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Novel highly efficient fluoroionophores with a *peri*-effect and strong electron-donating receptors: TICT-promoted PET and signaling response to transition metal cations with low background emission

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Abstract—Novel fluoroionophores with piperazine frameworks as receptors for transition metal cations have been designed with the aid of calculation and synthesized. They exhibited low background emission and highly efficient fluorescence enhancements upon complexation with different transition metal cations, which could be ascribed to the special contribution of the TICT-promoted PET processes caused by the *peri*-effect and strong electron-donating receptors. © 2003 Elsevier Science Ltd. All rights reserved.

The search for highly sensitive and selective fluoroionophores for transition and heavy metal ions is currently attracting great interest all over the world.¹ Photoinduced electron transfer (PET) fluoroionophores in the 'fluorophore-spacer-receptor' format,² and intramolecular charge transfer (ICT) ones in the 'fluorophore-receptor' format³ are the two most important classes.

PET fluoroionophores⁴ with 'amino-alkyl-amino' type receptors, exhibit considerable fluorescence enhancement (FE) upon binding to a great variety of transition metal cations. Samanta et al.^{4a,b} found that an increase of electron-deficiency of the fluorophore moieties improves the sensitivities of these PET fluoroionophores; Brown et al.4c studied the relationship between alkyl spacer length (or the carbon number between the two nitrogens) and PET sensitivity. Since the two nitrogen atoms of the receptor play critical roles for the photophysical processes, there are possibly ways to improve the sensitivity of fluorescence response. We suggested that the PET of the fluoroionophores could be strengthened via TICT (twisted ICT), so that even slight differences in the disturbance to the receptor caused by the cations might be translated into a sharply different FE factor of a fluorophore. To achieve these requirements, a semirigid piperazine substituent with a peri-effect, and as a



Scheme 1. The studied compounds.

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strong electron-donating receptor, which could result in TICT-promoted PET processes, was successfully used to build new fluoroionophores (A5, B3, C3) with high sensitivity (Scheme 1).

The origin of this molecular design can be traced back to A1 and A2, two derivatives of 4-amino-1,8-dicyanonaphthene (ADCN),⁵ A2 with the stronger electrondonating dimethylamino, exhibits much weaker fluorescence than A1 with a butylamino electron-donor. ZINDO/S calculations showed that (Fig. 1) in the lowest excited singlet state (S₁) of A1, the electron density on the nitrogen atom at the 4-position decreases greatly (compared with ground state S₀, not listed here), but still remains in small part. However, in the S₁ of A2, the electron density on the nitrogen at position 4 totally disappeared.

Obviously, A2 formed a TICT⁶ excited state of much higher polarity than A1, which was non-radiative⁷ because of rapid internal conversion (or intersystem crossing) to ground state (or triplet state). The dimethylamino made a double contribution to the TICT state: its strong electron-donating effect stabilized the highly polar state, and the pretwisted geometry due to steric hindrance between the *peri*-proton and *N*-methyl group favor a further twist to form the TICT state.

The study on A1 and A2 inspired us to design A4 and A5 (with A3 as reference) for the possibility of obtaining fluoroionophores in a TICT-promoted PET mechanism. As de Silva⁸ had previously suggested, a

photogenerated electron field could accelerate the PET process if properly orientated. The S_1 of A4 and A5 had similar electron distribution to that of A2, while S_1 of A3 was similar to A1. So, A4 and A5 also formed TICT states and a very strong positive electron field on the 4-position nitrogen following excitation to accelerate the PET process, while A3 formed an ordinary ICT state and a relatively weaker electron field.

The distance between the two nitrogen atoms in the 'amino-alkyl-amino' type receptor was also crucial in determining the PET rate:⁹ a short distance favors orbital overlap. The molecular mechanics calculations (Hyperchem 6.0) provided N-N distances of 3.173, 3.265 and 2.807 Å for A3, A4, and A5 respectively; this difference in the distances is understandable in terms of steric factors. For A4, the hindrance from the peri-proton and the N-methyl group make the dimethylaminoethyl group adopt an extended geometry, for A5, the structure of the piperazine ring prevents the geometry from extending, while A3 adopts a geometry with little steric hindrance. A5 could be reasonably expected to undergo the fastest PET process, and as for A3 and A4 it is impossible to decide which is faster because A4 has a stronger photogenerated electron field, while A3 has the shorter N–N distance.

