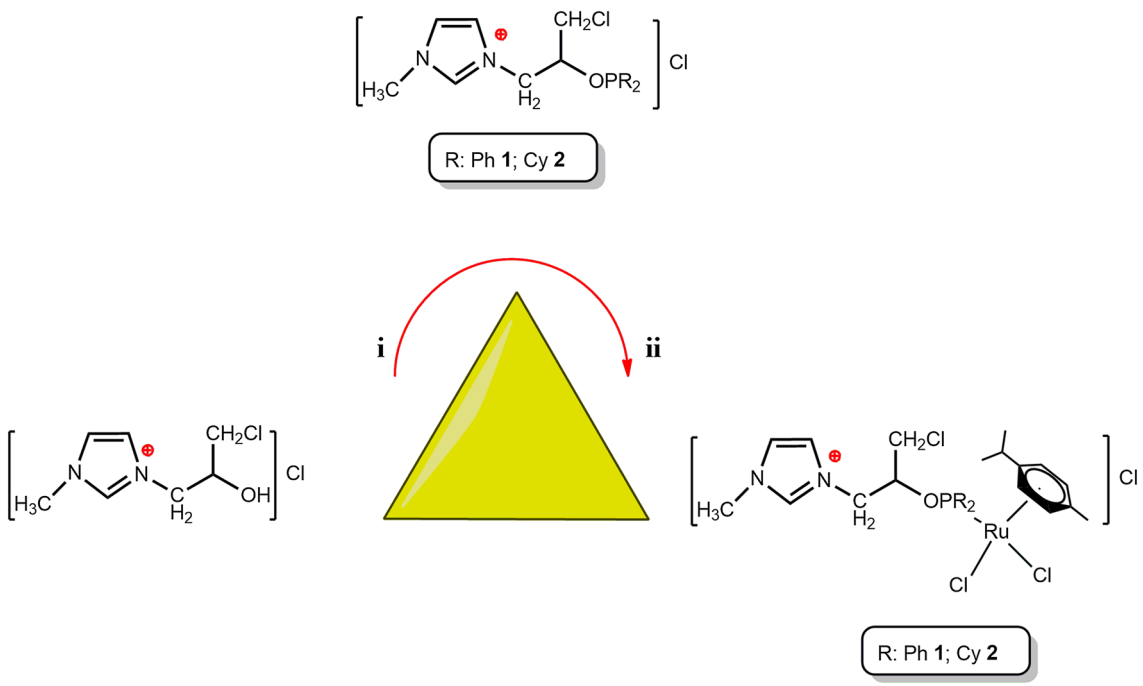
Phosphinite-based ionic liquids can play a dual role both as reaction medium and also as potential complexing agent through the phosphinite group that they bear (Iranpoor et al. 2007). Recently, the preparation of imidazolium-based phosphinite ionic liquids and their applications were reported

(Iranpoor et al. 2006, 2010; Valizadeh and Gholipour 2010; Valizadeh and Halili 2012; Valizadeh et al. 2011). Attracting features of this type of compounds prompted us to focus on phosphinite-based ionic liquids (Aydemir et al. 2014; Meriç et al. 2014a, b; Elma Karakaş et al. 2016). In the present study, IL-OPR_2 (R:Ph, Cy) phosphinites were prepared from the two-step reaction of 1-methylimidazole, epichlorohydrin, and chlorodiphenylphosphine or chlorocyclohexylphosphine (Aydemir et al. 2014; Meriç et al. 2014a, b) in 95–97% yields (Scheme 1) (Chen 2010; Hauptman et al. 1998; Ruhlan et al. 2008; Hariharasarma et al. 1999; Esquius et al. 2002; Ak et al. 2015a, b; Elma et al. 2013).

Reactions of $[Ru(\eta^6\text{-}p\text{-cymene})(\mu\text{-Cl})Cl]_2$ with $[(Ph_2PO)\text{–}C_7H_{11}N_2Cl]Cl$, **1** or $[(Cy_2PO)\text{–}C_7H_{11}N_2Cl]Cl$ **(2)** in CH_2Cl_2 in a ratio of 1/2:1 at room temperature gave red complexes, $[Ru((Ph_2PO)\text{–}C_7H_{11}N_2Cl)(\eta^6\text{-}p\text{-cymene})Cl_2]Cl$, **(3)** and $[Ru((Cy_2PO)\text{–}C_7H_{11}N_2Cl)(\eta^6\text{-}p\text{-cymene})Cl_2]Cl$, **(4)**. The coordination of the ligand through the P donor was confirmed by the $^{31}P\text{-}\{^1H\}$ NMR spectroscopy (Fig. 1). (Ak et al. 2013; Aydemir et al. 2010a, b; Milton et al. 2004; Zhang et al. 2003; Aydemir et al. 2014).

