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ORIGINAL PAPER

Incorporation of Siderophore Binding Sites in a Dipodal Fluorescent Sensor for Fe(III)

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Abstract A new fluorescent probe **3**, has been developed for the detection of Fe(III) in water based samples. The design of **3** involved the incorporation of Fe(III) binding sites observed in naturally occurring Siderophores into a synthetic sensing assembly. The probe, containing two Schiff base receptors connected to a mesitylene platform, was prepared in two steps. The dipodal sensor displayed good selectivity for Fe(III) when tested against other physiological and environmentally important metal ions, in HEPES buffered solution at pH 7.0, through a quenching of the fluorescent intensity. Stern-Volmer analysis of this quenching interaction indicated a 1:1 (host : guest) binding stoichiometry between the probe and Fe(III). The association constant, K_a calculated using the Benesi-Hildebrand equation was found to be 3.8×10^4 M^{-1}. Crucially, the sensor was capable of measuring Fe(III) competitively in solutions containing both Fe(III) and Cu(II). Thus, the adoption of Fe(III) binding sites found in nature, into synthetic luminescent assemblies has proven an effective design strategy for the development of new Fe(III) probes.

Keywords Fluorescence · Sensor · Fe(III) · Diopodal · Schiff base

Introduction

Iron plays a key role in numerous physiological processes and is one of the most important microelements for human health [1]. For example, iron complexes are actively involved in oxygen transport and exchange reactions and several prominent enzymes also contain ferric ions as part of their catalytic site [2]. Even though iron is responsible for normal physiological functioning, a surplus of iron can result in organ damage and dysfunction [3]. Iron levels become enhanced in patients who require multiple blood transfusions, such as patients with β-thalassemia major or those with oncohematologic malignancies [4]. Therefore, the accurate determination of iron is essential to enable the effective diagnosis of certain disease states. Among the various methods known for the estimation of Fe(III), fluorescent probes have been actively investigated because of the rapid response rates and high sensitivity they offer [5–12]. However, Cu(II) can cause interference in the estimation of Fe(III), [10, 11] as both are quite abundant in biological systems, [15, 16] require similar types of coordination sphere [17, 18] and are often involved together in several structural units and biological processes [15–18]. Thus, to develop a selective receptor for Fe(III) over Cu(II), some design guidelines may be taken from the Siderophores, which are the iron chelating compounds secreted by microorganisms to facilitate the active transport of iron [19, 20]. In particular, it has been demonstrated that many siderophores and iron chelating agents comprise of a phenol substitiuent adjacent to a sp^2 hybridised nitrogen atom as depicted in structure 4 (Scheme 1) [21–28]. Here, we design a fluorescent sensor that incorporates this structural motif in its structure (compound **3**, scheme 1). Two Schiff base receptors were joined to a mesitylene platform by a thioether linkage to produce sensor **3**. It is hoped that the dipodal arrangement of receptors in **3** will provide sufficient binding sites to complete the co-ordination sphere of Fe(III). The presence of the naphthalene unit in each receptor enables the possibility of detecting any metal-sensor interactions by changes in the fluorescence signature of **3**.

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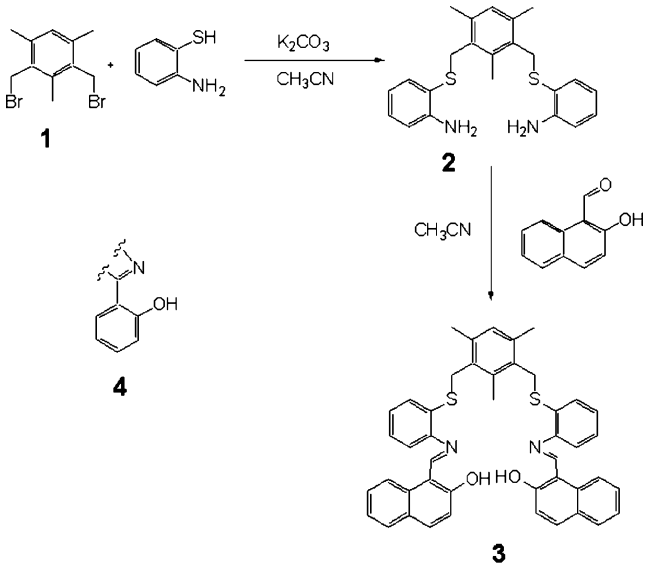