A4 and A5 were synthesized (Scheme 2) with high yields via substitution reactions of 4-nitro-1,8-dicyanonaphthalene with the corresponding amine, and identified via ESI MS, NMR, IR etc.¹⁰ This reaction took advantage of the mild conditions for nucleophilic substitution



Figure 1. ZINDO/S calculation of the electron distribution of A1, A2, A3, A4 and A5 in the singlet excited state.



Scheme 2. Synthetic procedure for A4 and A5. (a) NaNO₃, H₂SO₄, rt 3 h, 75% yield. (b) Sulfamide, anhydrous ethanol, dry HCl, reflux 3 h, 85% yield. (c) Under vacuum, heating to 220°C, 30 min, 68% yield. (d) Corresponding amines, DMSO, rt 16 h, 82% and 85% yield for A4 and A5, respectively.

by readily-oxidizable amines, over our previously reported procedure⁵ with 4-bromo-1,8-dicyanonaphthalene as a precursor of substitution carried out under relatively high temperature. The key intermediate 4nitro-1,8-dicyanonaphthalene, was readily synthesized via a three-step procedure (nitration, cyclization, and thermal decomposition) from acenaphthalenequinone, and each step proceeded in good yield. The emission properties of A4, A5 and reference compound A3, were also recorded. In the absence of cations, the fluorescence quantum yields (Φ_F) of A3, A4 and A5 in ethanol were 0.051, 0.015 and 0.006, respectively.

The weak fluorescence or low background emission of A5 indicated the strongest fluorescence quenching, which was caused by TICT-promoted PET, as TICT made the positive-negative charge at the fluorophore separate totally and more efficiently stimulate PET. A3 could just undergo the usual ICT-PET process, so the fluorescence quenching effect was the weakest. A4 is situated between A5 and A3, although it could undergo TICT-promoted PET similar to A5, its long N-N distance lowered the PET rate to some extent. The TICT-promoted PET occurring in A4 and A5 is different from the usual PET² or PET in the presence of ICT action.⁴

Transition metal cation sensitivity experiments were carried out and, in Table 1, the maximum values of the EF factors and the corresponding concentration of the added cations are listed. Since some of the salts were used in their hydrated forms, we purposely carried out blank experiments: small amounts of water were added to the ethanol solutions of the studied compounds, but no apparent fluorescence change was observed, which ruled out the disturbance from protons. Actually, during our previous investigation, we had found that even in water, transition metal cations and protons made totally different fluorescence changes to the fluoroionophores,¹¹ and the influence of trace amounts of protons generated by hydration of the metal salts is probably small enough to be ignored, compared to the influence of the cation-complexation itself.

The data in Table 1 clearly indicates that A3 exhibited considerable FE toward most of the cations (except Zn^{2+} , and Hg^{2+}), and the difference of FE factors for different cations was not large; A4 exhibited somewhat stronger FE, but the sensitivity was not improved. Interestingly, A5 exhibited significant FE, and for different cations, the FE factors and changes were different (also shown in Fig. 2): in the presence of a small amount of Cr³⁺ and Fe³⁺, the FE factors were higher, up to 102 and 114, respectively at concentrations of 25 and 15 µM. Cu²⁺ and Ni²⁺ also induced strong FE, up to 82 and 71 fold at much higher concentrations (up to 150, 150 μ M, respectively). Pb²⁺, Co²⁺ and Mn²⁺, had smaller FE factors and high concentrations, and lastly, no FE was observed in the presence of Hg^{2+} and Zn^{2+} . The fluorescence signaling high sensitivity of A5 towards different cations is possibly due to the amplification effect of TICT-promoted PET (in terms of larger FE factors) to the small difference in the cationsfluroionophore interaction.

In addition, a series of naphthalimides **B** and nitrobenzoxadiazoles **C** were designed and synthesized (Schemes 1 and 3). With **B1**^{4c} and **C1**^{4b} as references, some similar phenomena or relationships to the **A** series were found in the **B** and **C** series. **B3** and **C3** with a 4-methylpiperazino electron donor attached to the aromatic electron acceptor exhibited much stronger sensitivity towards certain transition metal ions (Fe³⁺, Cr³⁺, Cu²⁺), than the counterparts with (N',N'-dimethylaminoethylamino or (N,N',N'-trimethyl)aminoethylamino groups.

