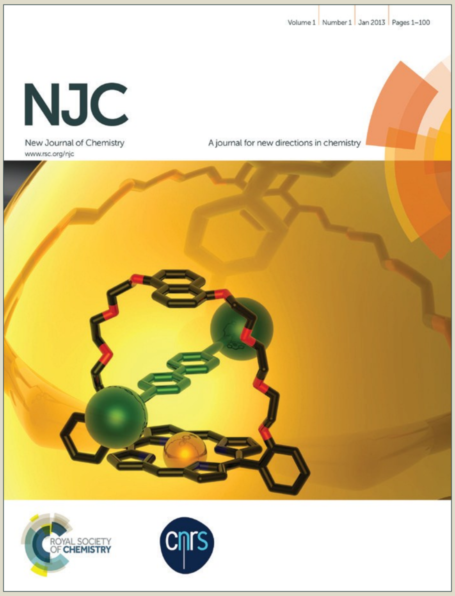
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Graphical Abstract

A naphthalimide-based 'Pourbaix sensor': A redox and pH driven AND logic gate with photoinduced electron transfer and internal charge transfer mechanisms

Jake C. Spiteri, Jonathan S. Schembri and David C. Magri*

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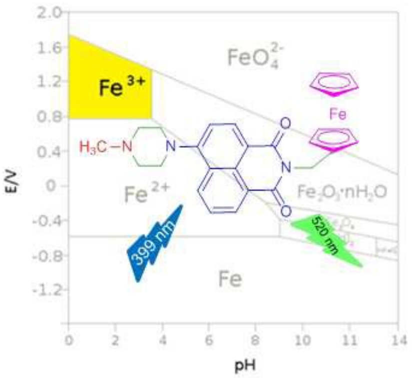

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A naphthalimide-based AND logic gate displays a fluorescence output in aqueous methanol on oxidation of the ferrocene moiety and protonation of the tertiary amine. The molecule introduces a ‘receptor–spacer–fluorophore–spacer–redox-unit’ format for simultaneous monitoring of redox potential and pH.

Information processing and computing with molecules is a stimulating research field with an established track record for conceptual innovation.[1] A plethora of switchable molecular logic gates and arrays consisting of two or more physical and/or chemical inputs continue to be demonstrated using inputs including light, redox potential, pH, ions, and organic molecules.[2,3] Much thought and discussion has been devoted to contemplating how stimuli-response molecules may be used to surpass the current performance of silicon-based technologies.[4] Within the realm of molecular biology, molecular probes and logic devices are advantageously suited to intracellular tasks, unlike semiconductor devices, which are restricted to nanometer dimensions. Hence, intelligent molecules at sub-nano dimensions serve a noble purpose of providing information on the particularities within cell compartments.[5]

From the cross-fertilization of fluorescence acid-base indicators[6] and redox switches[7] we recently defined a new class of AND logic gates capable of simultaneously sensing for pH and redox potential (pE).[8,9] Our earlier examples of ‘Pourbaix sensors’ were comprised of a ‘fluorophore–spacer–receptor–spacer–redox-unit’ format. Gan and co-workers reported a molecule with a similar design over a decade ago as a “dual-mode chemical (protons)/electrochromic molecular device”.[10] Other examples of multi-state optoelectronic logic gates incorporating a redox-active ferrocene unit have been reported in recent years.[11,12] However molecular logic gates specifically combining acid-base and redox equilibria are still rather rare.[13] We envision that logic gates based on redox potential and pH could be useful for a host of applications ranging from corrosion detection,[14] cell biology[15] and blood disorder diagnostics.[16]

