DOI: 10.1002/ejoc.200500617

Multiple Logical Access with a Single Fluorophore–Spacer–Receptor System: Realization of Inhibit (INH) Logic Function

Sandip Banthia[a] and Anunay Samanta*[a]

Keywords: Fluorescence spectroscopy / Molecular recognition / Sensor / Molecular electronics / Solid-state structures

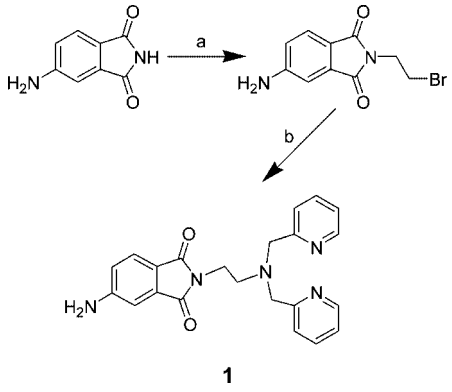
A new fluorescent PET sensor (**1**) has been synthesized, the fluorescence of which switches "On" with a blue-to-green color change in the presence of Zn^{2+}, Cd^{2+}, or Pb^{2+} (OR logic). X-ray structure analyses of **1** and its Zn^{2+} complex reveal that the solid-state conformation is in accordance with the results observed in solution. Sensor **1** also acts as an "Off-On-Off" switch stimulated by protons. The H^+-driven "Off-On-Off" switch is integrated with a Zn^{2+}-, Cd^{2+}-, or Pb^{2+}-induced OR logic gate to construct a first INH logic gate employing these ionic inputs.

Introduction

Considering the growing interest in molecules capable of performing logic operations,[1–4] special attention needs to be focused on the importance of heavy and transition metal (HTM) ions in such devices serving as molecular switches.[5,6] Another area of interest is the detection of HTM ions at the molecular level. This has practical applications as these metal ions represent an environmental concern when present in uncontrollable amounts and at the same time some of them such as iron, zinc, copper and cobalt are present as essential elements in biological systems. Herein we present a versatile system (**1**) that not only acts as a chelation-enhanced fluorescent sensor[7,8] for Zn^{2+}, Cd^{2+}, or Pb^{2+} ions[9–14] but, more importantly, can be switched to OR, "Off-On-Off", and Inhibit (INH) logic behavior by simply varying the combination and levels of ionic inputs. While photonic OR logic function is easy to achieve and therefore well-documented,[15,16] molecules behaving as an "Off-On-Off" switch are rare.[17–19] The INH function is even scarcer[20–23] and so far no molecular system acting as an INH logic gate employing HTM ions has been demonstrated. Moreover, most of them are restricted to one or specific logic operations. Thus, we present a unique system performing multiple logic functions, some of which being not very common.

Results and Discussion

Compound **1** has been prepared in two steps as illustrated in Scheme 1. The first step consisted of the preparation of the 2-bromoethyl derivative of 4-aminophthalimide, according to a published procedure,[24] which was then refluxed with bis(2-picolyl)amine (DPA) in acetonitrile to obtain the desired product after purification by column chromatography.



Scheme 1. Synthetic route to **1**; conditions: (a) NaH, DMF, 1,2-dibromoethane, room temp., 24 h; (b) bis(2-picolyl)amine (DPA), acetonitrile, reflux, 24 h.

The 4-aminophthalimide moiety in this system gives rise to an intramolecular charge transfer (ICT) transition in the UV/Vis region due to the push-pull effect of the electron-donating amino and the electron-withdrawing carbonyl groups of the fluorophore. Addition of metal ions to a solution of **1** leads to a bathochromic shift of the absorption maximum (see Supporting Information). An isosbestic point was observed upon progressive addition of Zn^{2+}, Cd^{2+}, or Pb^{2+} salts, indicating the presence of only two species at equilibrium. The fluorescence quantum yield of **1** in THF was measured to be 0.08 with an ICT band at 454 nm (Table 1). A lower fluorescence quantum yield of **1** as compared to that of the parent fluorophore [Φ_f(4-aminophthalimide) = 0.70 in THF][25] is attributable to the photoin-

[a] School of Chemistry, University of Hyderabad, Hyderabad 500046, India
Supporting information for this article is available on the WWW under http://www.eurjoc.org or from the author.

duced electron transfer (PET) between the receptor and the fluorophore moieties.

Table 1. Absorption and fluorescence properties of **1**.[a]

Input[b]	λ_{abs} [nm][c]	λ_{flu} [nm][c]	Φ_f(FE)[d]	K[e]
None	367	454	0.08 (1)	–
H^+	375	517	0.70,[f] 0.18,[g] 0.02[h]	–
Zn^{2+}	375	487	0.61 (7.6)	1.7×10^6
Cd^{2+}	375	484	0.70 (8.7)	1.5×10^6
Pb^{2+}	374	468	0.62 (7.8)	2.2×10^5
Ni^{2+}	370	467	0.03 (0.34)	–[i]
Cu^{2+}	372	482	0.03 (0.35)	–[i]

[a] Alkali and alkaline earth metal ions did not result into any response from **1**; 2×10^{-5} M **1** in THF. [b] Perchloric acid and hydrated perchlorate salts of the metals were used. [c] ±2 nm. [d] For metal ion input, samples were excited at the isosbestic point and at 365 nm for H^+; ±10%. [e] Binding constants were evaluated from the analysis of the absorbance-ion concentration profiles. [f] $[H^+] = 10^{-5}$ M. [g] $[H^+] = 10^{-3}$ M. [h] $[H^+] = 10^{-1}$ M. [i] Binding constant could not be measured accurately.

