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8-Methoxyquinoline based turn-on metal fluoroionophores

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Abstract—Novel turn-on fluoroionophores **2** and **3** based on highly fluorescent 8-methoxyquinoline were developed in which a sequential singlet–singlet energy transfer, ISC, and triplet–triplet energy transfer occurred leading to a fluorescence 'off' state. They showed substantially enhanced fluorescence in the presence of transition metal ions such as Zn^{2+}, Cu^{2+}, Pb^{2+}, and Hg^{2+} and an extremely high selectivity toward Zn^{2+} by **3**.
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Fluorescence has long been widely utilized as an important signal to trace metal concentration in chemical, biological, and medical applications.[1] As far as sensitivity is considered, fluoroionophores showing fluorescence enhancement upon metal–ion binding are favored over those exhibiting fluorescence quenching.[2] The crucial issue therefore is the way of controlling the emission of a fluoroionophore so that it is nonfluorescent in the absence of metal ion, whereas highly fluorescent in its metal complex. Currently, photoinduced electron transfer (PET) that quenches the fluorescence is likely the dominant photophysical mechanism in the design of fluoroionophores of this kind.[3]

8-Hydroxyquinoline (8-HQ) is one of the most important chelators for metal ions. It is known that 8-HQ itself is weakly fluorescent due to an excited-state intramolecular proton transfer (ESIPT),[4] and metal binding blocks this ESIPT channel thus restoring the fluorescence. 8-HQ has therefore been widely employed to build metal fluoroionophores with enhanced fluorescence output. A drawback for the parent 8-HQ as a fluoroionophore is the lack of selectivity in metal binding. Introduction of additional binding sites to the parent aromatic ring at C-2 and/or C-7 positions has thus been extensively explored.[5,6] Few efforts, however, have been devoted to the derivation of the 8-OH group.[7] The reason might be that the 8-HQ ethers, as intensively investigated 8-HQ derivatives, are themselves highly fluorescent.[4] For example, 8-methoxyquinoline

(**1**, Fig. 1) has a quantum yield in acetonitrile (ACN) of 0.23. Fluorescence enhancement due to metal binding will therefore be limited. The high quantum yields of the 8-HQ ethers and their metal complexes,[7a] however, prompted us to develop new strategies for designing turn-on fluoroionophores based on them. We envisaged that this shall be possible by introducing an efficient quenching pathway in the 8-HQ ethers that can be blocked upon metal binding.

Reported herein are such turn-on fluoroionophores **2** and **3** (Fig. 1) derived from 8-HQ methyl ether **1** that was modified by attaching acetophenone moieties known to have a small singlet–triplet energy gap and a high intersystem crossing (ISC) efficiency close to 1.[8] **3** was expected to have a more rigid structure than **2**,[9] thereby affording better binding selectivity. Indeed, **2** and **3** were found sensitive turn-on fluoroionophores for transition metal ions and in particular **3** was highly selective as well for Zn^{2+}.

Compounds **2** and **3** were easily made available from acetophenone which was first treated dropwise by Br_2
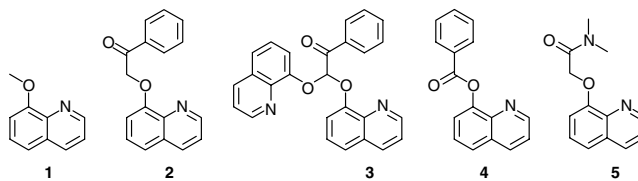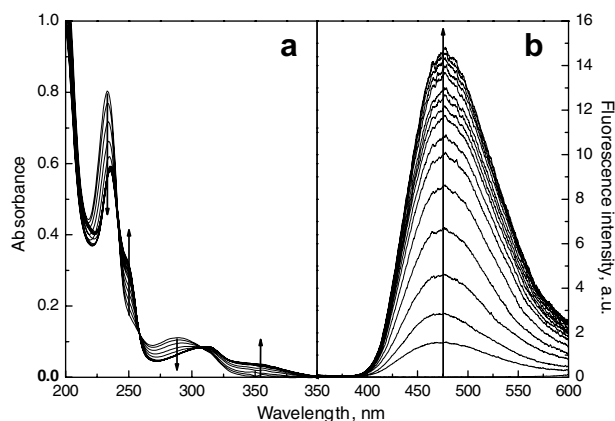

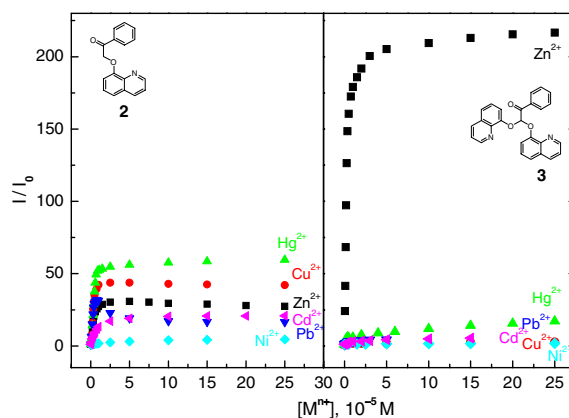**Figure 1.** Chemical structure of 8-HQ derivatives.

