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A sodium-enabled 'Pourbaix sensor': a three-input AND logic gate as a 'lab-on-a-molecule' for monitoring Na^+ , pH and pE^\dagger

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A novel supramolecular three-input AND logic gate is demonstrated as a 'lab-on-a-molecule' for monitoring the Na^+ , pH and pE levels in solution by communicating a fluorescence signal. The fluorescence signal is modulated by three photoinduced electron transfer reactions that are controlled by an unprecedented combination of two cation binding events and one redox reaction.

Molecular logic-based computation is now an established research discipline.^{1–4} Over the past two decades, an assortment of molecular and supramolecular logic gates^{5–11} and more complex logic gate arrays have been successfully demonstrated.^{12–14} These stimuli-responsive (supra)molecular systems perform information processing using chemical, electrical and/or optical signals.¹⁵ The primary motivation behind the use of molecules for computing strategies is the vision that one day we may advance beyond silicon-based technology resulting in computers of unprecedented small size and performance. Our interest is in the development of new concepts and applications using molecules with computing ability.

Recently we defined a new class of molecular logic gates for simultaneously monitoring the proton concentration (pH) and the oxidizability of a solution (pE).¹⁶ Based on a photoinduced electron transfer (PET) mechanism, we demonstrated chemosensors that operate as two-input AND logic gates driven by chemical (protons) and electrical (redox potential) inputs and a fluorescence output.¹⁷ As examples of optoelectronic molecular logic gates,^{18–21} they incorporate the important relationship between the potential and proton concentration as recognised long ago by Marcel Pourbaix and are applied nowadays to corrosion science, mining and geochemistry.²²

In this communication, we report a sodium-enabled²³ 'Pourbaix sensor'¹⁶ as a 'lab-on-a-molecule'²⁴ for monitoring the threshold concentrations of protons, sodium and iron(III)

ions by communication of a fluorescence signal. This rare example of a three-input AND logic gate monitors the physicochemical properties of saltiness, pH and pE.^{1,25} Moreover, there are only a few other examples of molecules that have been described as a 'lab-on-a-molecule'.^{26–29} In most of these reported examples, the strategy employed involves a multi-tasking molecule with one receptor monitored by various analytical techniques under varying conditions.

We now demonstrate molecule **1**, shown in Fig. 1, which detects the unprecedented combination of three biologically and environmentally relevant chemical species, Na^+ and H^+ and Fe^{3+} , in solution simultaneously. Sodium and protons have a long history as inputs in molecular logic gates, dating back to the first two-input AND logic gate.³⁰ The same cannot be said of Fe^{3+} . Iron(III) is known to be an efficient quencher of excited state fluorophores, hence the development of turn-on fluorescent chemosensors for this species has been challenging.³¹ We circumvent the issue by treating Fe^{3+} as an oxidant rather than an analyte. The result is that fluorescence signal modulation is controlled by three PET reactions regulated by an unprecedented

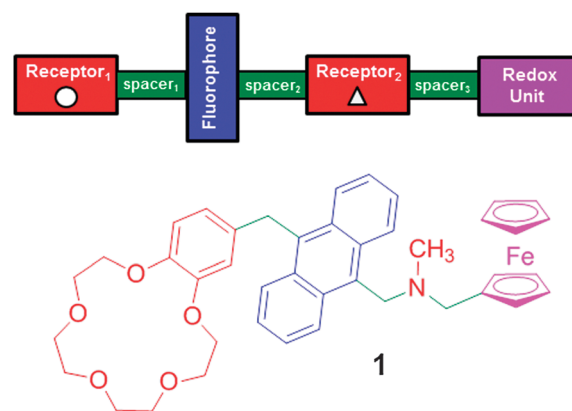


Fig. 1 The colour-coded design concept (top) and the corresponding molecular structure (bottom) of the three-input AND logic gate **1** for Na^+ (receptor₁), pH (receptor₂) and pE (redox unit).

