

Selective Speciation of Ferric Iron by a New Heterocyclic Ligand

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ABSTRACT: The synthesis and analytical applications of the new heterocyclic ligand are described. The complexation reaction of the ligand with some cations was studied in aqueous methanol at room temperature using the spectrophotometric method. Results revealed that only the absorption spectra of the Fe (III)–ligand complex show a high redshift of the absorption maximum in the aqueous methanol solution and the compound reacts with Fe (III) to produce a deep green complex (1:2 mol ratio of Fe(III)/ligand). Furthermore, a highly sensitive, selective and rapid spectrophotometric method is described for the determination of trace amounts of Fe (III) by using the ligand.

KEYWORDS: 3H-imidazo[4',5':3,4]benzo[1,2-c]isoxazole; Complexation reaction; Iron (III) complex; Absorption spectra; Selective detection.

INTRODUCTION

Benzo[1,2-c]isoxazoles are an important class of heterocyclic pharmaceuticals and bioactive compounds which are prescribed as antipsychotic risperidone [1] and anti-HIV drugs [2] and play a key role in many organic reactions [3]. 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 [4], 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.

On the other hand, iron is an important building block in supramolecular synthetic approach due to its significance and as a part of alcohol oxidation or hydrosilylation

in synthetic models of biological systems (metaloenzymes) [5] catalysts [6]. Determination of trace amount of iron in water for environmental protection, hydrogeology and some chemical processes is very important [7]. Extraction of the iron complex into an organic phase following spectrophotometric measurements of the complex is one of the best methods for determination of iron. For example, thiocyanate, acetylacetonate, cupferron, 4,7-diphenylphenanthroline, 8-quinolinol, dibenzoylmethane and *N,N*-bis(2-hydroxy-5-bromo-benzyl) 1,2-diaminopropane are used for a long time [8–11]. However, these methods were not satisfactory, because many other metals were extracted. In addition, literature data that concern the topic of isoxazole building blocks for the construction of preprogrammed ligands are relatively scarce and still need to be investigated.

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Herein we report the synthesis of new heterocyclic ligand 8-(4-chlorophenyl)-3-propyl-3*H*-imidazo[4',5':3,4]benzo[1,2-*c*]isoxazol-5-amine in high yield. The coordination ability of the ligand with some cations such as Cr³⁺, Ba²⁺, Zn²⁺, Hg²⁺, Fe³⁺, Ni²⁺, Al³⁺, Co²⁺, Mn²⁺, Pb²⁺, Sr²⁺ and Cu²⁺ has been examined by spectrophotometric method at rt condition. The stoichiometry and the thermodynamic properties of the metal complex have been obtained. In addition, a highly sensitive, selective and rapid spectrophotometric method is introduced for the determination of trace amounts of Fe (III) by the ligand.

EXPERIMENTAL SECTION

Equipment and Materials

Melting points were measured on an Electrothermaltpe-9100 melting-point apparatus. The FT-IR (as KBr discs) spectra were obtained on a Tensor 27 spectrometer and only noteworthy absorptions are listed. The ¹³C NMR (75 MHz) and ¹H NMR (300 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 spectra were recorded on a Varian Mat, CH-7 at 70 eV. Elemental analysis was performed on a Thermo Finnigan Flash EA microanalyzer. A 929 Unicam AAS Spectrometer was used and measurements carried out using an air-acetylene flame. Absorbance measurements were made using a Varian 0-bio UV-Visible spectrophotometer. UV-Vis scans were recorded from 200 to 1000 nm. A pH meter (Metrohm 691 pH Meter) was also used. 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. The rate constants were calculated with Pro-K II software (Applied Photophysics, UK). The absorbance spectrophotometer measurements were performed on a water bath (Julabo model F12) thermostated with a constant temperature maintained within ±0.01 °C. Compounds **1** [12], **3** [13] and **4** [3] were obtained according to the published methods. Other reagents were commercially available.

