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Aminoxy-linked rhodamine hydroxamate as fluorescent chemosensor for Fe^{3+} in aqueous media

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ABSTRACT

A novel feric ion-selective rhodamine-based fluorescent chemosensor, which contains a bis-aminoxy chain moiety, has been developed. The multi-dentate binding site of rhodamine fluorophore shows selective detection of ferric iron over other biologically important metal ions in aqueous media and also shows 1:1 binding stoichiometry.

Selective detection of biologically important metal ions has tremendously gained its importance because metal ions are involved in a variety of fundamental biological processes in organisms. Recently, numerous fluorescent chemosensors have been developed to detect biologically important metal ions, such as Hg^{II}, Ca^{II}, Zn^{II}, Cu^{II}, and Pb^{II}.[1]

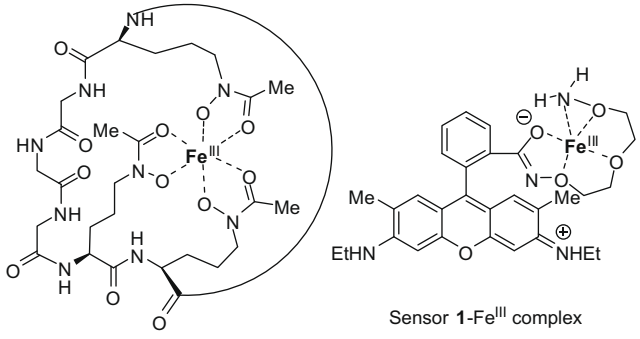
Iron is one of the most important metals in the biological systems and plays a key role in many biochemical processes at the cellular level. Especially, ferric ion (Fe^{III}) is widely retained in many proteins and enzymes either for structural purposes or as part of a catalytic site.[2] Recently, few examples of Fe^{III}-amplified fluorescent 'turn-on' systems in protic solvents have been reported,[3] but most of the known Fe^{III} sensors are based on the fluorescence quenching mechanisms due to the paramagnetic nature of ionic iron.[4]

Biological iron (III) uptake processes utilize siderophores,[5] such as analogues of ferrichrome which possess hydroxamates as binding units. Recently, we have reported a turn-on fluorescent chemosensor for Fe^{III} based on the biomimetic hydroxamate binding unit coupled with the rhodamine fluorophore.[6] Although the sensor showed highly selective and sensitive detection for Fe^{III} in organic solvent, we could not observe neither fluorescence increment nor color changes in aqueous media. Herein, we demonstrate a new turn-on fluorescent chemosensor for Fe^{III} based on the bis-aminoxy (diethylene glycol) binding unit coupled with rhodamine-6G fluorophore.

We expected that the flexible bis-aminoxy (diethylene glycol) chain could be a tailor-made binding subunit by using multiple binding sites of the chain, similar to the natural tripodal siderophores (Scheme 1). Moreover, this chain also could be expected to give stable sensor-metal ion complexes in aqueous media due to the terminal aminoxy group.

Compound **1** was synthesized from diethylene glycol in a three-step procedure (1. DIAD, PPh_3, THF, rt, 18 h, 80%; 2. $NH_2NH_2{\cdot}H_2O$, EtOH, reflux, 2 h, 89%; 3. rhodamine-6G, Et_3N, MeOH, reflux, 9 h, 35%). The resulting compound **1** was characterized by ^1H and ^{13}C NMR spectroscopy, high resolution mass spectrometry, and was shown to be in full agreement with the structures presented (Scheme 2). This substance forms a colorless solution in H_2O/DMSO (99:1 v/v) and shows no significant fluorescence signals, indicating that **1** exists predominantly as the spirocyclic form. Interestingly, the addition of Fe^{III} into the colorless aqueous solution of **1** generated a strong fluorescence and pink color instantly. At pH 6–9, probe **1** exhibits strong fluorescence enhancement in the presence of Fe^{III} (see Supplementary data).

A fluorescence titration of Fe^{III} was investigated using a 20 μM solution of **1** in H_2O/DMSO (99:1 v/v) under excitation at



Scheme 1. Structure of ferrichrome/Fe^{III} complex found in siderophores and proposed structure of sensor **1**/Fe^{III} complex.

