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New Fe(III) complex with 8-(4-chlorophenyl)-3-butyl-3*H*-imidazo[4′,5′:3,4]benzo[1,2-*c*]isoxazol-5-amine (5-AIBI) ligand: Synthesis, spectroscopic characterization and DFT calculations

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The new heterocyclic ligand 8-(4-chlorophenyl)-3-butyl-3*H*-imidazo[4′,5′:3,4]benzo [1,2-*c*]isoxazol-5-amine (5-AIBI) was synthesized from the reduction of 3-butyl-8-(4-chlorophenyl)-5-nitro-3*H*-imidazo[4′,5′:3,4]benzo[1,2-*c*]isoxazole in high yield. The coordination ability of the ligand with some cations was examined by spectrophotometric method at rt condition. Results showed that only the absorption spectra of the Fe^{3+}–5-AIBI complex show a high redshift of the absorption maximum in the aqueous ethanol solution. The effect of pH on the absorption spectrum of the green iron–5-AIBI complex was also investigated. In addition, density functional theory (DFT) calculations are performed to provide the optimized geometries, structural parameters, calculated chemical shifts and vibrational frequencies of the investigated Fe(III) complex.

1. Introduction

Coordination complexes are used as catalysts for a diverse range of organic reactions such as polymerization [1], hydrogenation [2], oxygen-, nitrogen- and carbon-atom transfer to alkenes [3], cross-coupling reactions [4], Lewis acid catalysts in organic synthesis [5], electrochemical reactions [6], etc. Also, the interaction of transition metal ions with biological molecules provides one of the most fascinating areas of coordination chemistry. There are many metal complexes that can use as drugs and chemotherapeutic agents. Farrell concentrates on Pt anticancer drugs and, particularly, the differing interactions of mono-, di- and trinuclear complexes with DNA and the differing antitumor effects this may produce [7].

On the other hand, isoxazoles and fused isoxazoles are an important class of heterocyclic pharmaceuticals and bioactive compounds because of their considerable and wide spectrum of biological activities, including potent and selective antagonism of the NMDA receptor [8] and anti-HIV activity [9]. Isoxazole-metal complexes are often postulated as intermediates in reactions of considerable synthetic utility, for example the reductive ring opening of isoxazoles. Several isoxazole-metal complexes have been reported and well characterized. In a review of the literature of isoxazole-metal complexes [10], the binding characteristics of the isoxazoles in the complexes have been examined, and some tentative conclusions regarding the regularity of isoxazole complexation behavior have been discussed. Also, it has been pointed that the behavior of the aminoisoxazoles was seen to be fairly well in the isoxazole-metal complexes.

Taking this body of research into consideration, we have synthesized a new heterocyclic ligand 8-(4-chlorophenyl)-3-butyl-3*H*-imidazo[4′,5′:3,4]benzo[1,2-*c*]isoxazol-5-amine (5-AIBI) in high yield and the coordination ability of the ligand with some cations such as Cr^{3+}, Ba^{2+}, Zn^{2+}, Hg^{2+}, Fe^{3+}, Ni^{2+}, Al^{3+}, Co^{2+}, Mn^{2+}, Pb^{2+}, Sr^{2+} and Cu^{2+} was examined by spectrophotometric method at rt condition. The stoichiometry of the Fe(III)–ligand complex were obtained by using the Job's method. Furthermore, density functional theory (DFT) calculations are performed to provide the optimized geometries and structural parameters of the investigated Fe(III) complex.

2. Experimental

2.1. Equipment and materials

Melting points were measured on an Electrothermal type-9100

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melting-point apparatus. The FT-IR (as KBr discs) spectra were obtained on a Tensor 27 spectrometer and only noteworthy absorptions are listed. The ^{13}C NMR (100 MHz) and ^{1}H NMR (400 MHz) were recorded on a Bruker Avance DRX-400 spectrometer. Chemical shifts are reported in ppm downfield from TMS as internal standard; coupling constant J is given in Hz. The mass spectrum was recorded on a Varian Mat, CH-7 at 70 eV and ESI mass spectrum was measured using a Waters Micromass ZQ spectrometer. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer. Absorption spectra were recorded on Varian 50-bio UV-Visible spectrophotometer. UV-vis scans were recorded from 200 to 1000 nm. All measurements were carried out at room temperature. Compounds **1**[11]**,** **3**[12] and **4**[13] were obtained according to the published methods. Other reagents were commercially available. Adjustment of pH was made with acetic acid, phosphoric acid, boric acid and their potassium salts. Sodium perchlorate was added to give a constant ionic strength of 0.1 M.