Scheme 1 Synthesis of the dipodal Schiff base sensor 3

Experimental

General

Chemicals were purchased from Aldrich Co. and used as received without further purification. Dibromide **1** was synthesised by following a literature procedure [26]. NMR spectra were recorded on a Bruker Ultrasheild 400 MHz. ^{1}H NMR samples were prepared by dissolving 5 mg of sample in 1.0 mL of $CDCl_3$. Chemical shifts are reported in parts per million (δ) downfield of TMS. Low resolution mass spectra were recorded on an Agilent LC/MS system using electrospray ionisation. Accurate Mass spectra were performed by the EPSRC national MS service. Fluorescence measurements were recorded on a Perkin Elmer LS55 Luminescence Spectrometer using 10 mm quartz cuvettes. Excitation slit size was 10.0 nm and emission slit size was 10.0 nm. Scan speed was set at 500.

Synthesis of Compound 2

Dipodal amine **2** was prepared by adding 2-aminothiophenol (250 mg, 2.0 mmol) to 1.00 g of K_2CO_3 in dry acetonitrile. The mixture was refluxed for 20 min and then dibromide **1** (304 mg, 1.0 mmol) was carefully added. Reflux was continued for 12 h and progress was monitored by TLC. Upon completion of the reaction, K_2CO_3 was filtered off and the acetonitrile solvent removed under reduced pressure. The crude product was purified with column chromatography and an off-white coloured product was obtained. Yield 75%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.35 (s, 6H, 2×CH_3), 2.37 (s, 3H, CH_3), 4.02 (s, 4H, 2×CH_2), 6.69 (t, 2H, ArH, J=7.2 Hz), 6.75 (d, 2H, ArH, J=8.0 Hz), 6.85(s, 1H, ArH), 7.15 (t, 2H, ArH, J= 7.2 Hz), 7.28 (d, 2H, ArH, J=7.2 Hz). 13C NMR ($CDCl_3$, 400 MHz): δ 15.2 (CH_3), 19.8 (CH_3), 35.0 (CH_2), 114.9 (Ar), 118.3 (Ar), 118.6 (Ar), 130.0 (Ar), 130.2 (Ar), 132.1 (Ar), 136.2 (Ar), 136.3 (Ar), 136.5 (Ar), 148.5 (Ar). Mass spectrum (FAB): ($M+H^+$) calculated for $C_{23}H_{27}N_2S_2$: 395.1616 found 395.1608.

Synthesis of Compound 3

The compound was prepared by the condensation reaction of **2** (394 mg, 1.0 mmol) with 2-hydroxy-1-naphthaldehyde (344 mg, 1.0 mmol) in dry acetonitrile. The reaction mixture was allowed to stir at room temperature for 5 h. Upon solvent evaporation, a dark yellow coloured crude product was obtained, which was purified with recrystalization from a chloroform-methanol solvent mixture. The crystals were filtered and washed with methanol and dried under vacuum. Yield 87%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.90 (s, 6H, 2×CH_3), 1.95 (s, 3H, CH_3), 3.81 (s, 4H, 2×CH_2), 7.01 (d, 2H, ArH, J=9.2 Hz), 7.16 (s, 1H, ArH), 7.18–7.29 (m, 8H, ArH), 7.36–7.40 (m, 4H, ArH), 7.61 (d, 2H, ArH, J=6.8 Hz), 7.14 (d, 2H, ArH, J=9.2 Hz), 8.05 (d, 2H, ArH, J=8.5 Hz), 9.09 (s, 2H, CH=N), 15.15 (s, 2H, OH). 13C NMR ($CDCl_3$, 400 MHz): δ 15.0 (CH_3), 19.6 (CH_3), 33.6 (CH_2), 109.2 (Ar), 118.0 (Ar), 119.2 (Ar),122.1 (Ar), 123.5 (Ar), 126.8 (Ar), 127.3 (Ar), 127.9 (Ar), 128.0 (Ar), 129.2 (Ar), 130.1 (Ar), 130.6 (Ar), 130.7 (Ar), 131.7 (Ar), 133.2 (Ar), 136.5 (Ar), 136.7 (Ar), 136.8 (Ar), 146.1 (Ar), 154.4 (Ar), 169.3 (CH=N). Mass spectrum (FAB): ($M+H^+$) calculated for $C_{45}H_{39}N_2S_2O_2$: 703.2453 found 703.2448