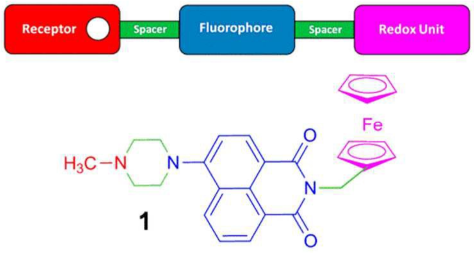
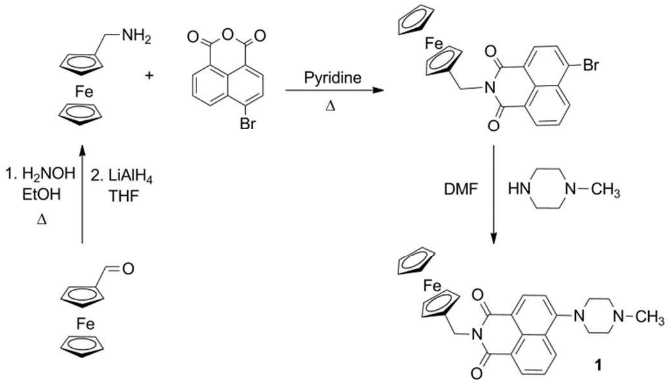


Fig. 1 A schematic diagram of the receptor–spacer–fluorophore–spacer–redox-unit design and the molecular structure of the AND logic gate **1**.

Herein we report a substantially improved fluorescent AND logic gate modulated by pE and pH. The ‘Pourbaix sensor’ **1** is designed based on a novel ‘receptor–spacer–fluorophore–spacer–redox-unit’ arrangement (Fig. 1). The molecule consists of a 1,8-naphthalimide fluorophore, a methylpiperazine receptor for protons and a ferrocene redox unit for oxidants. An enhanced fluorescence output is observed upon simultaneous oxidation of the ferrocene moiety with a suitable oxidant, in our case Fe^{3+}, and protonation of the tertiary amine with acid. Additionally, molecule **1** has superior characteristics over predecessor prototypes,[8] including longer excitation and emission wavelengths, aqueous solubility properties, an enhanced ‘*on*’ quantum yield of fluorescence and switching factor.

The naphthalimide-based logic gate **1** was synthesised by a three step procedure (Scheme 1). Reductive animation of ferrocenecarboxaldehyde with hydroxylamine and $LiAlH_4$ yielded ferrocenylmethylamine in 41% yield.[17] Subsequently, it was reacted with 4-bromo-1,8-naphthalic anhydride in pyridine to yield *N*-ferrocenyl-4-bromo-1,8-naphthalimide in 34% yield, which was reacted with 1-methylpiperazine in 72% yield.[18] The final product **1** was purified by column chromatography and recrystallised from 1:1 $EtOH/H_2O$ to yield a yellow solid. The compound was fully characterised by ^1H and ^{13}C NMR, IR and HRMS (Fig. S1-S3).[†]



Scheme 1: Synthesis of the 'Pourbaix sensor' **1**.

The UV-visible absorption properties were studied in methanol and 1:1 (*v/v*) methanol/water solution. A broad peak is observed with maximum wavelength at 399 and 390 nm with molar extinction coefficients of 12700 and 12000 cm^{-1} mol^{-1} L in methanol and 1:1 (*v/v*) methanol/water, respectively, (Fig. S4-S5). Addition of 25 mM methanesulfonic acid results in maxima at 378 and 386 nm. The hypsochromic shifts of 21 and 4 nm are attributed to the formation of a less stable internal charge transfer (ICT) excited state on protonation of the tertiary amine receptor. [18] Isosbestic points are observed at 390 and 399 nm in methanol and 1:1 (*v/v*) methanol/water, respectively. UV-visible titrations in aqueous methanol in presence of 0.25 mM acid showed no significant change at 390 nm on addition of up to 20 μM Fe^{3+} (Fig. S6).

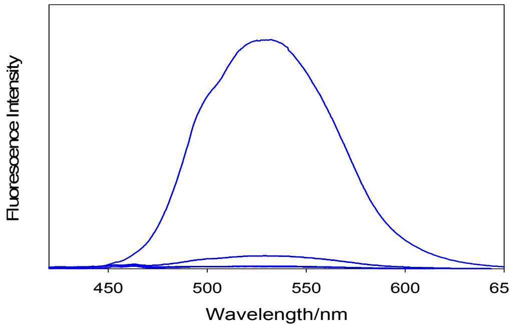


Fig. 2 Fluorescence spectra of 3 μM **1** in 1:1 (*v/v*) methanol/water excited at 399 nm. The concentration of methanesulfonic acid and iron(III) sulfate pentahydrate are 0.2 mM and 10 μM, respectively.