DPPH radical scavenging activity

The DPPH method is known as a simple, easy, and fast method to measure the radical scavenging activity of organic and inorganic compounds (Baykara et al. 2015). To assess the antioxidant activity, the decrease in absorbance is used by reducing the amount of DPPH in the medium. The results of radical scavenging activity as a percentage are shown in Fig. 2. As seen from the results, both compounds exhibited high activity even at low concentrations. Compound **4** (78.9%) showed a better activity than compound **3** (66.1%) at concentration of 200 µg/ml. It is well known that compounds having different functional groups such as –SH, –COOH, –N, –OH, –S–, and –O– can show antioxidant activity. Compounds **3** and **4** are only different from each other about the group on the phosphorus atom. In compounds **4**, the Cy (cyclohexyl group) on the phosphorus atom may show a better antioxidant activity than compound **3** which has the rigid planar phenyl group on the phosphorus atom. It is reported that Ru(II) complexes demonstrated good radical scavenging activity using DPPH (Appelt et al. 2017). Our compounds showed similar scavenging activity with these results. Trolox, used as a positive control, exhibited higher free radical scavenging activity than two compounds at all concentrations. As a result, compounds with radical scavenging activity may be used as promising therapeutic agents in conditions such as aging, cardiovascular diseases, and cancer, which are caused by stress-related pathological problems (Ejidike and Ajibade, 2015).



Scheme 1 Synthesis of the, $[(Ph_2PO)\text{–}C_7H_{11}N_2Cl]Cl$, **(1)**, $[(Cy_2PO)\text{–}C_7H_{11}N_2Cl]Cl$, **(2)**, $[Ru((Ph_2PO)\text{–}C_7H_{11}N_2Cl)(\eta^6\text{-}p\text{-cymene})Cl_2]Cl$, **(3)** and $[Ru((Cy_2PO)\text{–}C_7H_{11}N_2Cl)(\eta^6\text{-}p\text{-cymene})Cl_2]Cl$, **(4)** compounds. (1) 1equiv. Ph_2PCl or Cy_2PCl, 1equiv. *n*-BuLi, CH_2Cl_2; (2) 1/2equiv. $[Ru(\eta^6\text{-}p\text{-cymene})(\mu\text{-Cl})Cl]_2$, CH_2Cl_2

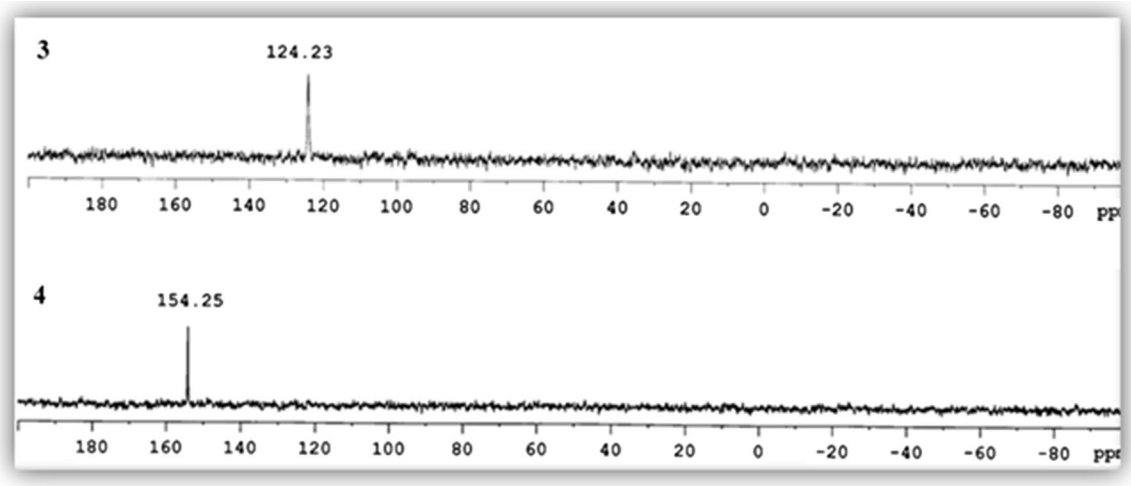


Fig. 1 The ^{31}P-{^{1}H} NMR spectra of complexes [Ru((Ph$_2$PO)–C$_7$H$_{11}$N$_2$Cl)(η^6-p-cymene)Cl$_2$]Cl, **(3)** and [Ru((Cy$_2$PO)–C$_7$H$_{11}$N$_2$Cl)(η^6-p-cymene)Cl$_2$]Cl, **(4)**

