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Original article

Silver(I) complexes of mono- and bidentate *N*-heterocyclic carbene ligands: Synthesis, crystal structures, and *in vitro* antibacterial and anticancer studies

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ABSTRACT

A series of benzimidazole-based N-heterocyclic carbene (NHC) proligands {1-benzyl-3-(2-methylbenzyl)-benzimidazolium bromide/hexafluorophosphate (**1**/**4**), 1,3-bis(2-methylbenzyl)-benzimidazolium bromide/hexafluorophosphate (**2**/**5**) and 1,3-bis(3-(2-methylbenzyl)-benzimidazolium-1-ylmethylbenzene dibromide/dihexafluorophosphate (**3**/**6**)} has been synthesized by the successive N-alkylation method. Ag complexes {1-benzyl-3-(2-methylbenzyl)-benzimidazol-2-ylidenesilver(I) hexafluorophosphate (**7**), 1,3-bis(2-methylbenzyl)-benzimidazol-2-ylidenesilver(I) hexafluorophosphate (**8**) and 1,3-bis(3-(2-methylbenzyl)-benzimidazol-2-ylidene)-1-ylmethylbenzene disilver(I) dihexafluorophosphate (**9**)} of NHC ligands have been synthesized by the treatment of benzimidazolium salts with Ag_2O at mild reaction conditions. Both, NHC proligands and Ag–NHC complexes have been characterized by ^1H and $^{13}C\{^1H\}$ NMR and FTIR spectroscopy and elemental analysis technique. Additionally, the structure of the NHC proligand **5** and the mononuclear Ag complexes **7** and **8** has been elucidated by the single crystal X-ray diffraction analysis. Both the complexes exhibit the same general structural motif with linear coordination geometry around the Ag centre having two NHC ligands. Preliminary *in vitro* antibacterial potentials of reported compounds against a Gram negative (*Escherichia coli*) and a Gram positive (*Bacillus subtilis*) bacteria evidenced the higher activity of mononuclear silver(I) complexes. The anticancer studies against the human derived colorectal cancer (HCT 116) and colorectal adenocarcinoma (HT29) cell lines using the MTT assay method, revealed the higher activity of Ag–NHC complexes. The benzimidazolium salts **4**–**6** and Ag–NHC complexes **7**–**9** displayed the following IC_{50} values against the HCT 116 and HT29 cell lines, respectively, 31.8 ± 1.9, 15.2 ± 1.5, 4.8 ± 0.6, 10.5 ± 1.0, 18.7 ± 1.6, 1.20 ± 0.3 and 245.0 ± 4.6, 8.7 ± 0.8, 146.1 ± 3.1, 7.6 ± 0.7, 5.5 ± 0.8, 103.0 ± 2.3 μM.

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1. Introduction

In the past decade there have been major advances in the design and synthesis of *N*-heterocyclic carbene (NHC)-based late transition metal complexes for various applications in catalysis and bioorganometallic chemistry [1]. Ag complexes of NHCs have evolved into a major sub-field in its own right, and their applications in NHC transfer chemistry and pharmacology have gone to a mainstream issue addressed in modern synthetic inorganic and organic chemistry. Ag–NHC complexes are playing an increasing role in inorganic chemistry and catalysis for the facile construction of Pd or Ni–NHC systems, which are not readily accessible by standard synthetic procedures [2]. This is one of the simplest techniques to access a library of compounds, which avoids the difficulty of handling free carbenes. This area now involves synthesis of a number of functionalized and non-functionalized NHC-transition metal complexes that can be used in various contexts ranging from catalysis to biology [3]. Based on this conceptually simple reactivity of Ag–NHC complexes with other transition metal

Abbreviations: NHC, N-heterocyclic carbene; *E. coli*, *Escherichia coli*; *B. subtilis*, *Bacillus subtilis*; HCT 116, human colorectal cancer; HT29, human colorectal adenocarcinoma; MTT, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide; IC_{50}, half maximal inhibitory concentration; μM, micromolar.

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sources for NHC transfer purpose, diverse new synthetically useful reactions have been developed. Furthermore, these Ag–NHC complexes are readily prepared by simple reaction of the azolium salts with Ag(I) oxide at mild reaction conditions, without the need to handle reactants or later workup under an inert atmosphere.