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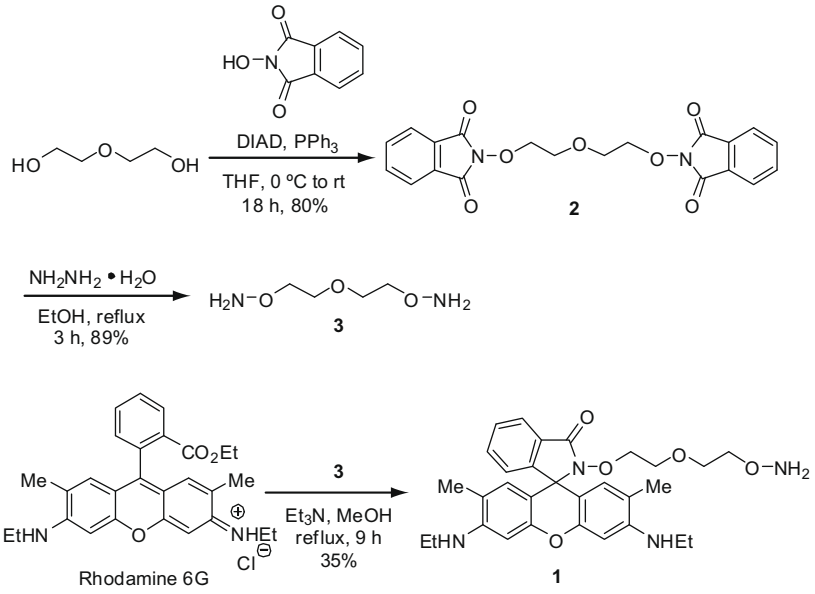

Scheme 2. Synthesis of bis-aminoxy chain-linked rhodamine-based fluorescent chemosensor **1**.

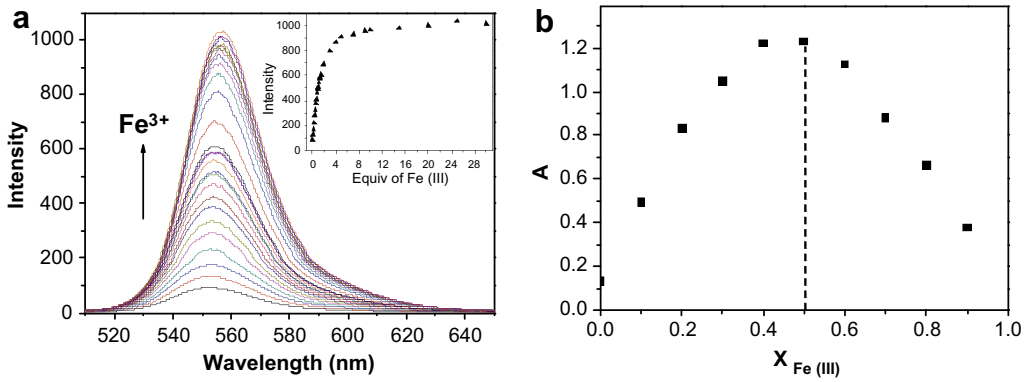

Figure 1. (a) Fluorescence emission spectra of a solution of **1** (20 μM) in H_2O/DMSO (99:1 v/v) upon addition of Fe^{III} (excitation at 500 nm). Inset: Plot of fluorescence intensity at 557 nm versus number of equivalents of Fe^{III}. (b) Job's plot according to the method of continuous variations, indicating the 1:1 stoichiometry of **1**/Fe^{III}.

λ_{ex} = 500 nm. Upon addition of Fe^{III}, the fluorescence intensity of the solution increases gradually (Fig. 1a) and saturates after addition of about 5 equiv of Fe^{III} (inset).

Job's plot according to the method for continuous variations[7] shows 1:1 binding stoichiometry between **1** and Fe^{III} as proposed (Fig. 1b). The calculated binding constant ($K_a = 8.0 \times 10^4$) in H_2O/DMSO (99:1 v/v) solution from the fluorescence and UV-titration experiments[8] based on the 1:1 binding model indicates a strong binding ability of **1** to Fe^{III} in aqueous solution. Furthermore, according to the titration using a 5 μM solution of **1** in H_2O/DMSO (99:1 v/v), 1 μM of Fe^{III} was readily detected (see Supplementary data).

