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Selective complexation of metals with isoxazolidine-containing fluorophores

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Abstract—A series of 1,3-dipolar cycloaddition products of functionalized nitrones with 1,3-propene sultone and maleimide was synthesized through a multi-step scheme. Their fluorescent response to different metal ions was examined. Selective quenching of the fluorescent materials by Cu(II), Fe(III), and Ru(III) in acetonitrile was demonstrated, providing access to new chemosensor design for selected transition metals.

The development of new molecular system for luminescent detection of transition metal ions is an important aspect for both environment and biological application.[1] In order to obtain new recognition property, we recently introduced an isoxazolidine ring into the sensor scaffold to replace the traditional binding site like free amine or pyridine as the recognition element.

As an effective dipolarophile and precursor of chiral auxiliary, α,β-unsaturated sultones have been developed by us for many years.[2] Recently, we did a systematic work on investigation of 1,3-dipolar cycloadditions of such sultones with nitrones, which give the corresponding isoxazolidine derivatives in highly stereo- and regioselective manners.[3] To explore analytical applications of these cycloadducts, fluorophores and potential chelating groups can be introduced onto the isoxazolidine ring by modifying the structure of nitrones prior to the 1,3-dipolar cycloaddition. One of the product **6** containing pyrenyl group shows highly selective and sensitive fluorescent response to Ag(I) ion in aqueous condition through intermolecular excimer formation.[4] Encouraged by the finding, based on compound **6**, a series of derivative analogues **5a–f** were synthesized. Their selective fluorescent response toward iron(III), ruthenium(III), and copper(II) provides us a direct access to design practical luminescence chemosensors for transition metal ions.

Synthesis of **5a–f** was undertaken according to the synthetic protocol developed in our laboratory.[3a] The functionalized nitrones were prepared in high yield by the multi-step synthesis as shown in Scheme 1. To qualify as potential fluorescent chemosensors, pyrene moiety was appended into the scaffold of the dipolar. However, in the last step of the 1,3-dipolar cycloaddition reaction, the chemical yields were varied by different substitute groups present in the dipolars. Starting with different *o*-substituted benzaldehydes gave us different products, which are modified on the sidearm of the isoxazolidine ring. Compounds **5b** and **5c** are polyether substituted while **5d** and **5f** contain ester moiety as a potential chelating group; **5e** was assembled by introducing a pyridine group onto the *N*-benzyl sidearm. In the cycloaddition, bicyclic adduct **5f** was obtained when maleimide was used as the dipolarphile instead of propene sultone.

With **5a** and its derivatives **5b–f** in hand,[5] we studied their fluorescence property and response to different metal ions. All the compounds mentioned above have strong fluorescent emission at wavelength of 378 and 397 nm due to the presence of a pyrenyl group. Under the same concentration (5×10^{-6} M), emission intensities of **5e** and **5f** are relatively lower than that of the other analogues, by 37% and 64%, respectively. The observation is conceivably due to the intra-molecular

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Keywords: Fluorophores; Quenching; Selective metal complexation; 1,3-Dipolar cycloaddition.

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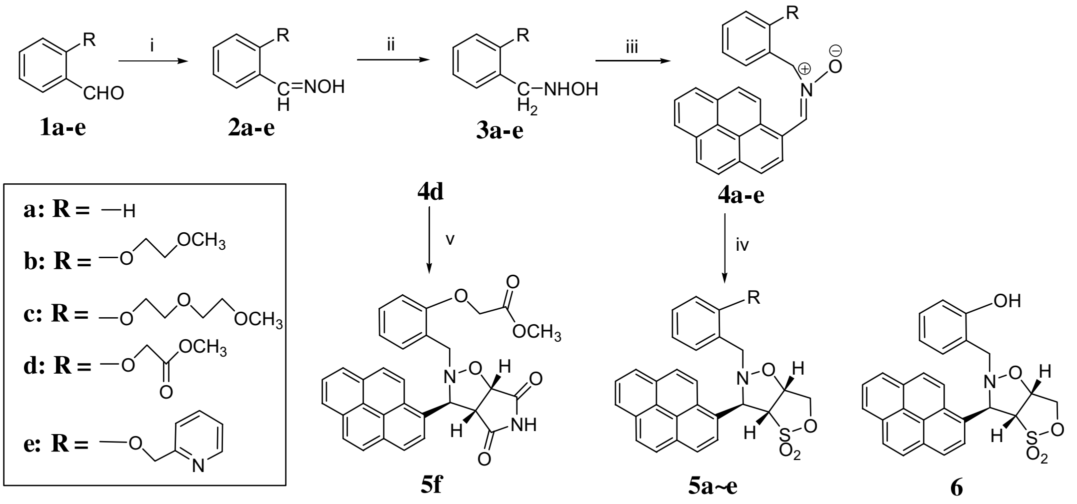