Cation recognition studies

The cation binding ability of **3** was determined by preparing solutions containing 25 μM solution of **3** along with 50 μM of a particular metal salt in THF:H_2O (9:1, v/v) HEPES buffered solution (pH=7.0±0.1). The fluorescence spectrum of each solution was recorded with excitation at λ_{max}=275 nm. The cation recognition behaviour was evaluated from the changes in fluorescence spectrum of receptor upon addition of that metal salt.

Receptor vs. Metal ion titration

Volumetric flasks were taken each containing 25 μM of receptor **3** along with varied amounts of Fe^{3+} salt in THF: H_2O (9:1, v/v) HEPES buffered solution (pH=7.0±0.1). The solutions were shaken thoroughly and their fluorescence spectra were recorded with excitation at λ_{max}=275 nm.

pH titration

The solutions were prepared under similar conditions as were used for receptor vs. metal ion titration experiment, except that the solutions were not buffered at a fixed pH value.

Stoichiometry determination

In order to determine stoichiometry of the complex formed between **3** and Fe(III), the Stern-Volmer plot and Job plot method were adopted. Solutions of **3** and Fe(III) were prepared as 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 (host : guest mixtures). These solutions were kept at 25±1 °C for 3 h, and were shaken occasionally. Their fluorescence spectra were recorded with excitation at λ_{max}=275 nm and fluorescence intensity at λ_{max}=375 nm was used for calculations (Fig. S11). For Stern-Volmer plot, the solutions of **3** and Fe(III) salt were prepared by fixing 25 μM concentration of receptor **3** and varying the concentration of Fe(III) in THF:H_2O (9:1, v/v) HEPES buffered solution (pH=7.0±0.1). These solutions were maintained at 25±1 °C and were shaken before fluorescent measurements. Their fluorescence spectra were recorded with excitation at λ_{max}= 275 nm and fluorescence intensity at λ_{max}=375 nm was used for calculations by using Stern-Volmer equation derived for different stoichiometries of complexes:

$$I_o/I = 1 + K_{SV}[\mathrm{Fe(III)}]^n$$

where I_o is the inherent fluorescence intensity of receptor **3** and I is the intensity in the presence of Fe^{3+}, n represent the stoichiometery of complex and K_{SV} is the Stern-Volmer constant.

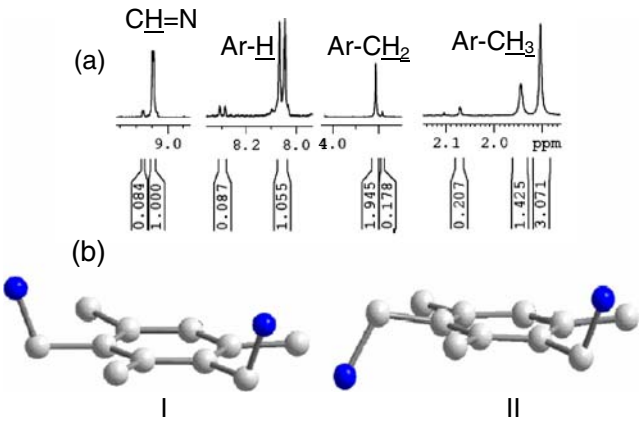

Fig. 1 **a** Partial ^{1}H NMR spectrum of compound **3** showing signals of methyl, methylene, aromatic, and CH=N protons. **b** Two possible conformations of a dipodal receptor based upon mesitylene platform

Competition studies

To evaluate any possible interference due to Cu(II) for the estimation of Fe(II), solutions were prepared containing receptor **3** (25 μM) along with different concentrations of Fe(III) both with and without Cu(II) background in THF: H_2O (9:1, v/v) HEPES buffered solution (pH=7.0±0.1). The fluorescence intensity of each solution was recorded at 375 nm.