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combination of two cation binding processes and one redox process. Furthermore, **1** is a rare example of a molecular logic gate that incorporates three different types of chemical equilibria: complexation, acid–base dissociation and redox equilibria.³²

Numerous sources in the scientific literature report that tumor cells have characteristically high Na^+ and H^+ concentration levels.³³ The intracellular vacuoles of tumor cells typically have an acidic pH below 5 and intracellular Na^+ levels up to three times higher than in normal tissue.³⁴ High concentration levels of protons and labile redox-active iron have also been attributed to various forms of cancer including colorectal and liver cancer.³⁵

The logic gate **1** was synthesised by reductive amination of 4-(10-aminomethylanthracen-9-ylmethyl)benzo-15-crown-5 ether²⁴ and ferrocenecarboxaldehyde with sodium triacetoxyborohydride.³⁶ The product was purified by column chromatography on silica gel using a gradient mixture of CH_2Cl_2 –MeOH to yield an orange crystalline solid. The compound was characterised using standard techniques including NMR spectroscopy and mass spectrometry as detailed in the ESI.†

The logic gate **1** is constructed in a modular receptor₁–spacer₁–fluorophore–spacer₂–receptor₂–spacer₃–redox donor format according to established principles of PET sensors (Fig. 1).³⁷ The design format allows the receptor and redox units to function independently, and yet allows all components to work in parallel as a collective molecular device. An enhanced fluorescence output is observed upon oxidation with Fe^{3+} , protonation with methanesulfonic acid, and complexation with sodium ions. The molecule monitors the proton concentration and the redox environment in solution in addition to the sodium levels. Upon binding of Na^+ to the crown ether, and H^+ to the tertiary amine, and oxidation of the ferrocenyl moiety, an enhanced fluorescence output is observed.

The fluorescence output in methanol under the eight experimental conditions is shown in Fig. 2. Table 1 summarises the eight experimental conditions including the input concentrations and the quantum yield outputs. The high concentration

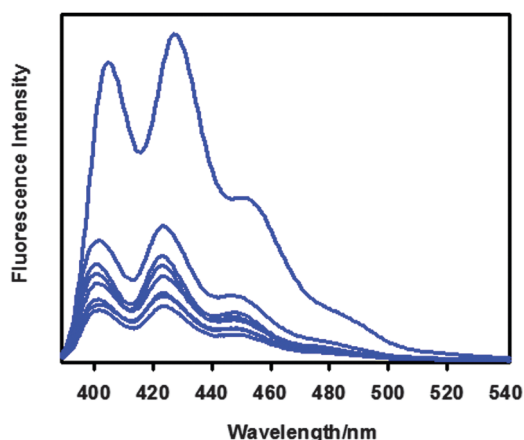


Fig. 2 Fluorescence spectra of 10^{-5} M **1** in methanol excited at 359 nm under eight experimental conditions as detailed in Table 1. A significant fluorescence output is observed when Na^+ , H^+ and Fe^{3+} levels are above threshold concentration levels.

Table 1 Truth table for the 3-input AND logic gate in methanol

Input ₁ (Na^+) ^a	Input ₂ (H^+) ^b	Input ₃ (Fe^{3+}) ^c	Output emission (Φ_F) ^d
0 (low)	0 (low)	0 (low)	0 (low, 0.012)
1 (high)	0 (low)	0 (low)	0 (low, 0.021)
0 (low)	1 (high)	0 (low)	0 (low, 0.014)
0 (low)	0 (low)	1 (high)	0 (low, 0.014)
1 (high)	0 (low)	1 (high)	0 (low, 0.019)
0 (low)	1 (high)	1 (high)	0 (low, 0.018)
1 (high)	1 (high)	0 (low)	0 (low, 0.029)
1 (high)	1 (high)	1 (high)	1 (high, 0.072)

