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A fluorescent AND logic gate based on a ferrocene-naphthalimide-piperazine format responsive to acidity and oxidizability

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Keywords: Naphthalimide, Ferrocene, Photoinduced electron transfer, Pourbaix sensor, Molecular logic gate, Fluorescence

ABSTRACT

A novel fluorescent molecular logic gate 1 is demonstrated as a two-input AND logic gate for the detection of acidity and oxidizability. Designed according to an electron-donor–spacer–fluorophore–spacer–receptor format, the modules are represented by ferrocene as the electron donor, 1,8-naphthalimide as the fluorophore and piperazine as the proton receptor. In the presence of elevated concentrations of H⁺ and Fe³⁺, the molecule switches ‘on’ emitting at λₘₐₓ = 530 nm with Φᵢ = 0.060 at 10⁻⁴ M H⁺ and 50 μM Fe³⁺. The H⁺ binding and apparent Fe³⁺ binding constants determined by fluorimetric titrations in 1:1 (v/v) methanol/water are log β₉₊₁ = 8.1 and log β₉Fe³⁺ = 4.7. Modulation of the fluorescence output results from controlling competing photoinduced electron transfer (PET) at the ferrocene end and internal charge transfer (ICT) at the piperazine end. Time-resolved fluorescence spectroscopy reveals a single fluorescent lifetime of 5.8 ns, while from absorption transient spectroscopy a remarkable fast decay signal < 2 ps is observed. Comparison is made with methylpiperazine 2 and piperazine fluorescent pH indicator 3 as model compounds.

1. Introduction

Many chemical and biological phenomena are dependent on pH and redox potential including corrosion [1], geochemistry [2], clinical chemistry [3] and anticancer treatments [4]. In recent years there has been a tremendous effort focused exclusively on pH sensing [5], notably for intracellular fluorescence imaging applications [6]. In contrast, the field of luminescent redox indicators has not received as much attention and offers much opportunity for future development [7]. Indeed, despite there being numerous molecular probes for specifically monitoring the pH or the redox environment in living cells, there are no commercially available probes that simultaneously probe pH and pE in living cells [8]. Molecular probes that are able to detect and measure high concentrations of both protons and redox active oxidants could be valuable diagnostic imaging tools for diseases such as cancer [9].

We are interested in engineering molecular logic gates that detect acidic and oxidizing conditions by emitting an optical signal. We deemed this class of smart molecule ‘Pourbaix sensors’ in honour of Marcel Pourbaix, the father of corrosion science [1]. Molecular logic gates specifically combining acid base and redox equilibria are still rather rare [10,11]. Our first proof of concept prototypes were based on the hydrophobic fluorophore anthracene [12,13]. We subsequently designed ‘Pourbaix sensors’ with the non-symmetrical naphthalimide fluorophore [15,16]. Naphthalimides are routinely used in molecular probe design due to their facile synthetic pathways, compatible water solubility and emission at longer wavelengths, among other favourable properties [17,18]. More specifically, chemosensors and molecular logic gates combining a naphthalimide fluorophore with a piperazine receptor represent a successful design strategy for many applications [19,23]. We and others who are interested in redox responsive optical molecules have employed the ferrocene naphthalimide piperazine platform to demonstrate proof of concepts of three input INHIBIT [24] and three input INHIBIT AND OR [25] combinational logic gate arrays. Other research groups have demonstrated pH/redox multi stimuli materials [26], nanogels [27], polymers [28], film materials [29] and degradable micelles [30].

Herein we report the synthesis and characterisation of a naphthalimide based logic gate 1 (Scheme 1) with an electron donor spacer fluorophore spacer receptor format [15]. ‘Pourbaix sensor’ 1 consists of ferrocene (electron donor) connected to 1,8-naphthalimide (fluorophore) by a methylene spacer, which is connected to piperazine (proton receptor/electron donor). The molecule is demonstrated as an...
AND logic gate responsive to protons and Fe$^{3+}$ as the oxidant in aqueous methanol. Previously reported methylimipiperazine prototype 2 and piperazine fluorescent pH indicator 3 are studied as model compounds (Scheme 1).