The logic characteristics of **1** were demonstrated in 1:1 methanol/water. In the presence of excess threshold levels of H^+ and Fe^{3+}, the fluorescence is substantially high relative to the other three permutations of input conditions as shown in Fig. 2. In the '*off*' states, the fluorescence output is low due to photoinduced electron transfer (PET) from the ferrocene module and/or ICT from the methylpiperazine to the excited state naphthalimide fluorophore (*vide infra*). The truth table according to AND logic and the relative quantum yields of fluorescence are given in Table 1.

Table 1 Truth Table for the AND Logic Gate **1** in 1:1 $MeOH/H_2O$.[a]

Label	$Input_1$ (H^+)[b]	$Input_2$ (Fe^{3+})[c]	Output Emission (Φ_F)[d]
A	0 (low)	0 (low)	0 (low, 0.0006)
B	1 (high)	0 (low)	0 (low, 0.0064)
C	0 (low)	1 (high)	0 (low, 0.0012)
D	1 (high)	1 (high)	1 (high, 0.086)

[a] 10^{-5} M **1** excited at the isosbestic point of 399 nm. [b] High input level $10^{-4.5}$ mM H^+ add as methanesulfonic acid. Low input level $10^{-8.5}$ mM H^+. [c] High input level 20 μM iron(III) sulfate pentahydrate. Low input level with no iron(III) added. [d] Relative quantum yield measured with reference to 10^{-7} M fluorescein in aerated water ($\Phi_F = 0.91$). Output level high when $\Phi_F > 0.040$.

The driving forces for the potential PET pathways can be predicted from the Weller equation.[19] The deactivation pathways are illustrated in Fig. 3. PET from ferrocene to the excited state fluorophore is highly favorably with a driving force of −1.59 eV (Fig. 3B). Such a negative value suggests the electron transfer occurs in the Marcus inverted region. However, a kinetic barrier due to a repulsive negative field effect must be overcome due to an orbital node on the imide nitrogen atom.[20] PET from the tertiary amine to the excited state naphthalimide is also predicted to be spontaneous with a ΔG_{PET} of −0.89 eV (Fig. 3C). However, it is not PET that is prevented on protonation of the piperazine moiety, but rather a destabilization of the ICT excited state as supported by the UV-visible spectra and structure-activity studies.[18] Electrostatic destabilization of the twisted ICT is strong due to a gauche arrangement in the unprotonated state, and an anti-periplanar geometry in the protonated state. Although the methylpiperazine moiety acts as the H^+ receptor, the fluorescence switching '*on*' is due to a non-emissive twisted ICT excited state.[18]

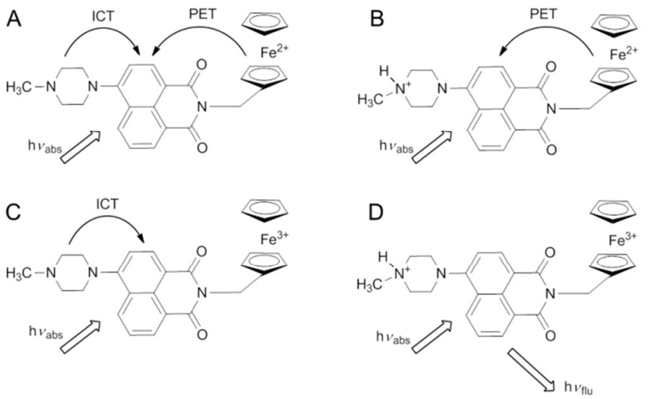


Fig. 3 Pictorial representation of the truth table showing the deactivation pathways and the four states of the AND logic gate **1**. The letter designations match the labelled vials in Fig. 4.

Compared to previous anthracene 'Pourbaix sensors'[8] the resulting quantum yield of fluorescence in the '*on*' state is much improved (Table 1, Label D). The emission output of 0.086 is five times higher than previous prototypes. Admittedly, this output fluorescence is less than the model naphthalimide-methylpiperazine compound.[18,21] A competing PET reaction from the excited naphthalimide to the ferrocenium radical cation with a driving force of −0.22 eV may explain the observed inefficiency. However, it should be possible to design logic gates with different moiety combinations so that even larger fluorescent enhancements may be obtained.