Cations ^b	A3		A4		A5		B1		B2		B3		C1		C2		C3	
	[M] ^c / μ M	FE ^d	[M]/ μM	FE	[M]/ µM	FE	[M]/ µM	FE	[M]/ μM	FE	[M]/ µM	FE	[M]/ μM	FE	[M]/ μM	FE	[M]/ µM	FE
Fe ³⁺	25	18	25	19	15	114	50	26	15	31	10	106	25	68	15	69	40	157
Cr ³⁺	25	15	25	20	25	102	25	25	50	30	50	104	25	62	25	63	75	122
Mn^{2+}	300	7.0	200	12	300	20	200	11	200	15	200	27	200	14	200	10	200	29
Co^{2+}	200	11	200	16	200	53	200	19	100	22	200	65	200	33	100	23	100	13
Ni ²⁺	150	15	100	18	150	71	200	23	100	26	200	60	200	41	300	30	300	56
Cu^{2+}	100	14	100	18	150	82	150	24	100	29	200	92	75	63	75	65	50	164
Zn^{2+}	200	0.5	200	1.9	200	0.6	200	1.0	100	2.2	100	3.4	300	2.8	200	0.7	200	0.2
Hg^{2+}	300	-0.5	300	0.1	300	0.03	300	-0.1	100	0.5	100	0.1	300	2.1	300	0.1	200	0.05
Pb ²⁺	250	15	200	19	250	57	300	21	200	24	300	69	200	28	200	22	250	15

Table 1. Maximum of fluorescence enhancements (FE) of the fluoroionophores induced by transition cations^a

^a Experimental conditions: 5 μ M ethanol solutions of the compounds were used at 298 K, $\lambda_{ex} = 385$, 355, 352, 422, 397, 377, 451, 467 and 454 nm for A1, A2, A3, B1, B2, B3, C1, C2 and C3, respectively.

^b Salts used for the experiments were CrCl₃·6H₂O, MnCl₂·2H₂O, FeCl₃·H₂O, CoCl₂·6H₂O, NiCl₂·6H₂O, CuCl₂·H₂O, ZnCl₂, HgCl₂, and Pb(NO₃)₂.

^c Represents the correlation of the metal ion for which FE was the maximum; a further increase in concentration beyond this led to fluorescence quenching.

^d With reference to the fluorescence intensity of the respective compound in the absence of cation.



Fig. 2. The fluorescence enhancement of A5 (5 μ M) in ethanol, induced by different cations.



Scheme 3. Synthetic procedures for B2, B3, C2 and C3. (e) DMSO, corresponding amines, rt 16 h, 88% and 92% yield for B2 and B3, respectively. (f) Dichloromethane, corresponding amines, rt 30 min, 82% and 80% yield for C2 and C3, respectively.

The fluoroionophores (A5, B3, and C3) exhibited highly sensitive fluorescence enhancements in the presence of different transition cations. Their high sensitivity and 'selectivity' could be up to, or even higher than some reported fluoroionophores³ with crown ether receptors, and can be ascribed to the special contribution of the TICT-promoted PET processes caused by the *peri*effect and strong electron-donating receptor.