2. Experimental

2.1. Materials

N Ferrocenyl 4 bromo 1,8 naphthalimide was synthesized as reported (Scheme S1) [15]. Piperazine (99%, Alfa Aesar) was used as received. Tetrabutylammonium hydroxide (25 wt % in H$_2$O), iron(III) sulfate pentahydrate (97%) and methanesulfonic acid (Analytical) were used for column and thin layer chromatography, respectively. Analytical) were used for column and thin layer chromatography, respectively.

2.2. Instrumentation

Melting points were recorded with a Stuart SMP40 automatic melting point apparatus. $^1$H and $^{13}$C NMR spectra were recorded on a Bruker Avance III HD NMR spectrometer at 500.13 MHz and 125.76 MHz, respectively. Chemical shifts are reported in ppm downfield from TMS at $\delta = 0.00$ ppm and $\delta = 77.00$ ppm for $^1$H and $^{13}$C NMR. Infra red spectra were recorded using a Shimadzu IR Affinity 1 spectrophotometer calibrated against 1601 cm$^{-1}$ polystyrene absorption peak as KBr disks. HRMS was performed by ES ToF technique and performed by Medac Ltd (UK). UV visible absorption spectra were obtained on a Jasco V 650 spectrophotometer. Fluorescence spectra were obtained on a Jasco FP 8300 spectrophotometer. Experiments were performed at room temperature 20 °C in 10 mm quartz cuvettes. The time resolved luminescence set up was previously described [16]. pH measurements were recorded with a Hanna Instruments pH 210 microprocessor meter with a HI 1131 electrode calibrated at pH 4.00 and pH 7.00.

2.3. Synthesis

Reactions were carried out in round bottom flasks (50 mL, 100 mL or 250 mL) partially immersed in an oil bath and heated using on a IKA C MAG HS 7 hotplate fitted with an IKA ETS D5 temperature probe. Silica gel 60 (70 230 mesh, Fluka Analytical) and silica coated aluminium foil (silica gel matrix with fluorescent indicator 254 nm, Fluka Analytical) were used for column and thin layer chromatography, respectively.

2.3.1. N Ferrocenylmethyl 4 piperazine 1,8 naphthalimide

N Ferrocenyl 4 bromo 1,8 naphthalimide (0.199 g, 0.420 mmol) and piperazine (0.897 g, 10.4 mmol) were dissolved in 25 mL of DMF and refluxed for 2 h. The reaction was diluted with 50 mL water and extracted with CH$_2$Cl$_2$ (3 x 30 mL), dried over anhydrous MgSO$_4$, filtered and the solvent removed in vacuo. The product was purified by column chromatography on silica gel eluted with 1:1 (v/v) CH$_2$Cl$_2$/MeOH and obtained as a yellow solid in 31% yield. $R_f = 0.50$ (20:1 (v/v) CH$_2$Cl$_2$/MeOH); m.p. = 132 135 °C; $^1$H NMR (CDCl$_3$, 500 MHz, ppm): $\delta$ 8.56 (dd, 1H, $J = 7.3$ Hz, 0.9, Ar H), 8.50 (d, 1H, $J = 8.1$ Hz, Ar H), 8.38 (dd, 1H, $J = 8.5, 0.9$ Hz, Ar H), 7.66 (dd, 1H, $J = 7.9, 0.9$ Hz, Ar H), 7.19 (d, 1H, $J = 8.1$ Hz, Ar H), 5.11 (s, 2H, —CH$_2$ spacer), 4.50 (t, 2H, $J = 1.8$ Hz, Cp), 4.20 (s, 5H, Cp), 4.06 (t, 2H, $J = 1.8$ Hz, Cp), 3.22 (m, 4H, —N(CH$_2$CH$_2$)$_2$NH), 3.20 (m, 4H, —N(CH$_2$CH$_2$)$_2$NH); $^{13}$C NMR (CDCl$_3$, 126 MHz, ppm): $\delta$ 164.2, 163.8, 156.2, 132.6, 131.2, 130.2, 129.9, 126.2, 125.6, 123.4, 116.9, 115.0, 83.4, 70.4, 68.6, 68.0, 54.2, 46.1, 39.1; IR (KBr, cm$^{-1}$): 3416 (N H), 2951 ( C H), 1690 ( C=O), 1659 ( C=O), 1587, 1516, 1418, 1383, 1371, 1331, 1240, 1175, 1134, 1105, 1022, 827, 785; HRMS (ES ToF): Calculated C$_{27}$H$_{25}$N$_3$O$_2$Fe [M] + 479.1296, found 479.1288.