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in 40% aqueous HBr at room temperature and then heated at 65 °C for 1 h to afford α-bromoacetophenone. Refluxing in ACN of the latter and 8-HQ in the presence of catalytic amount of KI and K_2CO_3 gave **2** in 73%. **3** was similarly prepared by varying the relative quantity of Br_2 and 8-HQ. **2** and **3** were fully characterized.[10]

Compounds **2** and **3**, despite ether derivatives of 8-HQ, emit extremely weak fluorescence in ACN with quantum yields of 10^{-4} orders of magnitude. Sensing behavior for metal ions such as Zn^{2+}, Cu^{2+}, Cd^{2+}, Hg^{2+}, Pb^{2+}, and Ni^{2+} in ACN was investigated by absorption and fluorescence monitoring. The absorption spectrum of **2** in ACN exhibits two bands at 238 and 296 nm, respectively, and are actually the sum of those of **1** and acetophenone, indicating no ground-state interaction of these two moieties in **2**. The same conclusion holds for **3** too. Addition of metal ions in ACN in general led to minor changes in the spectrum. Figure 2a shows the absorption spectra of **3** in the presence of Zn^{2+}. Other absorption spectra can be found in Figure S1 in the Supplementary data. The appearance of several well defined isosbestic points in the titration traces indicate a clean binding between **2** or **3** with involved metal ions, which was further confirmed by Job plots (Fig. S2, Supplementary data) revealing a 1:1 binding stoichiometry. In contrast to the relatively minor variations in absorption spectra, the hardly fluorescent **2** or **3** became fluorescent in the presence of metal ions. Figure 2b shows as an example the emission spectra of **3** in the presence of Zn^{2+} and Figure 3 the fluorescence enhancement factors as a function of metal concentration. Detailed fluorescence spectra can be found in Figure S3 in Supplementary data. It is worthy to note that such fluorescence enhancements were observed with heavy transition metal ions such as Hg^{2+}, Cu^{2+}, and Pb^{2+} (Fig. 3), the quantum yields of the metal complexes being ten to thousand times those of the free fluoroionophores (Table 1). As expected better selectivity in its fluorescence response toward metal ions were observed with **3** which actually showed an extremely highly selective and sensitive fluorescence response for Zn^{2+} against other ions, particularly the most competitive Cd^{2+} that exerted hardly any influence (Fig. 3). This is also seen from the metal binding constants obtained by nonlinear fitting of the fluorescence titration data (Table 1). The high metal affinity of **2** and **3** of up to 10^7 M^{-1} orders of magnitude implies a potential practical utility of them in both apolar and polar environments. Indeed, preliminary data in 20% H_2O–ACN showed that **3** responded sensitively in its fluorescence toward Zn^{2+} (Fig. S4, Supplementary data).

The lower energy absorption band of **2** or **3** at ca. 290 nm (Fig. 2a) is associated with a transition in which a substantial charge is transferred from the 8-methoxy O atom to the quinoline moiety of the chromophore.[11] The observed red shift of this band in the presence of metal ions is therefore indicative of the involvement of their quinolino N atom in metal binding.[7a,11a] The fact that the emission maximum of **1**–Zn^{2+} in ACN (445 nm) differed very much from that of **2**(**3**)–Zn^{2+} (Table 1) suggests that the ketone carbonyl O atom in **2** and **3** coordinated to the metal ions. It is likely that the quinolino N and carbonyl O atoms are metal binding sites.