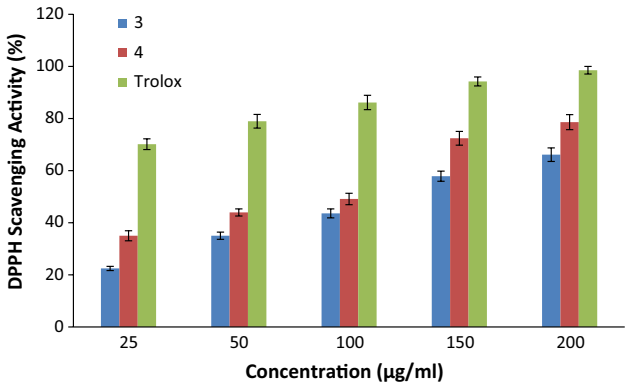


Fig. 2 Radical scavenging activities percent of the Ru(II) compounds

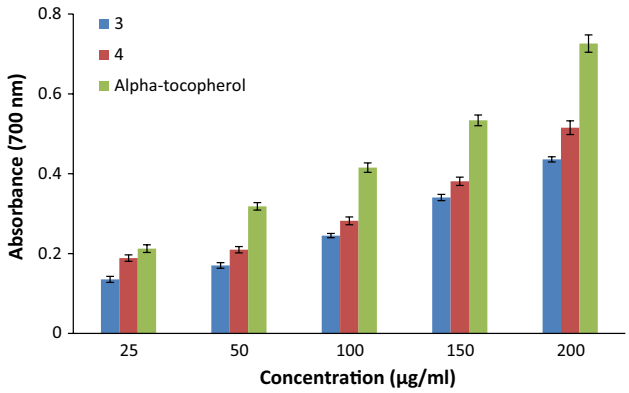


Fig. 3 Reducing power of the ruthenium compounds

Reducing power

Reducing power and antioxidant activity are associated and can provide us with significant data about antioxidant activity. Compounds with reducing power which are electron donors can reduce oxidative intermediates in the lipid peroxidation process; for this reason, they may be used as primary and secondary antioxidants (Zhang et al. 2017). The reducing power of Ru (II) compounds is shown in Fig. 3. The reducing power of compounds depends on the concentration, and both compounds showed high activity. When the two compounds are compared, the **4** has more reducing power activity. Among the test materials, the highest reducing power capability was attained from α-tocopherol as 0.719 at 200 µg/ml, and this is followed by **4** as 0.547 and **3** as 0.436 at the same concentration. The reason for these activity differences may be due to the difference in functional groups of complexes as described in DPPH radical scavenging activity section.

Table 1 Inhibition zone of Ru compounds against bacteria

Bacteria	Ruthenium compounds and standard antibiotic discs[a]			
	3	**4**	S	TE
S. aureus	12	11	16	24
B. cereus	15	12	18	20
E. hirae	14	10	19	22
E. coli	7	7	24	23
P. aeruginosa	10	9	22	14
L. pneumophila	8	10	15	21

S streptomycin (10 µg), *TE* tetracycline (30 µg)

[a]Inhibition diameter in millimeters

Antimicrobial activity

The inhibition zones of the Ru(II) compounds against three Gram-negative and three Gram-positive bacteria are given in Table 1. According to the results, compounds **3** and **4** were observed to have antibacterial activity against all tested bacteria and 7–15 mm inhibition zones obtained from them. Both Ru(II) compounds were found to be more effective against Gram-positive bacteria. This difference in the activity of different compounds against different bacterial species may be caused by the permeability of bacterial cells or the difference in ribosomes (İlhan et al. 2014). Devagi et al. (2018) studied four Ru (II) complexes antimicrobial activity against three Gram-positive bacteria (*S. aureus, E. hirae, and B. subtilis)* and found the inhibition zones in the range of 4–9 mm. Our compounds showed inhibition zones against Gram-positive bacteria in the range of 10–15 mm. Although the compounds were active against all tested bacterial strains, they were not as effective as the standard streptomycin and tetracycline.

DNA-binding activity

In this study, DNA-binding activity was assessed by gel electrophoresis and CT-DNA was used for this purpose. It has been reported that the charge, flexibility, and size of DNA play an important role in its movement on the agarose gel. The binding of DNA to the compounds causes it to move more slowly on the gel, because the bound DNA turns into a larger structure than the free DNA, and the total charge of DNA is reduced (Anjomshoa et al. 2015). Figure 4 shows the extent of DNA-binding activity with three concentrations (50, 100, and 200 µg/ml) of two Ru (II) compounds. The DNA exposed to a concentration of 50 and 100 µg/ml of the tested compounds were found to move less than the control, and the DNA exposed to the 200 µg/ml concentration showed almost no movement from the agarose gel well. The results showed that both compounds demonstrated excellent DNA-binding capability.