2.4. Spectroscopic measurements

Solutions of 1 3 were prepared in 1:1 (v/v) methanol/water with an absorbance of 0.1. The excitation and emission slits were set at 2.5 nm and 5.0 nm, respectively, with a scan rate of 200 nm min$^{-1}$ and emission range of 400 650 nm. The acid dissociation constants ($p\beta_{H^+}$) were determined from fluorescence intensity pH plots and fitted to a line arized Henderson Hasselbalch equation adapted for spectroscopic measurements eq.(1) [31]:

$$\log \left( \frac{I_{\text{max}} - I}{I - I_{\text{min}}} \right) = pH - p\beta_{H^+}$$

(1)

Fe$^{3+}$ titrations were performed in acidified 1:1 (v/v) methanol/ water to prevent the formation of insoluble iron hydroxides. Known aliquots of Fe$^{3+}$ were added by micropette. A modified Henderson Hasselbalch equation was employed for determining the apparent Fe$^{3+}$ binding constant ($p\beta_{H^+}$) according to eq. (2):

$$\log \left( \frac{I_{\text{max}} - I}{I - I_{\text{min}}} \right) = -log[Fe^{3+}] - p\beta_{H^+}$$

(2)

The molar extinction coefficients ($\epsilon$) were determined according to the Beer Lambert Law eq. (3) where $A$ is the absorbance, $c$ is the concentration and $l$ is the cuvette path length. The relative fluorescence quantum yields ($\Phi_f$) were determined by eq. (4) from the area under the fluorescence spectra ($I$), the absorbance at the excited wavelength ($A$) and the solvent refractive index ($n$). Reference values are denoted by the subscript ‘ref’.

$$A = \varepsilon \cdot l \cdot c$$

(3)

$$\Phi_f = \Phi_{ref} \left( \frac{I_{ref}}{I} \right) \left( \frac{A_{ref}}{A} \right) \left( \frac{n_f}{n_{ref}} \right)^2$$

(4)

3. Results and discussion

3.1. Synthesis and characterisation

2 Ferrocenylmethyl 6 (piperazin 1 yl) 1H benzo[de]isoquinoline 1,3 (2H) dione 1 was synthesized from N ferrocenyl 4 bromo 1,8 naphthalimide reacted with piperazine in 31% yield after purification (Scheme S1). We fully characterised 1 by $^1$H and $^{13}$C NMR, FTIR and HRMS (Figs. S1 S4). Compound 1 was previously reported from the synthesis of 6 (piperazin 1 yl)benzo[de]isochromene 1,3 dione with ferrocenylmethylyamine in 16% yield [24]. In this previous work, 1 was used as a synthetic intermediate and not satisfactorily characterised. We note that $^{13}$C NMR resonances at ca. 39.1 ppm and 130.2 ppm were not reported, and it is unclear whether the reported $^1$H NMR resonances are for CDCl$_3$ or DMSO $d_6$. From the FTIR spectrum one can clearly identify the diagnostic broad secondary N H stretching vibration at 3416 cm$^{-1}$ and the intense carbonyl stretches at 1690 cm$^{-1}$ and 1659 cm$^{-1}$. 

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**Scheme 1.** The 1,8-naphthalimide-based fluorescent logic gates 1 3.
Similar photophysical characteristics were observed when either one or both inputs are absent. The fluorescence output to the naked eye on irradiation with 365 nm light. The four possible conditions are (A) low H+ and no oxidant, (B) high H+ and no oxidant, (C) low H+ and high oxidant and (D) high H+ and high oxidant. A green fluorescence is observed by the naked eye, the maximum fluorescence is only observed by the naked eye in the presence of 50 μM Fe3+ (Fig. 2, vial D). In the other three cases, no fluorescence is observed by the naked eye, the maximum emission quantum yield being Φf ≤ 0.01. Hence, compound 1 functions as a two input AND logic gate for acidity and oxidizability.