Importantly, the formation of sensor **1**/Fe^{III} complex is promptly completed and reversible. As shown in Figure 2a, fluorescence intensity is maximized within a minute and shows no changes in fluorescence intensity over 1 h. The reversible binding mode of **1** and Fe^{III} was tested with CN^- ion which is known to bind strongly with Fe^{III}. Addition of excess CN^- ion into the solution of **1**/Fe^{III} showed immediate disappearance of fluorescence and color (Fig. 2b). And the fluorescence intensity of the solution was completely recovered after additional treatment with Fe^{III} (Fig. 2c).

Next, to evaluate the Fe^{III}-selective nature of **1**, fluorescence changes caused by the addition of other biologically important metal ions, including Fe^{II}, Zn^{II}, Pb^{II}, Ca^{II}, Co^{II}, Mn^{II}, Mg^{II}, Cu^{II}, Cd^{II}, Ag^{I}, Na^{I}, Li^{I}, Ni^{II}, K^{I}, and Ba^{II} were tested. Fluorescence intensity changes of **1** (20 μM) in the presence of 5 equiv of each of these metal ions were analyzed in H_2O/DMSO (99:1 v/v). As shown in Figure 3a, metal ions other than Fe^{III} do not cause significant fluorescence intensity changes. This means that the selectivity profile for Fe^{III} over other metal ions is remarkably high. Furthermore, the influence of other metal ions to the fluorescence intensity changes caused by Fe^{III} is significantly low (Fig. 3b).[9]

The selectivity observed by using fluorescence monitoring is matched when **1** is employed as a colorimetric detector for Fe^{III}. In contrast to the visually observed clear to pink color change associated with the binding of **1** (10 μM) with Fe^{III}, no significant color changes are prompted by addition of other metal ions (Fig. 4).

In summary, we have developed a highly selective and sensitive ferric ion chemosensor in aqueous media. The flexible bis-aminoxy (diethylene glycol) chain linked to a rhodamine-6G fluorophore showed to be a tailor-made binding subunit by using multiple binding sites of the chain, similar to the natural tripodal sidero-

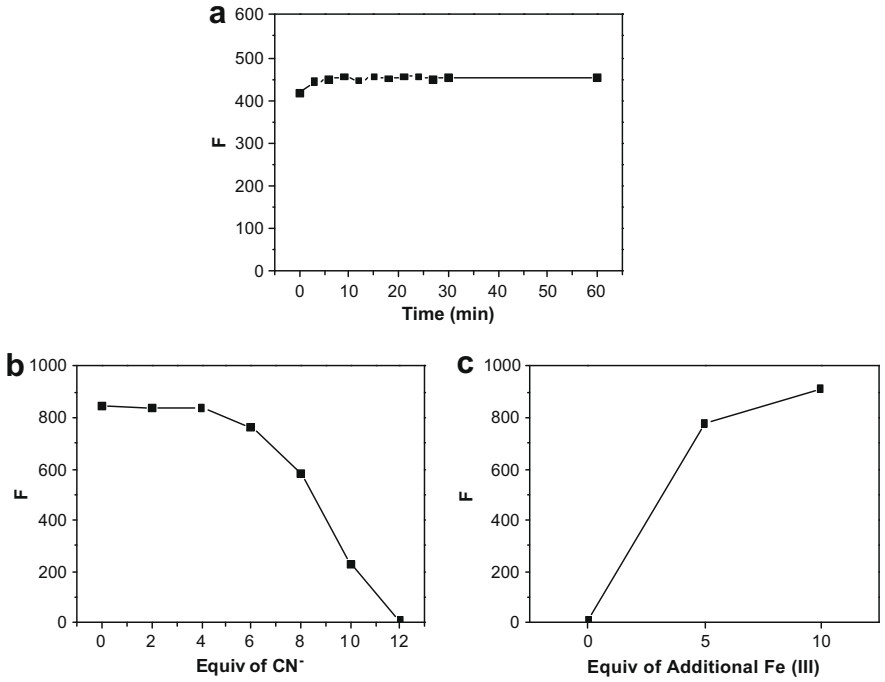

Figure 2. (a) Fluorescence intensity changes at 557 nm of a solution of **1** (20 μM) with Fe^{III} (0.5 equiv) in H_2O/DMSO (99:1 v/v), (b) fluorescence intensity changes of a solution of **1** (20 μM) in H_2O/DMSO (99:1 v/v) solution in the presence of Fe^{III} (5 equiv) with increasing concentrations of CN^- ion (read at 557 nm) and (c) regenerated fluorescence by addition of Fe^{III} into the quenched solution.

