A highly selective charge transfer fluoroionophore for Cu^{2+}†

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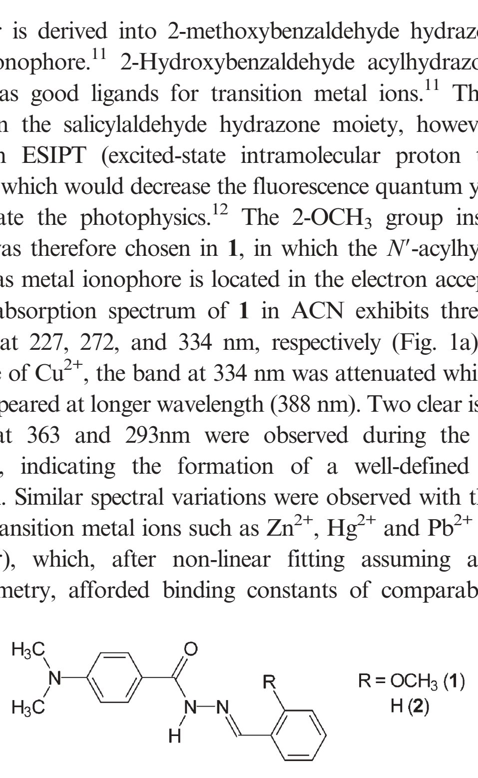
A dual fluorescent charge transfer fluoroionophore (1) with its ionophore incorporated in the electron acceptor was developed and was found to show a highly selective fluorescent response to Cu^{2+} with a dramatic enhancement in its CT emission.

Because of its biological and environmental importance, detection and monitoring of Cu^{2+}, especially *via* methods that allow selective and sensitive assays, are highly demanding. Fluorescence signaling is one of the first choices due to its high detection sensitivity and intrinsic operation simplicity. Designing fluoroionophores for Cu^{2+} has drawn much recent attention.[1] These fluoroionophores consist in principle of a metal ionophore and a signaling fluorophore that are either conjugated or connected by a flexible spacer.[2] As a transition metal ion known for its efficient fluorescence quenching character, detection of Cu^{2+} by fluoroionophores hitherto reported operates mostly in fluorescence quenching mode under an electron or energy transfer mechanism.[3,4] Due to sensitivity reasons, fluoroionophores showing fluorescence enhancement as a result of metal-ion binding are to be favored over those exhibiting fluorescence quenching. A number of fluoroionophores have been reported for Cu^{2+} that show fluorescence enhancement.[5–7] Among those reported, Cu^{2+} binding resulting in the inhibition of photo-induced electron transfer (PET) in the fluoroionophores has been an important mechanism,[6] with the metal ionophore located in the electron donor. Obviously, the metal binding selectivity is subject to the choice of a sophisticated ionophore that is selective for this metal ion. Intramolecular charge transfer (CT) fluoroionophores for Cu^{2+} were also reported that showed an enhancement in the short-wavelength emission of the locally excited state (LE state), at the expense of the long-wavelength CT emission.[7] This is in principle similar to PET inhibition, with the metal ionophore incorporated in both the electron donor[7a,c] and acceptor.[7b] Cu^{2+} fluoroionophores showing enhanced excimer emission were recently reported.[8] Herein is described a new CT dual fluorescent fluoroionophore **1** (Scheme 1)[9] that shows a highly selective and sensitive fluorescent response toward Cu^{2+}.

1 was designed on the basis of the dual fluorescent CT fluorophore 4-(*N*,*N*-dimethylamino)benzamide[10] whose electron acceptor is derived into 2-methoxybenzaldehyde hydrazone, the metal ionophore.[11] 2-Hydroxybenzaldehyde acylhydrazones are known as good ligands for transition metal ions.[11] The 2-OH group in the salicylaldehyde hydrazone moiety, however, may open an ESIPT (excited-state intramolecular proton transfer) channel which would decrease the fluorescence quantum yield and complicate the photophysics.[12] The 2-OCH_3 group instead of 2-OH was therefore chosen in **1**, in which the *N*′-acylhydrazone moiety as metal ionophore is located in the electron acceptor.