General procedure for the synthesis of **5** from **4**

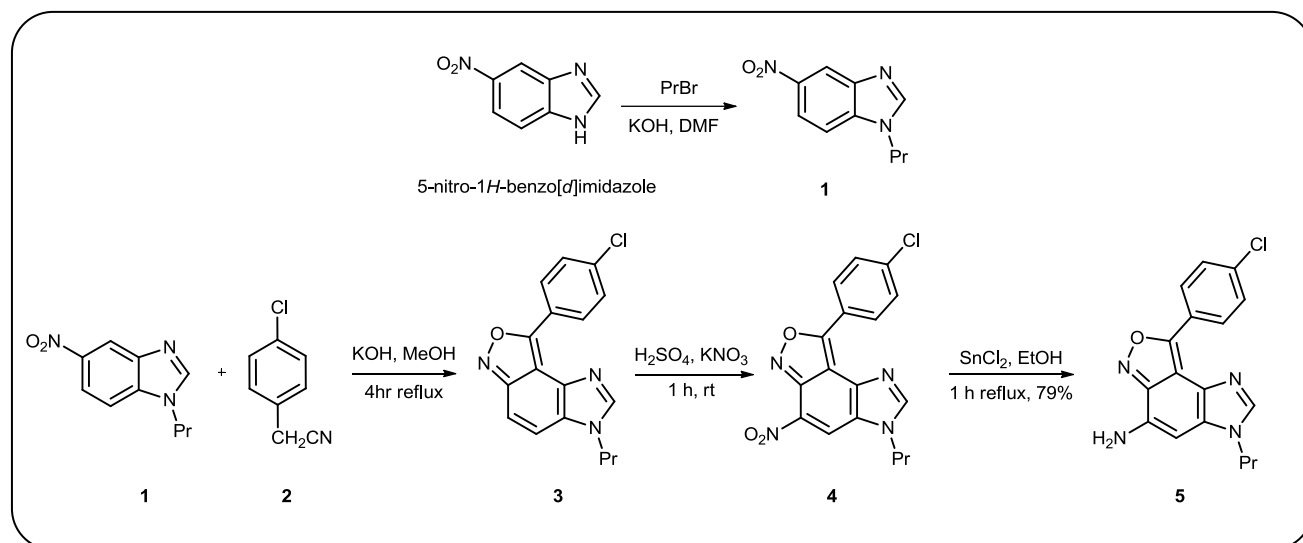
SnCl₂·2H₂O (3.01 g, 15.0 mmol) was added to

a solution of **4** (0.75 g, 0.90 mmol) in ethanol (20 mL). The reaction mixture was refluxed for 1 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 (MgSO₄) 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-propyl-3*H*-imidazo[4',5':3,4]benzo[1,2-*c*]isoxazol-5-amine **5** (79%).

8-(4-chlorophenyl)-3-propyl-3*H*-imidazo[4',5':3,4]benzo[1,2-*c*]isoxazol-5-amine (**5**) was obtained as a yellow powder. mp 187–189 °C. ¹H NMR (CDCl₃): δ 0.97 (t, *J* = 7.2 Hz, 3H, CH₃), 1.86–1.95 (m, 2H, CH₂), 4.17 (t, *J* = 7.2 Hz, 2H, NCH₂), 4.30 (br s, 2H, NH₂), 6.49 (s, 1H, Ar H), 7.56 (d, *J* = 8.4 Hz, 2H, Ar H), 7.68 (s, 1H, Ar H), 8.83 (d, *J* = 8.4 Hz, 2H, Ar H) ppm; ¹³C NMR (CDCl₃): δ 12.5, 23.9, 55.3, 94.5, 109.3, 126.2, 126.7, 128.3, 129.1, 130.8, 131.9, 135.5, 137.0, 153.2, 161.7 ppm. IR (KBr): 3440, 3305 cm⁻¹ (NH₂), MS (m/z) 328 [M (³⁷Cl)]⁺. Anal. Calcd for C₁₇H₁₅ClN₄O (326.8): C, 62.48; H, 4.63; N, 17.15. Found: C, 62.69; H, 4.60; N, 16.91.

Analysis of water

The seawater was obtained from The Caspian Sea and tap and underground water samples were obtained from Mashhad, Iran. The determine of Fe (III), 100 mL of water samples was extracted with 20 mL of 10⁻³ M 5-AIBI in chloroform at pH 3.5 for 30 min and analyzed by the general procedure. For determining the total iron, 100 mL water samples were added to 2 mL of conc. HNO₃ and heated to boiling until volume 25 mL. Cool to room temperature. Fe (II) is oxidized to Fe (III) by boiling after adding HNO₃. In most cases distribution equilibrium was attained in less than 15 min and a shaking time of 30 min was sufficient to obtain reproducible results. The final volume of the organic phase after extraction was 17 mL. After phase separation the concentration of metal ion in the aqueous phase was measured by AAS, the absorbance of the organic phase was measured against reagent blank at 500 nm using a spectrophotometer.



Scheme 1: Synthesis of the new 8-(4-chlorophenyl)-3-propyl-3H-imidazo[4',5':3,4]benzo[1,2-c]isoxazol-5-amine (5).