DNA cleavage activity

A one-strand scission of the intact supercoil DNA (Form I) led to an open circular form (Form II) and double-strand scission led to a linear form (Form III). The lowest movement is the Form II and the fast movement is the Form I, and also Form III moves in between. The agarose gel picture displays the cleavage of supercoiled plasmid pBR322 DNA is shown in Fig. 5. According to the figure, one band (Form I) was observed for the control which was not exposed to compounds (Lane C), and three bands (Form I, II, and III) were observed for the samples incubated with Ru (II) compounds (Lane 1 and 2). In this study, it was clearly observed that the Ru (II) compounds showed two-strand cleavage activity of supercoiled DNA.

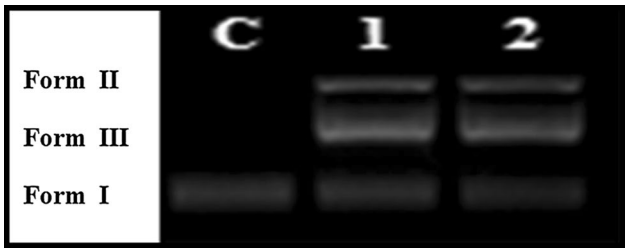


Fig. 5 DNA cleavage of Ru complexes. Lane C, Control, pBR 322 DNA; Lane 1, pBR 322 DNA + 100 µg/ml of **3**; Lane 2, pBR 322 DNA + 100 µg/ml of **4**

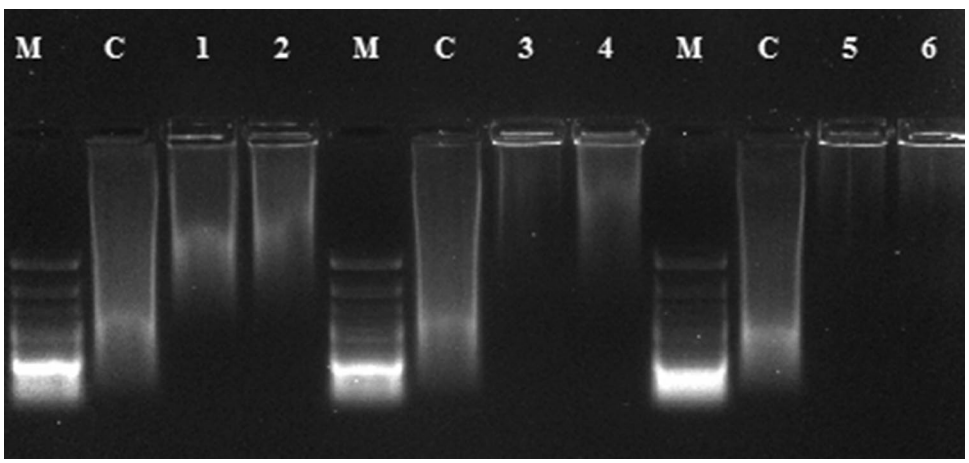


Fig. 4 DNA binding of Ru complexes. Lane M, DNA Marker; Lane C, Control, CT-DNA; Lane 1, CT-DNA + 50 µg/ml of **3**; Lane 2, CT-DNA + 50 µg/ml of **4**; Lane 3, CT-DNA + 100 µg/ml of **3**; Lane 4, CT-DNA + 100 µg/ml of **4**; Lane 5, CT-DNA + 200 µg/ml of **3**; Lane 6, CT-DNA + 200 µg/ml of **4**

Conclusions

In summary, we have synthesized phosphinite-based ionic liquids [(Ph_2PO)–$C_7H_{11}N_2Cl$]Cl, **(1)**, [(Cy_2PO)–$C_7H_{11}N_2Cl$]Cl **(2),** and their Ru(II) complexes Ru((Ph_2PO)–$C_7H_{11}N_2Cl$)(η^6-*p*-cymene)Cl_2]Cl **(3),** and [Ru((Cy_2PO)–$C_7H_{11}N_2Cl$)(η^6-*p*-cymene)Cl_2]Cl **(4)**. The compounds were characterized using several techniques such as multi nuclear NMR, IR spectroscopy, and microanalysis. Two ruthenium complexes were studied for biological assays such as free radical scavenging, reducing power, antibacterial, and DNA-binding and DNA cleavage activity. Especially, the compound [Ru((Cy_2PO)–$C_7H_{11}N_2Cl$)(η^6-*p*-cymene)Cl_2]Cl demonstrated highest free radical scavenging and reducing power activity. They were determined to be more efficient against Gram-positive bacteria than Gram-negative bacteria. Furthermore, both compounds showed very good DNA binding and DNA cleavage activity. According to the results of this study, our compounds can be considered as a type of drug treatment for the cancer therapy with DNA-binding and cleavage activities.

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