The absorption spectrum of **1** in ACN exhibits three bands peaked at 227, 272, and 334 nm, respectively (Fig. 1a). In the presence of Cu^{2+}, the band at 334 nm was attenuated while a new peak appeared at longer wavelength (388 nm). Two clear isosbestic points at 363 and 293nm were observed during the spectral titration, indicating the formation of a well-defined **1**–Cu^{2+} complex. Similar spectral variations were observed with the other tested transition metal ions such as Zn^{2+}, Hg^{2+} and Pb^{2+} (Fig. S1 in ESI†), which, after non-linear fitting assuming a 1 : 1 stoichiometry, afforded binding constants of comparable value



Scheme 1 Structure of **1** and its OCH_3-free control molecule **2**.

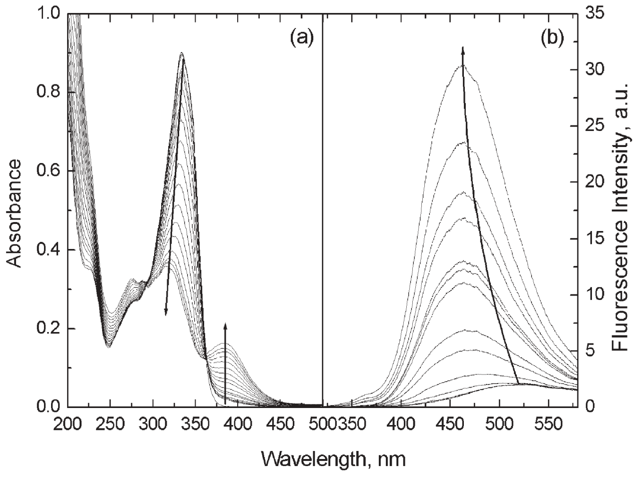


Fig. 1 Absorption (a) and fluorescence (b) spectra of **1** (2.0×10^{-5} M) in ACN in the presence of increasing concentration of Cu^{2+} (0–6.0×10^{-5} M in (a) and 0–5.0×10^{-5} M in (b)). The excitation wavelength for acquiring fluorescence spectra was 293 nm, an isosbestic wavelength observed in the absorption spectral titration. Cu^{2+} and other metal ions were used as their perchlorate salts.

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† Electronic supplementary information (ESI) available: Experimental procedures and full characterization of **1** and **2**; absorption and fluorescence spectra of **1** in the presence of metal ions; solvatochromic data, IR and ESI-MS of **1** and **1**–Cu^{2+} complex. See DOI: 10.1039/b510546c

at 10^4 M^{-1} orders of magnitude (Table S1 in ESI†). These observations indicate that Cu^{2+}, Zn^{2+}, Hg^{2+} and Pb^{2+} bind to a similar extent to **1** in the ground state.

1 in ACN emits dual fluorescence, with a total fluorescence quantum yield Φ of 0.0082 (Fig. 1b). This is indicative of the occurrence of the excited-state CT known for the parent CT fluorophore 4-(*N*,*N*-dimethylamino)benzamide.[10] The short-wavelength emission at *ca.* 350 nm assigned to the LE state of **1** showed very weak dependence on solvent polarity, whereas a continuous red-shift was observed in the long-wavelength emission from 410 nm in diethyl ether to 525 nm in ACN of increasing polarity, confirming the CT nature of its emissive state. A dipole moment of 24 D was deduced from the solvatochromic data for the CT state of **1** following a reported procedure,[13] see details and Fig. S2 in ESI.†

The response of the CT dual fluorescence of **1** toward a variety of metal ions was examined first in ACN. Upon addition of Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ba^{2+}, Al^{3+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Ag^+, Zn^{2+}, Cd^{2+}, Hg^{2+}, and Pb^{2+} to the ACN solution of **1**, a prominent fluorescence enhancement was *only* observed for Cu^{2+} (30 fold) with a substantial blue shift in its CT emission from 525 nm to 460 nm, Fig. 1b. Other transition metal ions, as expected, quenched the fluorescence to differing extents while the CT emission of **1** blue shifted too, whereas alkali and alkaline earth metal ions had hardly any effect on the emission of **1** (see Fig. S3 in the ESI† and Fig. 2). Different from the previously reported CT fluoroionophores for Cu^{2+} with which the LE emission was greatly enhanced upon Cu^{2+} binding whereas the CT emission was quenched,[7] **1** showed only minor changes in its LE emission in both the position and intensity, while its CT emission was dramatically enhanced and blue-shifted. The total fluorescence of **1** was enhanced 30 fold when 2.5 equivalent of Cu^{2+} was present and further increase in Cu^{2+} concentration led to slight fluorescence quenching (Fig. S3 in ESI†).