To date, a wide range of Ag complexes having both five and six-membered functionalized and non-functionalized NHC ligands have been reported [4]. Binuclear Ag complexes of bulky non-functionalized NHC ligands displayed interesting supramolecular chemistry through the most favourable d^{10}–d^{10} closed shell attractive interactions between two Ag centres [5]. Furthermore, nitrile-functionalized NHC ligands displayed interesting coordination behaviour yielding NHC and nitrile coordinated Ag complexes. Topology of these nitrile-functionalized Ag complexes however, can be controlled by varying the metal to NHC ratio [6]. Indeed, numerous Ag–NHC complexes displayed spectacular supramolecular arrangements having interacted with different counter ions or solvent molecules.

Apart from their use as NHC transfer candidates, Ag–NHC complexes feature quite prominent biomedicinal applications as antimicrobial as well as anticancer agents [7]. A large contribution toward the biomedicinal applications of Ag–NHC complexes having general formula [NHC–Ag–acetate/halide] has been made [8]. These complexes can promote a slow release of Ag ions at the infected site over a long period of exposure time suppressing the infection. This behaviour of site-specificity and slow release of Ag ions distinguishing them from other transition metal based anticancer agents and making them interesting candidates in the field of bioorganometallic chemistry [9]. Anticancer potential of Ag–NHC complexes can be easily tuned by varying the electronic and steric properties of NHCs, which in turn affect the hydrophilic and lipophilic nature of the complexes. It has been shown that the mode of action of these Ag–NHC and other linear transition metal NHC complexes as anticancer agents is particularly different from that of platinum-based coordination complexes. The latter complexes targeting specific sequence of DNA, while former candidates targeting the mitochondrial membrane of the infected cell or inhibiting thioredoxin reductase, leading to mitochondria initiated apoptosis (the programmed cell death) [10]. Thus, it is not surprising that numerous efforts on Ag and Au–NHC complexes have been paid in targeting mitochondria induced apoptosis to develop new drug candidates for cancer therapy. In continuation of our research contribution to this bioorganometallics field, herein we report on the synthesis, spectral and analytical characterizations, and a preliminary comparative antibacterial and anticancer study of a series of benzimidazolium salts and their respective Ag–NHC complexes.

2. Experimental

2.1. Reagents and instruments

All the chemicals used were of reagent grade; solvents were dried and distilled before use according to standard procedures. 1,3-Bis(bromomethyl)benzene, 2-(bromomethyl)toluene, (bromomethyl)benzene, benzimidazole, potassium hydroxide, potassium hexafluorophosphate and silver(I) oxide were purchased from Sigma–Aldrich and used as received. For X-ray single crystal structure analysis, Bruker SMART APEX2-2009 CCD area-detector diffractometer was used for the data collection. SAINT Bruker-2009 was used for the cell refinement, SAINT was used for the data reduction and SHELXTL was used to solve the structure. Calculations, structure refinement, molecular graphics and the material for publication were achieved using the SHELXTL and PLATON software packages. Structures were solved by direct methods and refined by full-matrix least-squares against F^2. Melting points were measured using a Stuart Scientific SMP-1 (UK) instrument. The FT-IR spectra of the compounds were recorded in potassium bromide disks using a Perkin Elmer 2000 system spectrometer in the range 4000–400 cm^{-1}. ^1H and ^{13}C NMR spectra were obtained at room temperature on a Bruker 500 MHz Ascend spectrometer from solutions either in DMSO-d_6 or CD_3CN-d_3 using TMS as an internal reference. All reported compounds were analysed for carbon, hydrogen and nitrogen by the CHN mircoanalyses using a Perkin-Elmer 2400 LS Series CHN/S analyzer.