Results and discussion

Compound **3** was synthesized by the steps shown in scheme 1. Dibromide **1** was prepared following a literature method [29]. The reaction of 2-aminothiophenol with dibromide **1** provided the dipodal amine **2**. This dipodal amine was subjected to a condensation reaction with 2-hydroxynaphthaldehyde to obtain target compound **3** in 87% yield. The product was characterized using nmr and mass spectrometry. Due to the presence of the mesitylene platform two main conformational possibilities exist for **3**, where the receptor units (shown as blue circles in Fig. 1b) can be either *cis* or *trans* to the plane of the mesitylene ring. The expanded ^{1}H NMR spectra for the methyl, methylene, aromatic and imine protons are shown in Fig. 1a and

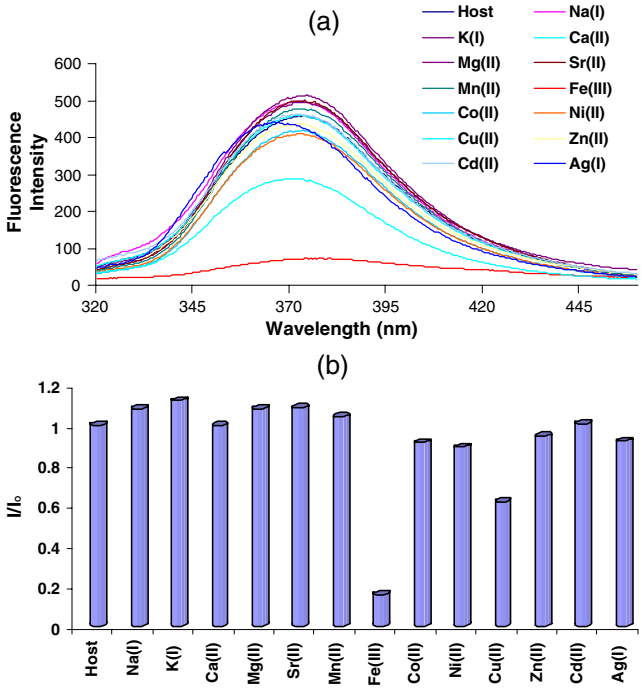

Fig. 2 **a** Changes in fluorescent intensity of **3** and **b** fluorescence ratio (I/I_o) of receptor **3** (at λ_{max}=375 nm) upon addition of a particular metal in THF/H_2O (9:1,v/v) HEPES buffer solution (pH 7.0±0.1), (Excitation at λ_{max}=275 nm), [3]=25 μM

illustrate the formation of the product as one predominant conformation [30, 31]. A very low proportion (<1% by integration) of a second conformation was also observed by the presence of small downfield resonances for the methyl, aromatic and imine signals and an upfield resonance for the methylene signal. Unfortunately, due to our inability to grow suitable crystals of **3**, we were unable to deduce the absolute structure of the pre-dominating conformation.

The photophysical properties of **3** were studied in a THF / H_2O (9:1,v/v) HEPES buffer solution (pH 7.0±0.1). A 25 μM solution of **3**, when excited at 275 nm gave a fluorescence spectrum exhibiting one main band with λ_{max} 375 nm. No other emission bands were observed at longer wavelength indicating the absence of any excited state proton transformation [32, 33] and π-π stacking [34] in pure **3** at this concentration. In the concentration range of 5–40 μM no self quenching of **3** was observed (Fig. S9, supporting information), and thus all the recognition studies were performed with 25 μM solution of **3**. The effect of solution pH on the fluorescence profile of **3** was also investigated (Fig. S10, supporting information). At intermediate pH (~6.0) the fluorescence intensity was observed to be relatively low. However, at low pH (~4.0), the fluorescence intensity increased, most likely due to the inhibition of a photoinduced electron transfer (PET) from the lone pair of the sp^2 nitrogen to the fluorophore.