^a High input level is 10 mM sodium methanesulfonate. Low input level with no added sodium salt. ^b High input level is 1.0 mM protons added as methanesulfonic acid. Low input level with aqueous tetrabutylammonium hydroxide. ^c High input level is 0.10 mM iron(III) sulfate pentahydrate. Low input level with no added iron(III) salt. ^d Output is considered high when $\Phi_F > 0.036$. Φ_F is obtained by comparison with anthracene in ethanol ($\Phi_F = 0.27$).³⁸ Φ_F uncertainty from triplicate measurements is $\pm 10\%$.

levels of Na^+ , H^+ and Fe^{3+} are the minimum amounts of each input required for a maximum fluorescence signal. A low concentration level of only one of the three inputs is sufficient to render a low fluorescence output. This is due to PET from either the benzo-15-crown-5 ether, or the tertiary amine, or the ferrocene to the excited state anthracene.

The free energy for PET in all three cases is estimated to be thermodynamically feasible with values of -0.10 V, -0.25 V and -0.95 V, for the benzo-15-crown-5 ether, tertiary amine and ferrocene, respectively.^{39,40} However, complexation of the crown ether with Na^+ , protonation of the tertiary amine by H^+ , and oxidation of the ferrocene unit by Fe^{3+} arrests all three PET pathways resulting in an enhanced fluorescent output. At least a three-fold fluorescence enhancement is observed, as shown in Fig. 2, when all three input levels are high in comparison to the presence of threshold concentrations of just one of the inputs.

The binding constants for Na^+ and H^+ were obtained from sigmoidal-shaped plots according to the Henderson–Hasselbalch equation in the form $\log[(I_{\text{max}} - I)/(I - I_{\text{min}})] = -\log[M] + \log \beta_{\text{M}}^+$.⁴¹ Titration experiments for the cations were performed in the presence of excess threshold concentrations of the other two inputs. A $\log \beta_{\text{Na}^+}$ of 3.1 was observed for the benzo-15-crown-5 ether, in agreement with earlier two-input AND logic gate models, while the measured $\log \beta_{\text{H}^+}$ of 2.8 is lower than reported.⁴² The apparent $\log \beta_{\text{Fe}^{3+}}$ of 4.9 is within the range we previously reported.¹⁶

For real-life application, water solubility is a desired trait. Anthracene-based logic gates with a tertiary ammonium group have a pK_a of 7.8.⁴³ Hence, the molecular device will be switched ‘on’ at acidic pH values. The benzo-15-crown-5 ether has a weak Na^+ binding constant of -0.3 in water,⁴³ which is ideal for measuring the salinity of seawater with a typical concentration of about 0.6 M. Blood medical diagnostics use for Na^+ would require a stronger binding receptor such as *N*-(2-methoxyphenyl)aza-15-crown-5 ether.⁴⁴ As for Fe^{3+} , it should be noted that **1** responds based on its oxidising potential. In principle another oxidant with a sufficiently high redox potential should give an identical output.

In conclusion, molecule **1** is the first example of a fluorescent molecular logic gate that combines two cation binding processes and one redox event in a single molecule. The detection of Na^+ , H^+ and Fe^{3+} could in principle be a diagnostic strategy for screening various cancers since tumor cells are thought to have elevated concentration levels of all three inputs.⁴⁵ Detection of this same trio of cations could perhaps also serve as an early warning method for corrosion of steel and other ferrous metals. Rust formation in automobiles, for example, is a common problem, particularly near sea waterfronts and in cold climates where a salt is routinely used for de-icing snowy roadways. Contrary to examples of 'lab-on-a-molecule' systems that rely on using an array of instrument-based detection methods,^{26–29} the clever engineering of molecules based on a single optical readout allows for 'in-the-field' analysis whether inside a living cell or in a blood sample. We envision that the concept of a 'lab-on-a-molecule' demonstrated here could find a host of useful applications from environmental and industrial analysis to intelligent medical diagnostics.^{1,46}