Nonetheless, complete digital switching is achieved as the '*off*' states are virtually colourless and non-fluorescent while the '*on*' state is a bright green fluorescence as shown in Fig. 4 Since the emission output is above 450 nm, there is no significant interference due to inner filter effects in the presence of micromolar concentrations of Fe^{3+} (Fig. S6). Furthermore, because of the longer emission wavelength, singlet energy transfer between the excited state naphthalimide and ferrocene or ferrocenium unit is quite remote since spectral overlap is minimal. The superior performance of **1** is at least partly due to the novel arrangement of modules with the fluorophore flanked on both sides by the proton receptor and redox unit.

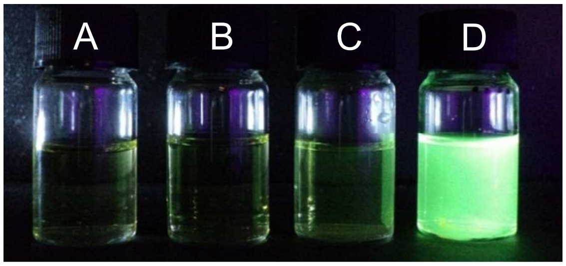


Fig. 4 Solutions of 10^{-5} M AND logic gate **1** in 1:1 (*v/v*) methanol/water in the presence of (A) no inputs (B) 0.2 mM CH_3SO_3H (C) 20 μM $Fe(SO_4)_3$ (D) 0.2 mM CH_3SO_3H and 20 μM $Fe(SO_4)_3$. Vials are irradiated with a handheld UV lamp at 365 nm in a dark cabinet. The labels correspond to those in Table 1 and Fig. 3.

Fluorescence titrations were carried out in 1:1 (*v/v*) methanol/water solution by titrating **1** with one input as the titrant whilst the other input was set above the threshold concentration. An increase in the acid concentration in the presence of 20 μM Fe^{3+} results in a sigmoidal-shaped fluorescence profile between pH 5.5-7.5 (Fig. S7-S8). A log β_{H+} of 6.6 was obtained using the equation $\log[(I_{max}–I)/(I–I_{min})] = –\log[H^+] + \log \beta_{H+}$ adopted for fluorimetric analysis[22] by monitoring the maximum emission at 525 nm (Fig. S9). This result is consistent with other naphthalimide-methylpiperazine model probes.[18,21] Similarly the apparent log $\beta_{Fe^{3+}}$ in the presence of acid is 5.1 (Fig. S10-12) corresponding to a Fe^{3+} concentration of 7.9 μM, which is typical of blood iron serum levels.[16] These values are significant to living cells as low intracompartmental pH in vesicles plays a key role in the activity of enzymes – such as ferric ion release from transferrin at pH 5.5.[23] Furthermore, many blood disorders are the result of abnormally high iron levels (iron overload).[16]

In conclusion, we have designed and synthesised a novel optoelectronic molecular device with an unexploited 'receptor–spacer–fluorophore–spacer–redox-unit' format. Molecule **1** is the first example of a 'Pourbaix sensor' for redox potential and pH based on a combination of PET and ICT mechanisms.[24] Protonation of the methylpiperazine and oxidation of the ferrocene moieties yields a respectable 13-fold fluorescence enhancement in mixed aqueous methanol. This latest prototype exhibits a number of key advantageous properties including water solubility, a longer emissive wavelength, a higher quantum yield of fluorescence and an enhanced switching ratio compared to existing prototypes. These recent results suggest the prospect of using 'Pourbaix sensors' in applications ranging from molecular biosensing to environmental diagnostics and corrosion science is promising.[δ]

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Notes and references

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δ A patent application has been filed. For further information contact the Knowledge Transfer Office of the University of Malta at knowledgetransfer@um.edu.mt

†Electronic Supplementary Information (ESI) available: [synthesis and characterisation data] are available free of charge via the internet at See DOI: 10.1039/c000000x/

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