The fluorescence spectra of 1 associated with the four viors are overlaid in Fig. 3. The fluorescence output is significantly greater when both inputs are simultaneously present, whereas a low output is observed when either one or both inputs are absent. The fluorescence enhancement for 1 is a 6 fold switching (I\text{max} (50 μM Fe3+ at pH 4)/I\text{max} (pH 4)) whereas with 2 we observed up to a 13 fold enhancement [15]. The switching between the ‘off’ and ‘on’ states is slightly better for 2 than 1. Surprisingly, this difference is not due to the different proton receptors because the Φf of 1 and 2 in the presence of 50 μM Fe3+ are rather similar.

3.2. Photochemistry of 1 and 2

The UV visible absorption spectra of 1 and 2 in 1:1 (v/v) methanol/ water display broad bands between 300 and 550 nm (Fig. S5). The peak maxima in acidic and basic solutions are situated at 386 nm and 405 nm, respectively, with an isosbestic point at 400 nm. A complete titration set of spectra are shown between pH 5 and pH 10 (Figs. S5a and c). The ε values of 8000 L mol⁻¹ cm⁻¹ and 10000 L mol⁻¹ cm⁻¹ in acid and base, respectively, correspond to π→π* electronic transitions within the naphthalimide fluorophore. The pH induced 20 nm hypsochromic shift in acidic solution is characteristic of an ICT mechanism associated with a less stable Franck Condon excited state. This at least partly attributed to the piperazine group, which directly interferes with the naphthalimide π conjugation due to a ‘pre twisted’ ICT in the ground state [33]. Similar photophysical characteristics were observed with 2 (Fig. S6a) [15] as summarised in Table 1.

The absorbance spectra of 1 under the four input conditions for AND logic are shown in Fig. 1. The λ\text{max} is observed to decrease with increasing proton concentration. Upon addition of 50 μM Fe3+ a slight increase is observed in the absorbance. A higher concentration of Fe3+ does result in a greater fluorescence emission; however, this increases the possibility of an inner filter effect.

### Table 1
Comparison of the photophysical data of 1–3 in 1:1 (v/v) MeOH/H2O.

| Condition | Input1 (H+) | Input2 (Fe3+) | Output 1 (Φf) | Output 2 (Φf) |
|-----------|-------------|---------------|---------------|---------------|
| A         | 0           | 0             | 0             | (low, 0.000)  |
| B         | 1           | 0             | 0 (low, 0.000) | 0 (low, 0.006) |
| C         | 0           | 1             | 0 (low, 0.001) | 0 (low, 0.001) |
| D         | 1           | 1             | 1 (high, 0.060) | 1 (high, 0.080) |

- a Sensors concentration ~5–10 μM.
- b pH adjusted with NaOH or (C2H5)2NNOH and CH3SO3H solutions.
- c Estimated errors for pKb, pKb, and log ε are ±0.2, ±0.2 and ±0.3, respectively. Duplicate measurements.
- d Molar absorptivity ε in L mol⁻¹ cm⁻¹.
- e Determined by log(I\text{max} /I\text{min}) = log[H+] + log βH, in absence of Fe3+.
- f In presence of 50 μM Fe3+.
- g Determined by log(I\text{max} /I\text{min}) = log[Fe3+] + log βFe.
- h At 10⁻⁴ M H+ and 50 μM Fe3+ in case of 1 and 2.
- i Fluorescence lifetimes in presence of 10⁻⁴ M H+ and 50 μM Fe3+.

**Fig. 1.** UV-visible absorption spectra of 8.2 μM 1 in 1:1 (v/v) MeOH/H2O at four different input conditions of H+ and Fe3+.

**Fig. 2.** Irradiation of 10⁻⁵ M 1 with UV light (365 nm) under AND logic conditions in 1:1 (v/v) MeOH/H2O: (A) 10⁻¹⁰ M H+, (B) 10⁻⁸ M H+ (C) 10⁻¹⁰ M H+ and 50 μM Fe3+ and (D) 10⁻⁶ M H+ and 50 μM Fe3+.