RESULTS AND DISCUSSION

As depicted in Scheme 1, the commercially available 5-nitro-1H-benzimidazole was alkylated with *n*-propyl bromide in KOH and DMF to give 5-nitro-1-propyl-1H-benzimidazole (**1**) at rt using literature method [12]. 8-(4-Chlorophenyl)-3-propyl-3H-imidazo[4',5':3,4]benzo[1,2-*c*]isoxazoles (**3**) was prepared from the reaction of compound **1** with **2** in basic MeOH solution [13]. Regioselective nitration of compound **3** which was accomplished using a mixture of sulfuric and potassium nitrate led to the formation of 8-(4-chlorophenyl)-5-nitro-3-propyl-3H-imidazo[4',5':3,4]benzo[1,2-*c*]isoxazole (**4**) in high yield [3]. Finally, compound **4** was reduced by SnCl₂ in EtOH and the new 8-(4-chlorophenyl)-3-propyl-3H-imidazo[4',5':3,4]benzo[1,2-*c*]isoxazol-5-amine (**5**) was obtained in high yield [14].

The structure of the new synthesized compound **5** was deduced from its spectral and microanalytical data. For example, the IR spectrum of **5** showed a stretching vibration band at 3440 cm⁻¹ indicating for NH₂ group. In the ¹H NMR spectrum of compound **5** there is an exchangeable peak at δ 4.30 ppm assignable to NH₂ group protons. Also, there are 14 different carbon atom signals in the ¹³C NMR spectrum of compound **5**. Moreover, the mass spectrum of **5** showed the molecular ion peak at *m/z* 328 [M (³⁷Cl)]⁺ corresponding to the molecular formula C₁₇H₁₅ClN₄O.

The coordination ability of the ligand dissolved in MeOH was studied with some cations such as Zn²⁺,

Al³⁺, Hg²⁺, Cr³⁺, Mn²⁺, Ba²⁺, Fe³⁺, Pb²⁺, Ni²⁺, Co²⁺, Sr²⁺, and Cu²⁺ by using a UV-Vis spectrophotometer at rt condition. Gratifyingly, these results clearly showed that only the absorption spectra of the Fe³⁺-ligand complex show a high red-shift of the absorption maximum in dilute (1 × 10⁻⁴ M) aqueous methanolic solution.

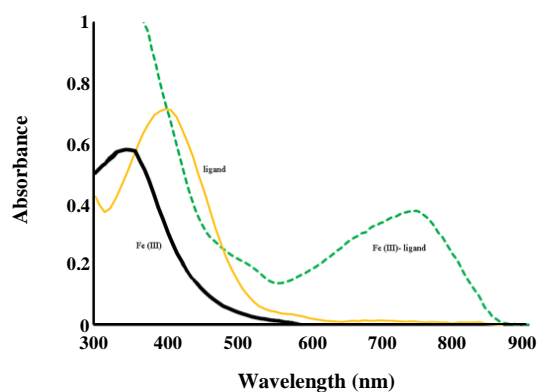
The absorption spectra of the Fe (III), ligand (5-AIBI) and iron (III)-5-AIBI complex are shown in Fig. 1. As seen, the spectrum of iron-5-AIBI complex has an absorption maximum at 745 nm (deep green) at which the ligand has no absorbance. So wavelength 745 nm has been used in all subsequent measurements of absorbance. Value of extinction coefficient (ε) which is calculated as the slope of the plot of absorbance of the iron-5-AIBI complex vs concentration is 3800 mol/L cm.

Also, the dependence of the UV-Vis absorption of the iron-5-AIBI complex on pH was examined. Fig. 2 shows the effect of pH on the absorption spectrum of the iron-5-AIBI complex. As can be seen in Fig. 2, the absorption of the iron-5-AIBI complex remains constant between pH 2 and 3.75 and then gradually decreased.

The stoichiometry of the Fe (III)-5-AIBI complex was determined by using the Job's method [15]. Nine aqueous ethanolic mixtures of 5-AIBI (0.6 mM) and Fe (III) (0.6 mM) were prepared. The pH was kept at a value of 3.5 by an acetate buffer solution and the ionic strength was kept at 0.1 M by adding NaClO₄ at 25 °C. The volumes of 5-AIBI solution used varied from 9 to 1 mL and those of iron (III) chloride solution from 1 to 9 mL;

Table 1: The rate constants of the Fe (III)–5-AIBI complex at different temperatures.