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- 10. A5. mp 178–180°C, ¹H NMR (400 MHz, CDCl₃) δ 8.47-8.45 (d, J=8.4 Hz, 1H), 8.09-8.07 (d, J=7.2 Hz, 1H), 8.03–8.01 (d, J=7.6 Hz, 1H), 7.64–7.60 (t, J=8Hz, 1H), 7.22-7.20 (d, J=8.0 Hz, 1H), 3.31 (br s, -N(CH₂CH₂)₂NCH₃, 4H), 2.90 (br s, -N(CH₂CH₂)₂-NCH₃, 4H), 2.55 (s, -N(CH₂CH₂)₂NCH₃, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 155.18, 138.58, 137.68, 130.59, 130.24, 128.61, 125.67, 117.42, 116.98, 115.49, 109.30, 102.45, 55.09, 52.83, 46.07; IR (KBr, cm⁻¹) 2221, 2211, 1575, 1511, 1454, 1371; ESI MS [M+H]⁺ (m/z 277). A4. oily product, ¹H NMR (400 MHz, DMSO- d_6) δ 8.65– 8.63 (d, J=8.0 Hz, 1H), 8.29-8.27 (d, J=7.2 Hz, 1H), 8.17-8.15 (d, J=8.4 Hz, 1H), 7.76-7.74 (t, J=8 Hz, 1H), 7.34–7.32 (t, J=8.0 Hz, 1H), 3.38–3.42 (t, J=6.8 Hz, CH₃NCH₂CH₂N(CH₃)₂, 2H), 2.99 (s, CH₃NCH₂CH₂N- $(CH_3)_2$, 3H), 2.75–2.79 (t, J=6.8 Hz, $CH_3NCH_2CH_2N$ -(CH₃)₂, 2H), 3.28 (s, CH₃NCH₂CH₂N(CH₃)₂, 6H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 156.11, 138.29, 137.57, 131.03, 130.83, 128.69, 125.18, 117.54, 117.01, 115.49, 108.99, 101.07, 56.90, 54.95, 45.71, 42.15; ESI MS [M+ H]⁺ (m/z 279). B2: oily product, ¹H NMR (400 MHz, CDCl₃) δ 8.51–8.49 (d, J=7.2 Hz, 1H), 8.46–8.44 (d, J=8.4 Hz, 1H), 8.43–8.41 (d, J=8 Hz, 1H), 7.61–7.58 (t, J = 7.8 Hz, 1H), 7.16–7.14 (d, J = 8 Hz, 1H), 4.14–4.10 (t, J = 7.4 Hz, NCH₂CH₂CH₂CH₃, 2H), 3.42–3.38 (t, J = 6.8Hz, CH₃NCH₂CH₂, 2H), 3.03 (s, CH₃NCH₂, 3H), 2.61 (br s, $CH_2N(CH_3)_2$, 2H), 2.22 (s, $CH_2N(CH_3)_2$, 6H), 1.69–1.66 (m, NCH₂CH₂CH₂CH₃, 2H), 1.41–1.38 (m, NCH₂CH₂CH₂CH₃, 2H), 0.95–0.92 (m, NCH₂CH₂CH₂-
- CH₃, 3H); ESI MS: $[M+H]^+$ (m/z 354). B3: mp 137– 139°C, ¹H NMR (400 MHz, CDCl₃) δ 8.58-8.56 (d, J=7.2 Hz, 1H), 8.52-8.50 (d, J=8.0 Hz, 1H), 8.40-8.37 (d, J=8.4 Hz, 1H), 7.71-7.67 (d, J=7.8 Hz, 1H), 7.24-7.22 (d, J=8.0 Hz, 1H), 4.18–4.14 (t, J=7.3 Hz, NCH₂CH₂CH₂CH₃, 2H), 3.35 (br s, N(CH₂CH₂)₂NCH₃, 4H), 2.83 (br s, N(CH₂CH₂)₂NCH₃, 4H), 2.45 (s, N(CH₂CH₂)₂NCH₃, 3H), 1.73–1.69 (m, NCH₂CH₂CH₂-CH₃, 2H), 1.48–1.44 (m, NCH₂CH₂CH₂CH₃, 2H), 0.99– 0.66 (m, NCH₂CH₂CH₂CH₃, 3H); IR (KBr, cm⁻¹): 1691, 1656, 1590, 1509; ESI MS: [M+H]⁺ (m/z 352). C2: mp 107-109°C, ¹H NMR (400 MHz, CDCl₃) δ 8.41-8.38 (d, J=9.2 Hz, 1H), 6.13–6.11 (d, J=9.2 Hz, 1H), 4.24 (br s, CH₃NCH₂-, 2H), 3.51 (s, CH₃NCH₂-, 3H), 2.73 (br s, $-CH_2N(CH_3)_2$, 2H), 2.37 (s, $-CH_2N(CH_3)_2$, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 145.57, 144.90, 144.65, 135.32, 122.76, 101.46, 57.09, 53.84, 45.85, 42.01; ESI MS: [*M*+H]⁺ (*m*/*z* 266). C3: mp 202–204°C, ¹H NMR (400 MHz, CDCl₃) δ 8.42–8.40 (d, J=8.8 Hz, 1H), 6.31–6.29 (d, J=9.2 Hz, 1H), 4.14–4.11 (t, J=4.8 Hz, $-N(CH_2CH_2)_2NCH_3$, 4H), 2.68–2.66 (t, J=5.0 Hz, -N(CH₂CH₂)₂NCH₃, 4H), 2.39 (s, NCH₃, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 145.23, 144.91, 144.84, 135.17, 123.70, 102.72, 54.75, 49.54, 46.06; IR (KBr) cm⁻¹: 1609, 1548, 1437, 1300; ESI MS: [M+H]⁺ (m/z 264), [M+Na]⁺ (m/z 286).
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