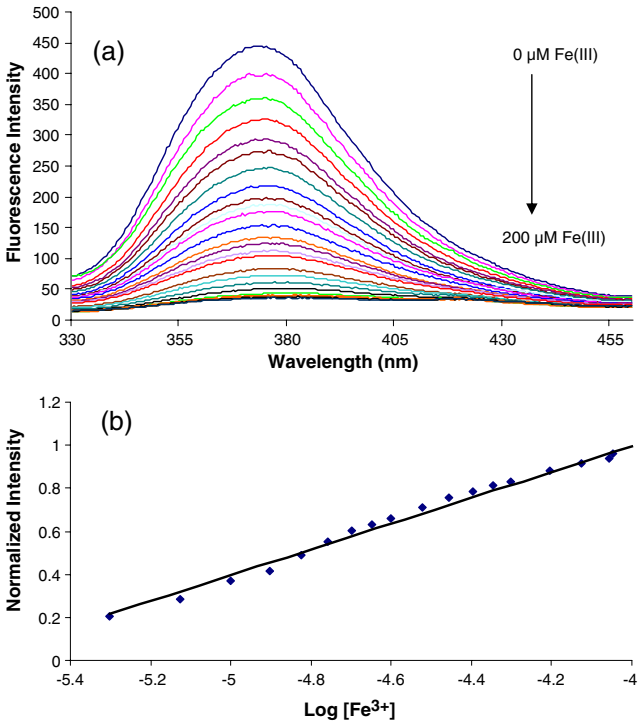

Fig. 3 **a** Changes in fluorescent spectra of **3** (25 μM) upon successive addition of Fe(III) (0–200 μM) in THF/H_2O (9:1,v/v) HEPES buffer solution (pH 7.0±0.1), (Excitation at λ_{max}=275 nm) **b** plot of normalized fluorescent intensity against the concentration of Fe(III) (5–80 μM)

Interestingly, high pH (~9.0) also switched "On" the fluorescence of **3**. We believe this is due to deprotonaton of the phenolic hydroxyl group which otherwise quenches the fluorescence by vibrationally coupling the excited state to water [35]. Therefore, working at pH 7.0 ensures the imine nitrogen remains unprotonated and can participate in ion-binding if required.

The selectivity of **3** was evaluated against a range of physiologically relevant metal ions present as their chloride salts. Specifically, 50 μM solutions of Na(I), K(I), Mg(II), Ca(II), Sr(II), Mn(II), Fe(III), Co(II), Ni(II) and Zn(II) were each added to a 25 μM solution of **3** and changes in the