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Notes and references

- 1 A. P. de Silva, *Molecular Logic-based Computation*, The Royal Society of Chemistry, Cambridge, UK, 2013.
- 2 K. Szacilowski, *Infochemistry*, Wiley-VCH, Chichester, UK, 2012.
- 3 *Molecular and Supramolecular Information Processing: From Molecular Switches to Logic Systems*, ed. E. Katz, Wiley-VCH Verlag, Weinheim, Germany, 2012.
- 4 *Biomolecular Information Processing: From Logic Systems to Smart Sensors and Actuators*, ed. E. Katz, Wiley-VCH Verlag, Weinheim, Germany, 2012.
- 5 E. Katz and V. Privman, *Chem. Soc. Rev.*, 2010, **39**, 1835.
- 6 J. Andréasson and U. Pischel, *Chem. Soc. Rev.*, 2010, **39**, 174.
- 7 H. Tian, *Angew. Chem., Int. Ed.*, 2010, **49**, 4710.
- 8 U. Pischel, *Aust. J. Chem.*, 2010, **63**, 148.
- 9 K. Szacilowski, *Chem. Rev.*, 2008, **108**, 3481.
- 10 V. Balzani, M. Venturi and A. Credi, *Molecular Devices and Machines—Concepts and Perspectives for the Nanoworld*, Wiley-VCH, Weinheim, 2nd edn, 2008.
- 11 A. Credi, *Angew. Chem., Int. Ed.*, 2007, **46**, 5472.
- 12 A. P. de Silva and S. Uchiyama, *Nat. Nanotechnol.*, 2007, **2**, 399.
- 13 A. P. de Silva, *Chem.-Asian J.*, 2011, **6**, 750.
- 14 G. de Ruiter and M. E. van der Boom, *Acc. Chem. Res.*, 2011, **44**, 563.
- 15 V. Balzani, A. Credi and M. Venturi, *Chem.-Eur. J.*, 2008, **14**, 26.
- 16 T. J. Farrugia and D. C. Magri, *New J. Chem.*, 2013, **37**, 148.
- 17 D. C. Magri, *New J. Chem.*, 2009, **33**, 457.
- 18 P. Audebert and F. Miomandre, *Chem. Sci.*, 2013, **4**, 575.
- 19 D. Canevet, M. Sallé, G. Zhang, D. Zhang and D. Zhu, *Chem. Commun.*, 2009, 2245.
- 20 U. Resch-Genger and G. Hennrich, *Top. Fluoresc. Spectrosc.*, 2005, **9**, 189.
- 21 L. Fabbri and A. Poggi, *Chem. Soc. Rev.*, 1995, **24**, 197.
- 22 M. Pourbaix, *Atlas of Electrochemical Equilibria in Aqueous Solutions*, Pergamon Press, Oxford, UK, 1966.
- 23 S. A. de Silva, B. Amorelli, D. C. Isidor, K. C. Loo, K. E. Crooker and Y. E. Pena, *Chem. Commun.*, 2002, 1360.
- 24 D. C. Magri, G. J. Brown, G. D. McClean and A. P. de Silva, *J. Am. Chem. Soc.*, 2006, **128**, 4950.
- 25 Examples of three-input AND logic gates: (a) O. A. Bozdemir, R. Guliyev, O. Buyukcakil, S. Selcuk, S. Kolenen, G. Gulseren, T. Nalbantoglu, H. Boyaci and E. U. Akkaya, *J. Am. Chem. Soc.*, 2010, **132**, 8029; (b) S. Ozlem and E. U. Akkaya, *J. Am. Chem. Soc.*, 2009, **131**, 48; (c) D. C. Magri, G. D. Coen, R. L. Boyd and A. P. de Silva, *Anal. Chim. Acta*, 2006, **568**, 156; (d) X. Guo, D. Zhang and D. Zhu, *Adv. Mater.*, 2004, **16**, 125; (e) A. P. de Silva, G. D. McClean and S. Pagliari, *Chem. Commun.*, 2003, 2010.
- 26 M. Schmitt and S. Qinghai, *Chem. Commun.*, 2012, **48**, 2707.