Scheme 1. Synthesis of **5a**–**f**. Reagents and conditions: (i) $NH_2OH{\cdot}HCl$, KOH/H_2O, 70°C, 2h, (ii) $NaBH_3CN$, HCl/methanol, rt, 2h, (iii) 1-pyrenecarboxaldehyde/benzene, N_2 atmosphere, reflux, 9–12h, (iv) 1,3-propene sultone/toluene, N_2 atmosphere, reflux, 24h, (v) maleimide/toluene, N_2 atmosphere, reflux, 24h.

photo-induced electron transfer (PET) from the extra nitrogen atom in the molecules to the fluorophores.[1f,6]

Fluorescent response of **5a**–**f** to cations was recorded in acetonitrile at a diluted concentration around 5×10^{-6} M. Addition of $CuCl_2$, $RuCl_3$, or $FeCl_3$ led to drastically immediate fluorescence quenching (Fig. 1). This effect could not be observed through addition of other metal ions including alkali metal ions, alkali earth metal ions, and common transition metal ions like Hg^{2+}, Ag^{+}, Zn^{2+}, Ni^{2+}, Mn^{2+}, and Co^{2+}, even a large excess (i.e., 50equiv) of the metal ions was used. On the other hand, excessive addition of these metal cations to the host molecules **5a**–**f** did not induce any change in their absorption spectra in the wavelength range of 300–380nm. Conceivably, **5a**–**f** have no association to the cations in acetonitrile.[7]

The fundamental mechanism of such fluorescent quenching is likely operative via Dexter typed electron transfer. When a metal ion and a fluorophore form complex via a specific spacer, the close distance between them allows energy transfer (ET) or electron transfer (eT) involving the d-orbitals of the metal ion and the excited fluorophore. Emission intensities of **5e** in presence of 20equiv of Fe^{3+}, Cu^{2+}, and Ru^{3+} do not regenerate at 77K compared with that at room temperature. Such observation corroborates that it is ET rather than eT process be responsible for the quenching.[1e,g] The low energy level (d-orbital) of Cu^{2+}, Fe^{3+}, and Ru^{3+} is suitable for a double electron exchange energy transfer.[8] This electronic ET process, which does not induce any separation of charge but only electron circulation, is not affected by solvent immobilization occurring at low temperature (Fig. 2). Even though we cannot exclude the heavy atom effect completely, observation of no quenching effect of other heavy metals like Hg^{2+} and Ag^{+} in the same condition leads us to believe that quenching by heavy atom effect is negligible in the present system.

Stability constants (K_s) of **5a**–**f** with Ru^{3+}, Cu^{2+}, and Fe^{3+} were measured through the decreasing fluorescence intensities when titrating the metal ions to the acetonitrile solutions of **5a**–**f** (Table 1).[9] Fully quenching of fluorescence intensity indicates a nonradiative complex formation. Furthermore, good linear Besesi–Hildebrand plots were obtained for the complexes, which is indica-