The possibility for the weak fluorescence of **2** and **3** being due to a low-lying $n\pi^*$ state[12] previously assigned for the weak fluorescence of **4**[7a] can be ruled out, since model molecule **5**[4b] (Fig. 1) with a higher electron density at the carbonyl oxygen exhibited a quantum yield in ACN of 0.24 which is close to that of **1** (0.23). The redox potentials[13] of acetophenone and 8-HQ and $E_{0,0}$ energy of 8-methoxyquinoline in **2** and **3** suggested that a proposed quinoline to ketone PET[9] is energetically possible. Fluorescence quenching in **2** or **3** due to this PET, however, can be excluded since the fluorescence of **1** was found not quenched by acetophenone in DEE and THF but in ACN, and **2** or **3** in DEE and THF turned to be fluorescent in the presence of Zn^{2+} as observed in ACN (Fig. S5, Supplementary data). Intramolecular energy transfer was hence assumed responsible for the quenching in **2** or **3**. The singlet

Figure 3. Plots against metal concentration of the fluorescence enhancement factors of **2** (1.0×10^{-5} M) and **3** (5.0×10^{-6} M) in ACN. I_0 and I refer to fluorescence intensity in the absence and presence of metal ion, respectively.

Figure 2. Absorption (1.0×10^{-5} M, a) and fluorescence (5.0×10^{-6} M, b) spectra of **3** in ACN in the presence of Zn^{2+} over 0 to 5×10^{-5} M (a) or to 2.5×10^{-4} M (b). The excitation wavelength was 308 nm, an isosbestic wavelength observed in the absorption spectral titrations. Metal ions existed in their perchlorates.

Table 1. Absorption and fluorescence spectral data of **2**, **3**, and their metal complexes in ACN

	λ_{abs} (nm)	ε (10^4 M^{-1} cm^{-1})	λ_{flu} (nm)	EF[b]	K_a (10^4 M^{-1})[c]	Φ[d]
2	239/293	4.93/0.47	378[a]	1.0	—	0.00061
2 + Zn^{2+}	241/301	4.04/0.47	420/500	29	>10^3	0.0068
2 + Cu^{2+}	246/301	3.92/0.47	503	29	>10^3	0.008
2 + Hg^{2+}	248/350	5.00/0.28	482	59	>10^3	0.030
2 + Pb^{2+}	241/301	4.73/0.47	503	16		0.0065
2 + Cd^{2+}	241/301	4.37/0.47	415	23	19.28 ± 2.35	0.011
2 + Ni^{2+}	239/293	4.83/0.47	503	4.5	2.93 ± 0.22	0.0012
3	233/289	8.16/1.05	376[a]	1.0	—	0.00023
3 + Zn^{2+}	235/250/313	6.02/3.24/0.86	476	217	>10^3	0.26
3 + Cu^{2+}	233/250/313	6.05/3.42/1.16	486	2.6	11.04 ± 9.42	0.0017
3 + Hg^{2+}	233/250/303	5.96/3.57/0.77	478	17	0.51 ± 0.33	0.0059
3 + Pb^{2+}	233/250/303	6.12/3.94/0.77	478	4.4	18.41 ± 7.81	0.0048
3 + Cd^{2+}	233/250/303	6.57/2.62/0.88	473	5.5	1.44 ± 0.58	0.0041
3 + Ni^{2+}	233/250/300	7.43/2.42/0.94	486	1.7	1.80 ± 0.15	0.0007

[a] Compounds **2** and **3** are extremely weakly fluorescent, their emission maxima were therefore located at ca. 375 nm with uncertainty.
[b] Fluorescence enhancement factor, ratio of the intensity of **2** (1.0×10^{-5} M) and **3** (5.0×10^{-6} M) in the presence of 50 equiv of metal ion to that in the absence of metal ion.
[c] Metal binding constant was obtained via nonlinear fitting of the fluorescence titration data assuming a 1:1 binding stoichiometry, see: Ref. 14.
[d] The uncertainties in the fluorescence quantum yields are within 30% for metal complexes of **2** and **3**.

energy of acetophenone of 78.02 kcal/mol[8b] is lower than that of **1** (84.36 kcal/mol), whereas its triplet energy of 73.76 kcal/mol[8b] is higher than that of **1** (see the phosphorescence data of **2** and **3** given later), a sequential singlet–singlet energy transfer from 8-methoxyquinoline to acetophenone moiety in **2** and **3**, ISC in the ketone, and triplet–triplet energy transfer from the ketone to 8-methoxyquinoline moiety could hence be expected. Indeed, phosphorescence was observed in 77 K EtOH glass matrix with vibronic structure peaked at 494, 527 and 569 nm for **2** (lifetime τ_P 170 ms) and 487, 519, 553 nm for **3** (τ_P 140 ms), respectively, whereas no phosphorescence was seen with **1**. In the presence of Zn^{2+}, however, phosphorescence of **3** was quenched (Fig. 4). This is understandable since the singlet emission of **3**–Zn^{2+} complex was seen at 475 nm which is energetically lower by 16 kcal/mol than that of free **3** at 375 nm, as such the initial singlet–singlet energy transfer to the ketone moiety in **2** or **3** is stopped and the complex is thereby fluorescently switched on. The fluorescence

turn-on mechanism is therefore completely different from that in **4** previously reported from this group[7a] in which a change in the lowest excited-state from (nπ^*) to ($\pi\pi^*$) was concluded.