2.2. Computational methods

All of the calculations have been performed using the DFT method with the B3LYP functional [14] as implemented in the Gaussian 03 program package [15]. The 6-311 + G(d,p) basis sets were employed except for the Fe atom where the LANL2DZ basis sets were used with considering its effective core potential. Geometry of the Fe complex was fully optimized, which was confirmed to have no imaginary frequency of the Hessian. Geometry optimization and frequency calculation simulate the properties in the gas/solution phases.

. The fully-optimized geometry was confirmed to has no imaginary frequency of the Hessian. Also, the calculation were done in both states of the Fe(III) complex, the high spin and low spin.

Obviously, the solvent plays an important role in chemical reactions. In this work, the solute-solvent interactions have been investigated using one of the self-consistent reaction field methods, i.e., the sophisticated Polarizable Continuum Model (PCM) [16]. In both of the gas phase and ethanolic solution, the zero-point-energy (ZPE) corrections were made to calculate energies.

2.3. General procedure for the synthesis of 5 from 4

$SnCl_2 \cdot 2H_2O$ (4.52 g, 20.0 mmol) was added to a solution of **4** (1.0 g, 2.70 mmol) in ethanol (20 mL). The reaction mixture was refluxed for 2 h until the reaction was complete as indicated by TLC analysis. The solvent was removed under reduced pressure and the crude residue was partitioned between ethyl acetate and 2M KOH. The aqueous layer was extracted with further portions of ethyl acetate (3 × 50 mL) and the combined organic extracts were washed with brine (2 × 50 mL) and water (3 × 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The crude residue was subjected to flash silica gel column chromatography (40% ethyl acetate in hexanes) yielding 8-(4-chlorophenyl)-3-butyl-3*H*-imidazo[4′,5′:3,4]benzo[1,2-*c*]isoxazol-5-amine **5** (85%).

8-(4-chlorophenyl)-3-butyl-3H-imidazo[4′,5′:3,4]benzo [1,2-c]isoxazol-5-amine (**5**) was obtained as a yellow powder. mp 179–182 °C. ^{1}H NMR ($CDCl_3$): δ 0.96 (t, J = 7.2 Hz, 3H, CH_3), 1.33–1.41 (m, 2H, CH_2), 1.79–1.89 (m, 2H, CH_2), 4.10 (t, J = 7.2 Hz, 2H, NCH_2), 4.38 (br s, 2H, NH_2), 6.48 (s, 1H, Ar H), 7.54 (d, J = 9.0 Hz, 2H, Ar H), 7.67 (s, 1H, Ar H), 8.83 (d, J = 9.0 Hz, 2H, Ar H) ppm; ^{13}C NMR ($CDCl_3$): δ 13.6, 19.9, 32.3, 45.1, 94.3, 108.9, 126.1, 126.9, 128.4, 129.2, 130.7, 131.7, 135.5, 137.2, 153.4, 161.9 ppm. IR (KBr): 3455, 3302 cm^{-1} (NH_2), MS (m/z) 342 (M^{+}+2). Anal. Calcd for $C_{18}H_{17}ClN_4O$ (340.8): C, 63.44; H, 5.03; N, 16.44. Found: C, 63.29; H, 5.01; N, 16.34.

2.4. Synthesis of complex

To the yellow solution of ligand 5-AIBI (200 mg, 588.2 μM) in aqueous ethanolic solution (20 mL, EtOH, H_2O, 10:90) iron (III) chloride (47.6 mg, 294.1 μM) was added, resulting in color change to deep green. The reaction was carried out for another 1 h. The complex was isolated by evaporation of the solvent and washed with acetonitrile.