T (°C)	k_1	k_{-1}	$K = k_1/k_{-1}$
7	18.8	10.12	1.857708
15	21.3	10.81	1.970398
25	26.6	12.48	2.13141
35	31.1	13.3	2.338346
45	36.9	14.84	2.486523
55	44.3	15.89	2.787917

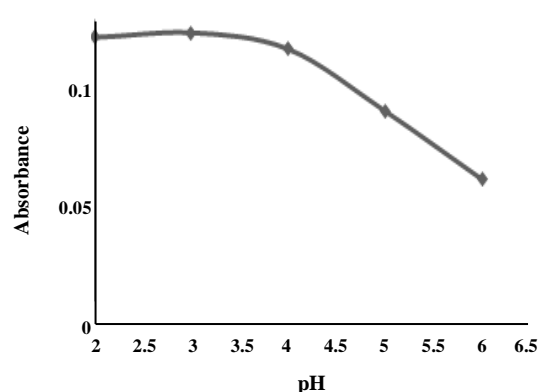
**Fig. 1: The absorption spectra of the Fe (III), ligand (5-AIBI) and Fe (III)–5-AIBI complex in aqueous methanolic solution (10^{-4} M).**

total volume was always 10 mL. The absorption spectra of the complex achieved immediately after mixing the ligand and iron (III) chloride solutions.

The Job's plot (Fig. 3) reached a maximum value at a mole fraction of 0.31, which confirmed that molar ratio between Fe (III) ions and 5-AIBI in the complex is 1:2.

Table 1 shows the rate constants of the Fe (III)–5-AIBI complex which are calculated with Pro-K II software using the spectrophotometric method at different temperatures. Preliminary experiments indicate that the dissociation of the Fe (III)–5-AIBI complex is slow and, therefore, it must be studied in higher temperature.

Separation, speciation, and determination of Fe (III) in natural waters were also investigated by using ligand 5-AIBI. The obtained results for Fe (II) and Fe (III) speciation results obtained from water samples which were compared with those obtained by 1,10 phenanthroline spectrophotometric method [16] show that the proposed procedures present very good precisions. In different water samples, no ion has interference. For determination of total iron in water samples, sample

**Fig. 2: The effect of pH on the absorption spectrum of the iron–5-AIBI complex.**

boiled with conc. HNO_3 until volume 25 mL. As a result, Fe (II) is oxidized to Fe (III). Total iron was extracted and then analyzed by the general procedure. To determine Fe (III) in the same water sample, 100 mL sample was extracted and analyzed by the general procedure (Atomic absorption spectroscopy). The amount of Fe (II) was calculated by subtracting Fe (III) from total iron. Table 2 shows the results of the determination of Fe (II) and Fe (III) in water samples.

CONCLUSIONS

In summary, we have synthesized a new heterocyclic ligand 8-(4-chlorophenyl)-3-propyl-3H-imidazo[4',5':3,4]benzo[1,2-c]isoxazol-5-amine in high yield. This compound reacts with Fe (III) in the range of pH 2–6 to produce a deep green complex (1:2 mol ratio of Fe(III)/ligand) soluble in chloroform. The stability constants of the complex were also determined using a GEPASI computer program. In addition, separation, speciation, and determination of Fe (III) in natural waters were investigated by using the ligand.

Table 2: Determination and speciation of iron in natural waters.

Sample	Extraction		1,10-phenantroline	
	Fe (III)	Fe(II)	Fe (III)	Fe(II)
Sea water (mg l ⁻¹)	85.4 ± 1.4	8.5 ± 0.6	82.1 ± 4.9	6.3 ± 3.4
Underground water (mg l ⁻¹)	67.1 ± 2.0	21.4 ± 0.8	64 ± 1	19.1 ± 2.3
Tap water (mg l ⁻¹)	57.0 ± 3.5	15.1 ± 1.9	55 ± 5	9.7 ± 2.5

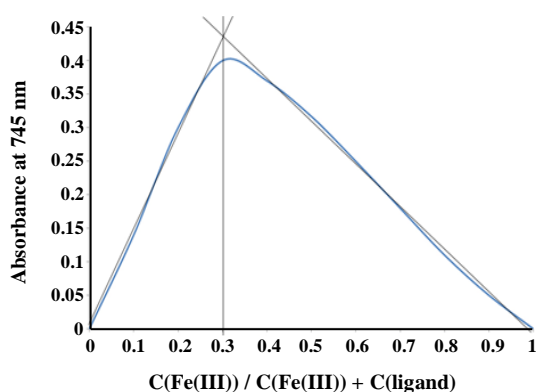


Fig. 3: Job's curve of equimolar solutions for 5-AIBI – Fe (III) complex in aqueous methanolic solution.

Such ligands would appear to offer a suitable template for the speciation of iron in different samples and further studies are under way to this end in our laboratory and will soon be reported elsewhere.

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