In conclusion, we developed a novel means of constructing turn-on metal fluoroionophores on the basis of the highly fluorescent 8-alkoxyquinolines by introducing an efficient quenching pathway. This was realized in **2** and **3** by attaching aromatic α-ketones in the alkyl arm so that a sequential singlet–singlet intramolecular energy transfer to the ketone, efficient ISC in the ketone, and triplet–triplet energy transfer to the 8-methoxyquinoline moiety occurred, leading to the fluorescently 'off' state of **2** and **3**. The emission was turned on upon metal binding that stops the initial singlet–singlet energy transfer as the donor energy was lowered. Significantly such fluorescence enhancements were observed with heavy transition metal ions such as Hg^{2+}, Pb^{2+}, and Cu^{2+} known as efficient quenchers and in particular **3** is a highly selective and sensitive turn-on fluoroionophore for Zn^{2+} of important biological relevance. **2** and **3** represent novel turn-on fluoroionophores based on 8-HQ ether framework that follow a sensing mechanism which shall be applicable in general for the design of turn-on fluoroionophores.

Supplementary data

Supplementary material includes experimental details, and absorption and fluorescence spectra of **1**–**3** in the presence of metal ions. Supplementary data associated
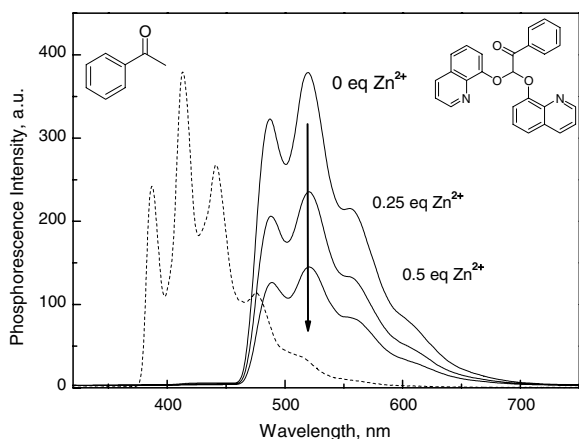
Figure 4. Phosphorescence spectra of acetophenone and **3**/Zn^{2+} in 77 K EtOH glass. [acetophenone] = [**3**] = 1.0×10^{-5} M.

with this article can be found, in the online version, at
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10. Compound **2**: ¹H NMR (400 MHz, CDCl₃), δ (ppm): 5.65 (s, 2H), 6.97 (dd, $J = 1.5$ and $J = 7.4$ Hz, 1H), 7.37–7.46 (m, 3H), 7.50 (t, $J = 7.39$ Hz, 2H), 7.60 (tt, $J = 1.5$ and $J = 7.4$ Hz, 1H), 8.09 (d, $J = 7.2$ Hz, 2H), 8.14 (dd, $J = 1.7$ and $J = 8.3$ Hz, 1H), 8.97 (dd, $J = 1.7$ and $J = 4.2$ Hz, 1H). ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 71.89, 110.12, 120.78, 121.70, 126.42, 128.18, 128.83, 129.60, 133.85, 134.52, 135.97, 140.19, 149.39, 153.82, 194.45. HRMS: calcd for $(C_{17}H_{13}O_2N + H)^+$ *m/z* 264.1032, found 264.1030. Compound **3**: ¹H NMR (400 MHz, CDCl₃), δ (ppm): 7.33–7.40 (m, 4H), 7.48 (m, 4H), 7.55 (d, $J = 7.4$ Hz, 3H), 7.63 (s, 1H), 8.09 (dd, $J = 1.3$ and $J = 8.3$ Hz, 2H), 8.54 (d, $J = 7.5$ Hz, 2H), 8.72 (dd, $J = 1.5$ and $J = 4.2$ Hz, 2H,). ¹³C NMR (100 MHz, CDCl₃), δ (ppm): 101.34, 117.11, 121.36, 122.85, 126.47, 128.38, 129.56, 129.93, 133.28, 134.46, 135.93, 140.73, 149.11, 151.76. HRMS: calcd $(C_{26}H_{18}O_3N_2 + H)^+$ *m/z* 407.1401, found 407.1395.
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