$[Fe(5\text{-AIBI})_2]\,Cl_3 \cdot 2(H_2O)$: was obtained as a dark green powder. mp > 300 °C (decomp). ^{1}H NMR (DMSO-d_6): δ 0.75 (t, J = 7.0 Hz, 3H, CH_3), 1.14–1.22 (m, 2H, CH_2), 1.34–1.42 (m, 2H, CH_2), 4.30 (t, J = 7.0 Hz, 2H, NCH_2), 5.63 (br s, 2H, NH_2), 7.48 (s, 1H, Ar H), 7.52 (d, J = 9.0 Hz, 2H, Ar H), 7.94 (s, 1H, Ar H), 8.97 (d, J = 9.0 Hz, 2H, Ar H) ppm; ^{13}C NMR ($CDCl_3$): δ 13.3, 19.5, 31.8, 45.4, 97.2, 108.1, 127.3, 126.5, 128.3, 129.7, 131.6, 132.7, 135.8, 136.2, 155.0, 162.3 ppm. IR (KBr): 3436, 3302 cm^{-1} (NH_2), ESI-MS (+) m/z (%): 736 $[Fe(5\text{-AIBI})_2]^{3+}$. Anal. Calcd for $C_{36}H_{38}Cl_5FeN_8O_4$ (879.85): C, 49.14; H, 4.35; N, 12.74. Found: C, 48.81; H, 4.31; N, 12.49.

3. Results and discussion

The processes to obtain the desired new ligand are depicted in Scheme 1. In the first place, the commercially available 5-nitro-1*H*-benzimidazole was alkylated with *n*-butyl bromide in KOH and DMF to give 1-butyl-5-nitro-1*H*-benzimidazole (**1**) at rt [11]. 3-Butyl-8-(4-chlorophenyl)-3*H*-imidazo [4′,5′:3,4]benzo[1,2-*c*]isoxazoles (**3**) was obtained from the reaction of 1-butyl-5-nitro-1*H*-benzimidazole **1** with (4-chlorophenyl)acetonitrile (**2**) in basic MeOH solution [12]. Regioselective nitration of compound **3** was carried out using a mixture of sulfuric and potassium nitrate and led to the formation of 3-butyl-8-(4-chlorophenyl)-5-nitro-3*H*-imidazo[4′,5′:3,4]benzo[1,2-*c*]isoxazole **4** in high yield [13]. Finally, reduction of **4** in EtOH by $SnCl_2$, gave the new 8-(4-chlorophenyl)-3-butyl-3*H*-imidazo[4′,5′:3,4]benzo[1,2-*c*]isoxazol-5-amine (**5**) in high yield. The NOESY spectrum of the compound **4** and ^{1}H NMR and ^{13}C NMR spectra of compound **5** can be found in Supporting Information (Figures S1–S3 and Table S1).

Structural assignments of the new compound **5** were based on its spectral and microanalytical (C, H, and N) data. In the ^{1}H NMR spectrum of compound **5** there is an exchangeable peak at δ 4.38 ppm assignable to NH_2 group protons. Also, there are two doublet signals (δ = 8.83 and 7.54 ppm) and two singlet signals (δ = 7.68 and 6.47 ppm) attributed to six protons of aromatic rings. In addition, 15 different carbon atom signals are observed in the ^{13}C NMR spectrum of compound **5**. Moreover, the IR spectrum of compound **5** in KBr revealed a broad absorption band at 3455 cm^{-1} assignable to NH_2 group. All this evidence taken in conjunction with molecular ion peak at m/z 342 $[M+2]^{+}$ support the structure of ligand **5**.

The coordination ability of the 8-(4-chlorophenyl)-3-butyl-3*H*-imidazo[4′,5′:3,4] benzo[1,2-*c*]isoxazol-5-amine (5-AIBI) dissolved in EtOH was studied with some cations such as Cr^{3+}, Ba^{2+}, Zn^{2+}, Hg^{2+}, Fe^{3+}, Ni^{2+}, Al^{3+}, Co^{2+}, Mn^{2+}, Pb^{2+}, Sr^{2+} and Cu^{2+} by using a UV-vis spectrophotometer at rt condition. Results revealed that only the absorption spectra of the Fe^{3+}–5-AIBI complex show a high redshift of the absorption maximum in dilute (1×10^{-4} M) aqueous ethanolic solution and color change to deep green.

The absorption spectra of the ligand (5-AIBI) and iron (III)–5-AIBI complex are shown in Fig. 1. As seen, the spectrum of iron–5-AIBI complex has an absorption maximum at 740 nm at which the ligand has no absorbance. So wavelength 740 nm has