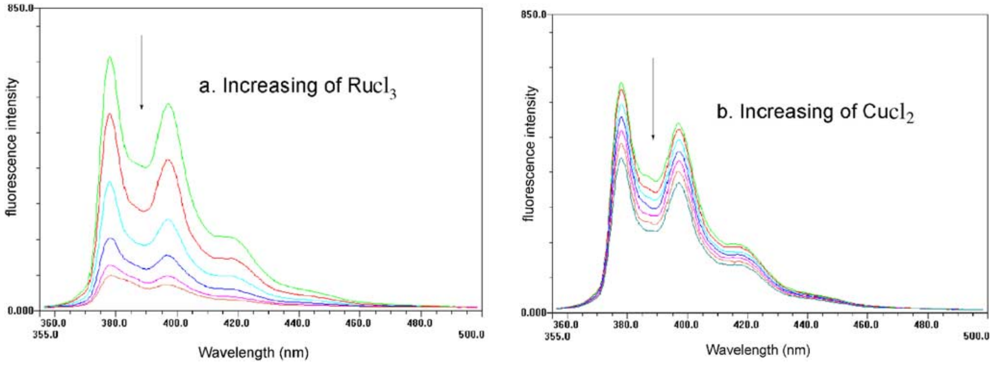

Figure 1. Fluorescence emission spectra of compound **5e** (5.6×10^{-6}M): (a) titrated with $RuCl_3$, C_{Ru}: 9.2, 18.4, 27.6, 36.8, 46, 55.2 (10^{-6}M), (b) titrated with $CuCl_2$, C_{Cu}: 8, 16, 24, 32, 40, 48, 98 (10^{-6}M).

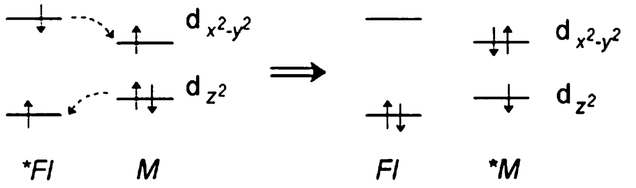

Figure 2. Electron circulation of the energy transfer process (double-electron exchange mechanism) involving an excited fluorophore and a d^9 metal ion.

Table 1. The complex stability (K_s) constant of **5a–f** versus different metal ions ($10^4\,M^{-1}$)

K_s	Ru^{3+}	Cu^{2+}	Fe^{3+}
5a	1.2 ± 0.1	0.57 ± 0.06	1.8 ± 0.2
5b	1.7 ± 0.2	0.71 ± 0.08	2.0 ± 0.2
5c	1.4 ± 0.1	0.55 ± 0.06	1.9 ± 0.2
5d	1.2 ± 0.1	0.68 ± 0.08	1.7 ± 0.2
5e	4.8 ± 0.5	0.53 ± 0.06	1.9 ± 0.2
5f	1.7 ± 0.2	0.68 ± 0.07	1.8 ± 0.2

tive to the formation of a 1:1 complex. It is noteworthy that Ru(III) and Fe(III) exhibited stronger quenching abilities than that of Cu(II).

Changing the structure of the sidearm groups of **5a–f** gave no different K_s except for **5e** with Ruthenium(III). It may due to the too weak binding abilities of polyether and ester groups in **5b–d** and **5f** toward metal cations. On the other hand, the imide and sultone moiety incorporating into the fluorescent materials seemingly exerted no influence to the chelation. Higher K_s observable for the complex of **5e** and Ru(III) demonstrates the potential means to improve the binding capacity of a sensor by modification of the *N*-sidearm of isoxazolidine derivatives. If the chelating group on the benzyl *o*-sidearm is strong enough, a sensor with highly affinity and selectivity to Ru(III) or Fe(III) based on isoxazolidine structure could be developed.

In summary, we have synthesized isoxazolidine-containing fluorophores **5a–f** in considerable yields by a convenient procedure, we also studied their selective complexation toward Fe(III), Cu(II), and Ru(III), which provides us a new insight into the design of chemosensors for transition metals.

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7. The UV–visible absorption spectra of **2a–f** (5×10^{-6} M) with different cations (20 equiv) in acetonitrile was measured in the wavelength range of 300–380 nm (λ_{max} = 342 nm). It is impossible to analyze the details of absorption change when $RuCl_3$, $FeCl_3$, and $CuCl_2$ were added to the hosts because these inorganic compounds

themselves have absorption bands in such wavelength range.

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