Fluorescence emission spectra of 1 and 2 were obtained on excitation at 400 nm providing broad emission spectra with a peak maximum at 530 nm (Fig. S5). Emission intensity pH profiles revealed sigmoidal shaped curves ranging three pH units (Figs. S5c and g). The calculated binding constants from the analysis of eq (1) by fluorimetric titration provided pKb, values of 8.1 and 7.7 for 1 and 2, respectively (Figs. S5c and g). pH titrations in the presence of 50 μM Fe3+ gave pKb, values of 8.0 and 7.2. (Fig. S6f). Fluorimetric Fe3+ titrations at constant pH 4 gave pKb, values of 4.7 and 4.6 for 1 and 2, respectively (Fig. S7).

The AND logic test of 1 in vials is qualitatively shown in Fig. 2. The truth table including Φf are given in Table 2. The ‘vial test’ of 1 displays a fluorescence output to the naked eye on irradiation with 365 nm light. The four possible conditions are (A) low H+ and no oxidant, (B) high H+ and no oxidant, (C) low H+ and high oxidant and (D) high H+ and high oxidant. A green fluorescence is only observed by the naked eye in the presence of 10⁻⁴ M H+ and 50 μM Fe3+ (Fig. 2, vial D). In the other three cases, no fluorescence is observed by the naked eye, the maximum emission quantum yield being Φf ≤ 0.01. Hence, compound 1 functions as a two input AND logic gate for acidity and oxidizability.

### Table 2
Truth tables and fluorescence quantum yields of 1 and 2 in 1:1 (v/v) MeOH/H2O by steady-state fluorescence spectroscopy.

| Condition | Input1 (H+) | Input2 (Fe3+) | Output 1 (Φf) | Output 2 (Φf) |
|-----------|-------------|---------------|---------------|---------------|
| A         | 0           | 0             | 0             | (low, 0.004)  |
| B         | 1           | 0             | 0 (low, 0.000) | 0 (low, 0.006) |
| C         | 0           | 1             | 0 (low, 0.001) | 0 (low, 0.001) |
| D         | 1           | 1             | 1 (high, 0.060) | 1 (high, 0.080) |

- a Sensors concentration ~5–10 μM.
- b pH adjusted with NaOH or (C2H5)2NNOH and CH3SO3H solutions.
- c Estimated errors for pKb, pKb, and log ε are ±0.2, ±0.2 and ±0.3, respectively. Duplicate measurements.
- d Molar absorptivity ε in L mol⁻¹ cm⁻¹.
- e Determined by log(I\text{max} /I\text{min}) = log[H+] + log βH, in absence of Fe3+.
- f In presence of 50 μM Fe3+.
- g Determined by log(I\text{max} /I\text{min}) = log[Fe3+] + log βFe.
- h At 10⁻⁴ M H+ and 50 μM Fe3+ in case of 1 and 2.
- i Fluorescence lifetimes in presence of 10⁻⁴ M H+ and 50 μM Fe3+.

**Fig. 3.** Fluorescence output of 1 in vials is significantly greater when both inputs are simultaneously present, whereas a low output is observed when either one or both inputs are absent.
similar. It would be expected that the ICT efficiencies from the piperazine and methylpiperazine to the naphthalimide fluorophore would be nearly the same.

3.3. Model piperazine compound 3

Comparison to the naphthalimide piperazine model 3 provides in sight into the structural effect on the pH dependent fluorescence switching (See Table 2) [33]. A peak maximum is observed at 407 nm (6900 L mol⁻¹ cm⁻¹) in basic solution and 384 nm (8700 L mol⁻¹ cm⁻¹) in acidic solution with a clear isosbestic point at 401 nm. These values are in good agreement with those of 1 confirming that the ferrocene moiety is electronically decoupled from the naphthalimide fluorophore by the methylene spacer. The Φ₁ of 3 is 0.20 when monoprotonated at pH 4 and 0.002 when unprotonated at pH 10, yielding a remarkable 138 fold fluorescence enhancement factor, which is due to the enhanced twisted piperazine ground state [33]. In contrast, the maximum Φ₂ of 1 is a more modest 0.060 even on protonation and oxidation, while in the absence of both input conditions the minimum Φ₁ is 0.004 at pH 10. We observed a similar trend on comparing pyrazoline based fluorescent pH probes with pyrazoline ferrocene INH logic gates [34]. The cause of this limitation of fluorescent enhance ment is not fully understood. While protonation of the piperazine nitrogen atom results in a covalent bond, which implicates the electron lone pairs, oxidation of ferrocene by Fe³⁺ generates a radical cation intermediate. A recent comprehensive DFT study by us suggests there are localised deactivation pathways associated with ferrocene that may render a lower fluorescent quantum yield [35].