Preliminary examination of the response of its dual fluorescence toward Cu^{2+} in ACN–H_2O buffer solutions promised practical applications of **1** as a highly selective and sensitive fluoroionophore for Cu^{2+} (Fig. 2). Compared to that in pure ACN, the dual fluorescence of **1** was quenched by 75% with a total Φ of 0.002 in ACN–H_2O (9 : 1, v/v). However, an unexpectedly dramatic enhancement of the CT emission was observed when Cu^{2+} was added to the solution of **1** in ACN–H_2O (9 : 1, v/v) buffered by 0.005M tris-HCl (pH = 7.2). A substantial blue shift was also observed in the long-wavelength CT emission, now from 530 nm to 482 nm. The fluorescence of **1** was enhanced 170 fold when 2.5 equivalents of Cu^{2+} were introduced (Fig. 2), together with a substantial increase in the CT to LE intensity ratio (Fig. S4 in ESI†). The fluorescence enhancement factor decreased with increasing water content in ACN–H_2O, but could still be more than 40 fold when the water content was 90% by volume (Table S2 in ESI†). With increasing water content in ACN, a continuous red-shift from 460 nm to 526 nm was observed in the long-wavelength emission of the **1**–Cu^{2+} complex (Table S2 in ESI†), establishing its CT nature of the emissive state. The dipole moment of the CT state of the **1**–Cu^{2+} complex was similarly deduced as 23 D by assuming an unchanged ground-state dipole moment of the fluoroionophore upon binding to Cu^{2+}, see details and Fig. S5 in ESI.†

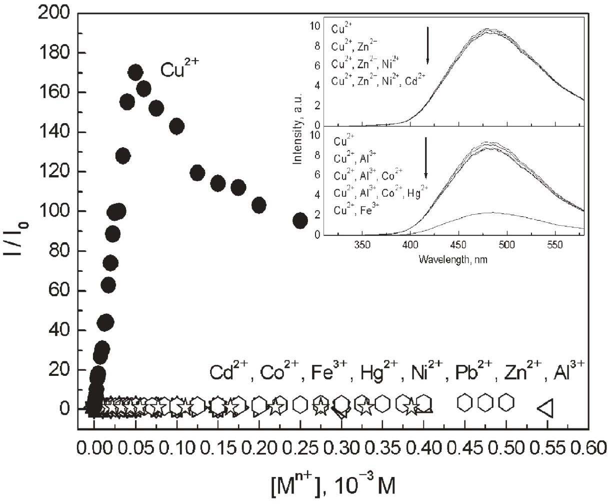

Fig. 2 Plot of the fluorescence enhancement (I/I_0 or Φ/Φ_0) *versus* concentrations of Cu^{2+} and other metal ions in a mixture of ACN and tris-HCl (0.005 M, pH = 7.2) aqueous buffer solution (9 : 1, v/v). Inset shows the fluorescence spectra of **1** (2.0×10^{-5} M) in the presence of 2 equiv of Cu^{2+} and 2 equiv of Cu^{2+} plus 10 equiv of other metal ions, respectively.

The total fluorescence intensity of **1** in aqueous ACN solution was found to be independent of the aqueous phase pH over 3–12 (Fig. S6 in ESI†), all of the experiments were hence carried out in the 9 : 1 (v/v) mixture of ACN and 0.005 M tris-HCl (pH = 7.2). The fluorescence of **1** was only slightly altered by Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Ba^{2+}, Al^{3+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, and Pb^{2+}, whereas Fe^{3+} at high concentration led to substantial quenching. Meanwhile, the fluorescence of **1** in the presence of 2 equivalents of Cu^{2+} was hardly changed by the co-existence of 10 equivalents of other metal ions except Fe^{3+}; in the latter case half of the fluorescence of **1**–Cu^{2+} was quenched, Fig. 2 inset. These results indicated that **1** was highly selective for Cu^{2+} *via* substantial enhancements in its CT fluorescence. Preliminary data indicated that **1** can be employed to detect Cu^{2+} down to 1.8×10^{-8} M when **1** was used at 2.5×10^{-6} M.