2.2. Syntheses of benzimidazolium salts

2.2.1. Synthesis of 1-benzyl-3-(2-methylbenzyl)-benzimidazolium hexafluorophosphate (**4**)

A mixture of (bromomethyl)benzene (0.171 g, 1 mmol) and 1-(2′-methyl)benzyl benzimidazole (0.222 g, 1 mmol) were stirred in 1,4-dioxane (30 mL) at 100 °C for 48 h. The reaction mixture upon boiling yielded a pale yellow solid, which was isolated by filtration and washed with fresh 1,4-dioxane and diethyl ether. So obtained bromide salt **1** was directly converted into its hexafluorophosphate counterpart by metathesis reaction using KPF_6 (0.276 g, 1.5 mmol) in methanol (20 mL). The mixture was stirred for 4 h and was left to stand overnight. The white precipitate **4** was filtered and washed with distilled water (3 × 5 mL) to remove unreacted KPF_6, then was left to dry at room temperature. Yield: 87.9%. M.P.: 142 °C. ^1H NMR (500 MHz, d_6-DMSO): δ 2.33 (3H, s, CH_3–Ar), 5.77 (2H, s, CH_2-2-methylbenzyl), 5.78 (2H, s, CH_2-benzyl), 7.18 (1H, s, Ar–H), 7.24 (1H, m, Ar–H), 7.40 (5H, m, Ar–H), 7.45 (2H, m, Ar–H), 7.64 (2H, m, Ar–H), 7.97 (2H, m, Ar–H), 9.81 (1H, s, benzimidazolium 2-CH). $^{13}C\{^1H\}$ NMR (125 MHz, d_6-DMSO): δ 18.7 (CH_3–Ar), 48.5 (CH_2-methylbenzyl), 50.0 (CH_2-benzyl), 128.1, 128.8, 129.0, 131.0, 133.9 (Ar–C, benzyl), 128.4, 128.9, 130.9, 136.6 (Ar–C, methylbenzyl), 114.0, 126.5, 126.9, 131.4, 131.6 (Ar–C, benzimidazole), 142.6 (benzimidazolium C2′). FTIR (KBr disk) cm^{-1}: 1607 ν(C=N, benzimidazole), 3089, 3147 ν(C–H, aliphatic and aromatic). Anal. Calcd for $C_{22}H_{21}N_2F_6P$: C 57.6, H 4.6, N 6.1%. Found: C 58.5, H 4.4, N 6.0%.

2.2.2. Synthesis of 1,3-bis(2-methylbenzyl)-benzimidazolium hexafluorophosphate (**5**)

This compound was prepared in a manner analogous to that for **4**, only with 2-(bromomethyl)toluene (0.185 g, 1 mmol) instead of (bromomethyl)benzene.

Yield: 86.6%. M.P.: 168 °C. ^1H NMR (500 MHz, CD_3CN): δ 2.33 (6H, s, CH_3–Ar), 5.62 (4H, s, 2 × CH_2-2-methylbenzyl), 7.15 (2H, d, Ar–H, $J = 8$ Hz), 7.24 (2H, m, Ar–H), 7.34 (4H, m, Ar–H), 7.67 (2H, m, Ar–H), 7.77 (2H, m, Ar–H), 8.68 (1H, s, benzimidazolium 2-CH). $^{13}C\{^1H\}$ NMR (125 MHz, CD_3CN): δ 17.9 (CH_3–Ar), 48.9 (CH_2-methylbenzyl), 117.0, 127.1, 129.1, 130.4, 136.8 (Ar–C, methylbenzyl), 113.6, 126.4, 128.5, 130.8, 131.7 (Ar–C, benzimidazole), 140.9 (benzimidazolium C2′). FTIR (KBr disk) cm^{-1}: 1608 ν(C=N, benzimidazole), 3092, 3147 ν(C–H, aliphatic and aromatic). Anal. Calcd for $C_{23}H_{23}N_2F_6P$: C 58.5, H 4.9, N 5.9%. Found: C 58.1, H 4.7, N 6.4%.

2.2.3. Synthesis of 1,3-bis(3-(2-methylbenzyl)-benzimidazolium-1-ylmethylbenzene dihexafluorophosphate (**6**)

A mixture of *o*-(bromomethyl)toluene (0.370 g, 2 mmol) and 1,3-bis(benzimidazol-1-yl-methyl) benzene (0.338 g, 1 mmol) were stirred in 1,4-dioxane (30 mL) at 100 °C for 48 h. The reaction mixture upon boiling yielded a pale yellow solid, which was isolated by filtration and then washed with fresh 1,4-dioxane and diethyl ether. So obtained dibromide salt **3** was directly converted into its bis-(hexafluorophosphate) counterpart by metathesis reaction using KPF_6 (0.276 g, 1.5 mmol) in methanol (20 mL). The mixture was stirred for 4 h and was left to stand overnight. The

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