3.4. Time resolved fluorescence spectroscopy

A time resolved fluorescence study was undertaken to measure the fluorescence lifetimes of 1 at the four input conditions [16]. The fluorescence decay curve and 3D plot for the most fluorescent logic state are shown in Fig. 4. A complete set of fluorescence decay curves (a d) and 3D plots (e h) are available in the supporting information (Fig. S8). The experimental results highlight the efficient charge transfer processes between the piperazine and naphthalimide, and the ferrocene and naphthalimide fluorophore. For both 1 and 2, the fluorescence lifetime decay profiles are bi exponential in the absence of one or both inputs (Figs. S8a e). However, on addition of H⁺ and Fe³⁺ a mono exponential decay profile is observed (Fig. 4, Fig. S8d). In the logic states ‘A C’, with no inputs or only one input, the long lifetime component (~90%) results from the intrinsic properties of the naphthalimide fluorophore. The fluorescence lifetimes of 1 and 2 (in the absence of at least one input) span 4.4 5.5 ns and 6.6 7.4 ns, respec tively. The shorter lifetime component (~10%) corresponds to the suppressed fluorescence emission when one or both quenching me chanisms are operational: ICT from the proton receptor and/or PET from the ferrocene unit to the excited state fluorophore with a time constant less than 1 ns. The addition of acid and oxidant deactivates the PET and ICT pathways and yields a single fluorescent lifetime compo nent (>99%). The fluorescence lifetimes are 7.3 ns for 2, whilst 1 has a slightly shorter lifetime of 5.8 ns in 1:1 (v/v) methanol/water. It is plausible that the discrepancy originates from the positive inductive effect of the methyl group in 2, which better stabilises the protonated amine resulting in a longer lifetime in the excited state. The 3D surface plots (Figs. S8c h) provide similar information as the lifetime decay curve, but with the additional dimension of the emission wavelength. From these plots it is easy to appreciate how the fluorescence is re markably enhanced in the presence of both inputs H⁺ and Fe³⁺ com pared to the other three input conditions.

3.5. Femtosecond transient absorption spectroscopy

Further insight into the photophysics of 1 was gained from femto second transient absorption studies. The transient map of 1 is shown in Fig. 5. After excitation (< 1 ps) 1 experiences a significant charge density shift within the naphthalimide fluorophore due to the inherent ICT character. Ground state bleaching is observed at 420 450 nm (red) and stimulated emission at 500 650 nm (blue). We previously noted that the transient signal recovery rate of 2 was faster compared to a methylpiperazine model (~50 ps) due to the faster excited state electro n transfer from ferrocene (~5 ps) [16]. In the case of 1, the transient signal recovery rate is remarkable fast at ~2 ps. In the absence of either input, the excited state absorption has bi exponential decays of 270 fs
Fig. 5. Transient absorption map of 1 in acetonitrile in presence of 10⁻³ M H⁺ and 50 μM Fe³⁺.

and 1.25 ps with almost equal pre exponential factors of 0.46 and 0.42 and stimulated emission 140 fs (23%) and 500 fs (62%). On addition of protons the contributions from the excited states are shorter at 120 ps and 1 ps with pre exponential factors of 0.47 and 0.42, respectively. In the presence of acid and oxidant the stimulated emission is mono exponential with an emission lifetime of 160 fs.

4. Conclusions

The successful operation of fluorescent logic gate 1 is another convincing illustration of the cross fertilization of fluorescent pH in dicators and fluorescent redox indicators [11]. Specifically, 1 in corporates a ferrocene naphthalimide piperazine format, which con sists of an electron donor, fluorophore and proton receptor/electron donor with PET and ICT mechanisms. Molecule 1 responds to an oxi dant and protons in accordance to two input AND logic by emitting a fluorescent signal in mixed aqueous methanol. Future engineering of systems responsive to pH and redox potential should continue to pro vide stimulating examples of information processing at the molecular level [36,37] and practical application in various realms including cell biology [8] and corrosion detection [1].

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