Absorption titration and ESI-MS data (Table S1 and Fig. S7 in ESI†) indicated that **1** bound with the tested transition metal ions such as Cu^{2+}, Pb^{2+} and Zn^{2+} *etc.* in a 1 : 1 stoichiometry. According to the reported coordination mode of 2-hydroxybenzaldehyde acylhydrazones with transition metals including Cu^{2+},[11c] **1** was assumed to chelate Cu^{2+} in a tridentate mode *via* its carbonyl O, imino N and 2-methoxy O atoms. This tridentate binding mode was supported by IR data. In the IR spectrum of **1** (Fig. S8 in ESI†) the peaks at 1624, 1609 and 1253 cm^{-1} ascribed to the C=O, C=N and C–O stretching, respectively, were found, upon Cu^{2+} binding, to shift to lower wavenumbers of 1609, 1570 and 1245 cm^{-1} respectively.[14]

Several factors can be listed for rationalizing the observed emission enhancement. (i) The low fluorescence quantum yield of **1** in ACN in the absence of Cu^{2+} (0.0082) might be attributed to radiationless channels from the nπ* state.[10a] Indeed, we observed in the absorption spectrum of **1** in cyclohexane a weak shoulder at 369 nm due to the nπ* transition.[15] In the presence of Cu^{2+} that coordinates with the lone pair of the carbonyl oxygen, the energy of the nπ* state would be raised so that the ππ* state becomes the lowest excited state, leading to a substantial increase in the fluorescence quantum yield.[7b,16] (ii) The blue shifted CT emission of **1** in the presence of Cu^{2+} actually pointed to an enlarged energy gap between the emissive CT state and its corresponding ground state and hence a decreased radiationless rate constant[17] and an increased quantum yield. (iii) Cu^{2+} binding to **1** could also induce a conformation restriction, resulting in increased fluorescence quantum yield[18] and preventing Cu^{2+} from quenching the fluorescence of the fluorophore. In supporting this assignment, it was observed that the OCH_3-free control molecule of **1**, **2** (Scheme 1) that chelates Cu^{2+} in a bidentate manner, showed only 10 or 70 fold fluorescence enhancement when fully complexed with Cu^{2+} in ACN or ACN–H_2O (9 : 1, v/v) solution, respectively (Fig. S9 in ESI†). It is of significance to indicate that, although all the tested transition metal ions such as Cu^{2+}, Pb^{2+} and Hg^{2+} bind to a similar extent to **1** in the ground state and the afore-listed factors should exist with all of them, *only* Cu^{2+} dramatically enhances the CT emission of **1**. This means that the coordination of **1** with Cu^{2+} in either the ground or the excited state is not exactly the same as that of **1** with other metal ions, although the detailed mechanism for this highly selective fluorescent response of **1** toward Cu^{2+} remains to be clarified. It was found that the blue-shifted CT emission in ACN of the **1**–Cu^{2+} complex appeared at more or less the same position as that of *N′*-isopropyl 4-(*N*,*N*-dimethylamino)benzamide at *ca.* 460 nm (Fig. S10 in ESI†). This suggests that the electron acceptor in **1** becomes smaller upon Cu^{2+} binding and might be a useful structural hint for clarifying the high selectivity observed for Cu^{2+}. We are currently working on a series of **1** derivatives with 4-substituents other than the electron donating $N(CH_3)_2$ in which the excited-state CT channel in **1** is removed.

In summary, we reported a simple yet highly selective and sensitive CT fluoroionophore for Cu^{2+}, in which the metal ionophore was incorporated in the electron acceptor of the CT fluorophore. A blue shift and dramatic enhancement in the CT fluorescence of **1** in ACN and aqueous ACN solutions were observed in the presence of Cu^{2+}, a transition metal ion known as an efficient fluorescence quencher. A noteworthy character of this CT fluoroionophore is that its highly selective fluorescent response toward Cu^{2+} is not due to the binding preference in the ground state. As both the electron donor (4-$N(CH_3)_2$) and the ionophore in the electron acceptor in **1** can be structurally modified or replaced, the results reported here provide a new strategy for constructing turn-on CT fluorophores for transition metal ions.

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