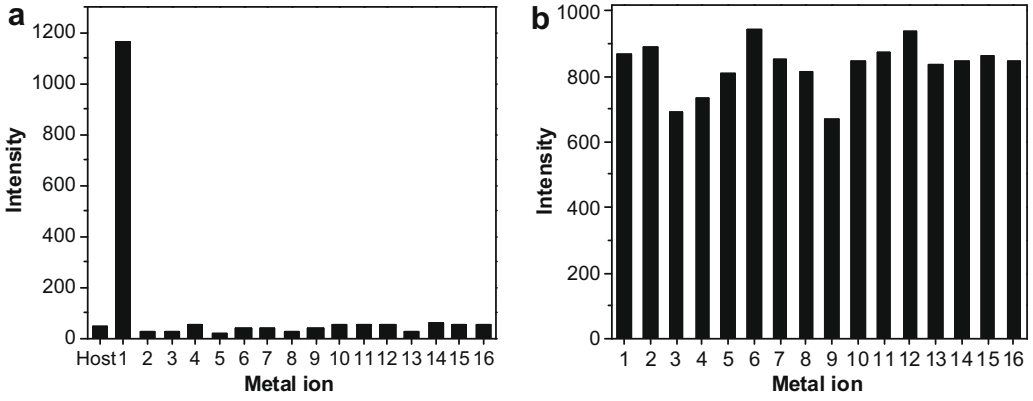

Figure 3. Fluorescence intensities of **1** (20 μM) in H_2O/DMSO (99:1 v/v) at 557 nm (a) in the presence of 5 equiv of the following metal ions: (1) Fe^{III}; (2) Fe^{II}; (3) Zn^{II}; (4) Pb^{II}; (5) Ca^{II}; (6) Co^{II}; (7) Mn^{II}; (8) Mg^{II}; (9) Cu^{II}; (10) Cd^{II}; (11) Ag^{I}; (12) Na^{I}; (13) Li^{I}; (14) Ni^{II}; (15) K^{I}; (16) Ba^{II}, (b) in the presence of 5 equiv of Fe^{III} and 5 equiv of the following metal ions: (1) none; (2) Fe^{II}; (3) Zn^{II}; (4) Pb^{II}; (5) Ca^{II}; (6) Co^{II}; (7) Mn^{II}; (8) Mg^{II}; (9) Cu^{II}; (10) Cd^{II}; (11) Ag^{I}; (12) Na^{I}; (13) Li^{I}; (14) Ni^{II}; (15) K^{I}; (16) Ba^{II}.

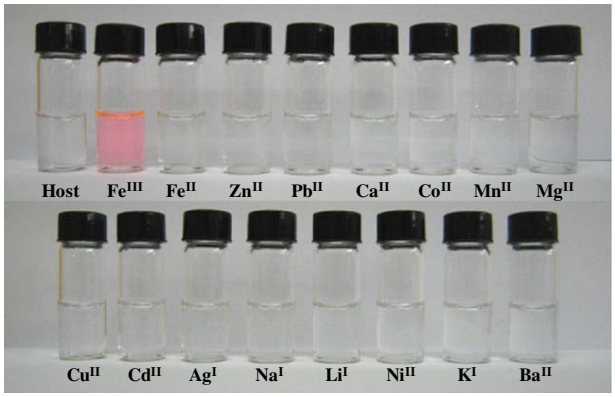

Figure 4. Color changes of **1** (10 μM) upon addition of metal ions in H_2O/DMSO (99:1 v/v).

phores. This chemosensor binds with Fe^{III} in a 1:1 stoichiometric manner to induce a large increment in the fluorescence intensity and a marked color change. Importantly, the selectivity of this system for Fe^{III} over other biologically important metal ions is extremely high.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures for the synthesis, spectral data, and copies of ^1H NMR and ^{13}C NMR, data for

UV–Vis, fluorescence of **1**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.04.068.

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8. See the Supplementary data.
9. Fluorescence intensities of **1** with Zn^{II}, Pb^{II}, and Cu^{II} are slightly quenched compared to other metal ions. This means that these metal ions slightly compete with Fe^{III} when binding to **1**.