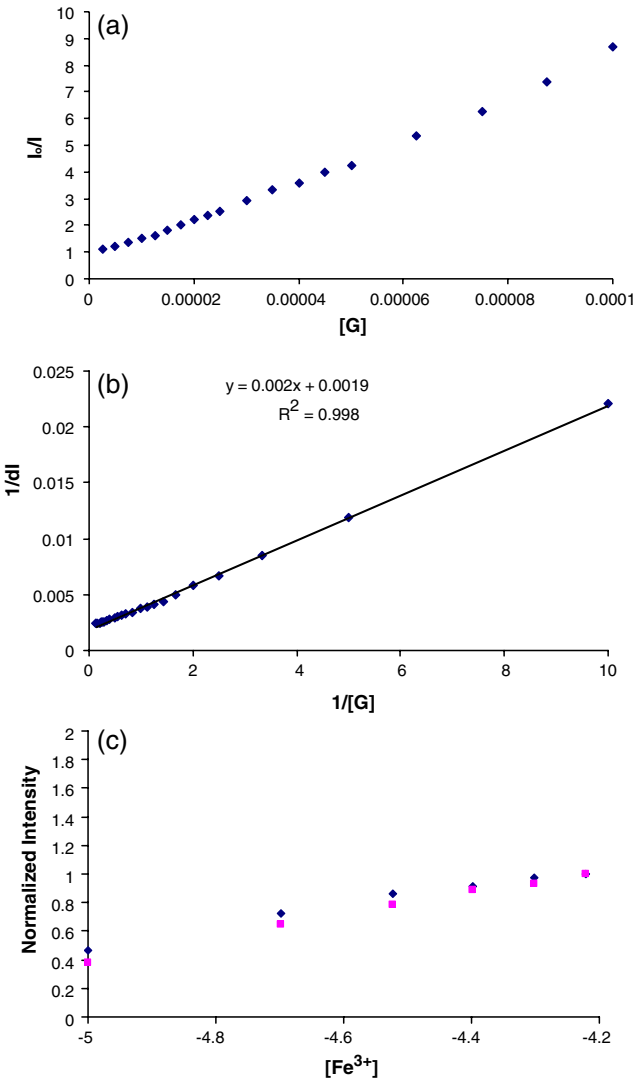

Fig. 4 **a** Linear Stern-Volmer plot for the fluorescence quenching of **3**, (25 μM) in presence of Fe(III), **b** Benesi-Hildebrand plot to calculate the association constant between **3** and Fe(III) and **c** plot of fluorescenec intensity of **3** against metal ion concentration for Fe(III) (♦); for Fe(III) in the presence of equimolar Cu(II) (■). Spectra were recorded in THF/H_2O (9:1,v/v) HEPES buffered solution (pH=7.0± 0.1). Excitation and emission wavelengths are λmax=275 nm and 375 nm respectively

fluorescence spectra were recorded. Figure 2 shows that upon the addition of 50 μM Fe (III), the intensity of emission band at 375 nm decreased significantly (~80%) with no noticeable shift in its λ_{max}. Of the other metal ions tested, only Cu(II) also produced a quench but only by ~30% of the original fluorescent intensity. The quenching effect caused by Fe(III) and Cu(II) upon binding is most likely due to an electron / energy transfer process occurring between the excited naphthalene fluorophore and the redox active metal ions, which opens a non-radiative deactivation pathway [36]. In addition to the quenching effects caused by Fe(III) and Cu(II), Ag(I) was observed to produce a small blue shift in the emission maximum of **3**, but there was no significant change in the intensity at 375 nm, meaning Ag(I) should not interfere with the determination of Fe(III) by **3**. Thus, as per our expectation, the incorporation of the functional groups present in siderophores in the design of **3** was found to be beneficial for the selective recognition of Fe(III).

To determine the range in which **3** is sensitive to changes in Fe(III) concentration, a titration was performed. A plot of normalized intensity against concentration is shown in Fig. 3b and illustrates good linearity in the range 5.0–80 μM. The quenching properties of Fe(III) were further evaluated using the Stern-Volmer equation [37] (see experimental). When the equation was derived for 1:1 (host : guest) stoichiometry an excellent fit was observed suggesting the binding interaction between **3** and Fe(III) is indeed 1:1 (Fig. 4a). Moreover, the 1:1 stoichiometry was also confirmed from Job plot analysis [38]. The association constant, K_a, calculated using the Benesi-Hildebrand equation [39] for a 1:1 complex, was calculated to be 3.8×10^4 M^{-1} (Fig. 4b). Unfortunately, due to the papramagnetic nature of Fe(III), we were unable to investigate the binding mode between **3** and Fe(III) in greater detail by nmr spectroscopy.

As already mentioned, Cu(II) was the only ion among those tested likely to cause potential interference in the measurement of Fe(III) by **3**. Therefore, we tested the ability of **3** to operate in solutions containing equimolar concentrations of both Cu(II) and Fe(III). Figure 4c shows the plot for solutions containing only **3** + Fe(III) and those containing **3** + Fe(III) + equimolar Cu(III), and shows good agreement between the two sets of data. This suggests that Fe(III) binds much more strongly to **3** than Cu(II), or any other ion for that matter, and occupies the available binding sites preferentially over other ions.

In conclusion, we have developed a dipodal fluorescent sensor for Fe(III), capable of operating in semi-aqueous solution. Good selectivity was observed for Fe(III) over other physiologically and environmentally relevant cations. The sensor was observed to bind Fe(III) in a 1:1 stoichiometry with an association constant of 3.8×10^4 M^{-1}. The sensor was competent of measuring Fe(III) in solutions containing both Fe(III) and Cu(II). Thus, the principle of incorporating binding sites present in naturally occurring iron chelators into synthetic luminescent assemblies has proven an effective design strategy for the development of new Fe(III) probes.

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