- 27 Q. Shu, L. Birlenbach and M. Schmitt, *Inorg. Chem.*, 2012, **51**, 13123.
- 28 M. Schmitt and H.-W. Lin, *Angew. Chem., Int. Ed.*, 2007, **46**, 893.
- 29 F. Otón, M. C. González, A. Espinosa, C. R. de Arellano, A. Tárraga and P. Molina, *J. Org. Chem.*, 2012, **77**, 10083.
- 30 A. P. de Silva, H. Q. N. Gunaratne and C. P. McCoy, *Nature*, 1993, **364**, 42.
- 31 S. K. Sahoo, D. Sharma, R. K. Bera, G. Crisponi and J. F. Callan, *Chem. Soc. Rev.*, 2012, **41**, 7195.
- 32 P. R. Ashton, V. Baldoni, V. Balzani, A. Credi, H. D. A. Hoffmann, M.-V. Martínez-Díaz, F. M. Raymo, J. F. Stoddart and M. Venturi, *Chem.-Eur. J.*, 2001, **7**, 3482.
- 33 P. Montcourrier, P. H. Mangeat, C. Valembois, G. Salazar, A. Sahuquet, C. Duperray and H. Rochefort, *J. Cell Sci.*, 1994, **107**, 2381.
- 34 I. L. Cameron, N. K. R. Smith, T. B. Pool and R. L. Sparks, *Cancer Res.*, 1980, **40**, 1493.
- 35 X. Huang, *Mutat. Res.*, 2003, **533**, 153.
- 36 A. F. Abdel-Magid, K. G. Carson, B. D. Harris, C. A. Maryanoff and R. D. Shah, *J. Org. Chem.*, 1996, **61**, 3849.
- 37 A. P. de Silva, T. P. Vance, M. E. S. West and G. D. Wright, *Org. Biomol. Chem.*, 2008, **6**, 2468.
- 38 W. R. Dawson and M. W. Windsor, *J. Phys. Chem.*, 1968, **72**, 3251.
- 39 A. Weller, *Pure Appl. Chem.*, 1968, **16**, 115. The driving forces for PET are calculated from $\Delta G_{\text{PET}} = E_{\text{OX}} - E_{\text{RED}} - E_{\text{S}} - e^2/\epsilon r$ where E_{OX} is the oxidation potential of ferrocene (0.45 V), tertiary amine (1.15 V) and benzo-15-crown-5 ether (1.30 V), E_{RED} is the reduction potential of anthracene (−1.90 V), E_{S} is the excited state singlet energy of anthracene (3.20 V) and $e^2/\epsilon r$ is the coulombic term (0.10 V). Potentials are versus SCE.
- 40 S. Fery-Forgues and B. Delavaux-Nicot, *J. Photochem. Photobiol., A*, 2000, **132**, 137. Energy transfer is also a competitive deactivation pathway due to partial spectral overlap between the emission spectrum of anthracene and the absorption spectrum of the ferrocenium radical cation.
- 41 R. A. Bissell, E. Calle, A. P. de Silva, S. A. de Silva, H. Q. N. Gunaratne, J.-L. Habib-Jiwan, S. L. A. Peiris, R. A. D. D. Rupasinghe, T. K. S. D. Samarasinghe, K. R. A. S. Sandanayake and J.-P. Soumillion, *J. Chem. Soc., Perkin Trans. 2*, 1992, 1559.
- 42 A. P. de Silva, H. Q. N. Gunaratne and C. P. McCoy, *J. Am. Chem. Soc.*, 1997, **119**, 7891.
- 43 D. C. Magri and A. P. de Silva, *New J. Chem.*, 2010, **34**, 476.
- 44 J. K. Tusa and H. He, *J. Mater. Chem.*, 2005, **15**, 2640.
- 45 <http://www.brighterdayfoods.com/PDFDocs/q/Q9XEQCKXX2R49KJUSH9EGHRGCA9K8X34.PDF>.
- 46 T. Konry and D. R. Walt, *J. Am. Chem. Soc.*, 2009, **131**, 13232.