A YES logic operation can be seen with metal ions such as Zn^{2+}, Cd^{2+}, or Pb^{2+} as input and the fluorescence as an output. Typical changes in the fluorescence spectra of **1** upon subsequent addition of these metal ions in THF are depicted in Figure 1. The fluorescence enhancement (FE) is attributed to the suppression of PET due to the guest–receptor interaction.

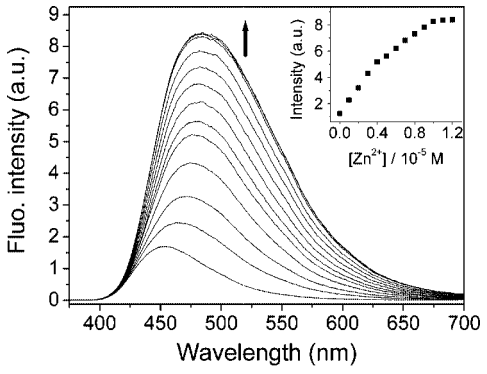


Figure 1. Fluorescence spectra of **1** in THF upon progressive addition of Zn^{2+} ions. [**1**] = 2×10^{-5} M, $[Zn^{2+}]$ = 0–1.2×10^{-5} M with increments of 1×10^{-6} M. Inset: fluorescence intensity at 480 nm vs. concentration of Zn^{2+} ions.

While alkali and alkaline earth metal ions such as Na^+, K^+, Mg^{2+}, and Ca^{2+} do not result in any significant response from **1**, transition metal ions such as Cu^{2+}, Ni^{2+} etc. quench the fluorescence of the system (see Supporting Information). Thus, **1** is an efficient fluorescent sensor able to discriminate post-transition metal ions from other 3d, alkali and alkaline earth metal ions. Further discrimination between Pb^{2+} and Zn^{2+} or Cd^{2+} can be achieved on the basis of Stokes shift of the emission maximum of **1** in the presence of these metal ions. While Zn^{2+} and Cd^{2+} show a 33 nm and a 30 nm shift of the emission maximum, respectively, only a 14 nm shift is observed in the presence of Pb^{2+}. It should be noted that the color of the fluorescence output signal is green. Thus, the input ions result in a bright fluorescence output with a color change from blue to green (a Stokes shift of 33 nm is observed).

The fluorescence enhancement (FE) caused by Zn^{2+}, Cd^{2+}, or Pb^{2+} ions are very similar with a maximum difference by a factor of 1.1 (Table 1). The metal ion concentrations required for the maximum FE are also not very different. Indeed, equal amounts of Zn^{2+} and Cd^{2+} are needed. The near-identical response for similar input levels has important implications for the use of the present system as a two-input photonic OR logic system (Figure 2) as this constitutes a good-quality truth table. However, there are still important and practical issues that need to be addressed before the realization of a pragmatic molecular device. The independence of the fluorescence output on the nature of the input ions requires that the fluorescence switching is due to ion-induced conformational changes of flexible systems[26,27] rather than due to mere proximity of the ions,[28] which has been the sole design basis in most of the systems. Furthermore, more advanced practical integration of such molecular-level logic gates into circuits is still desired. Therefore, in order to establish the potential of the present molecule for performing logic operations even when incorporated into a more advanced system, we have carried out single-crystal X-ray structure analyses for **1** and its Zn^{2+} complex.

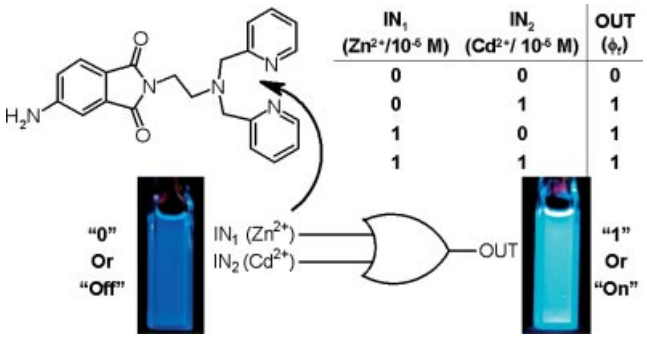


Figure 2. Structure of the molecule and preferred site of interaction with the metal ions. Truth table for the input-output relationships for Zn^{2+} and Cd^{2+} inputs. Equivalent logic circuit for the two-input OR gate with the visual fluorescence effect.

The molecular structures of **1** and its Zn^{2+} complex are shown in Figure 3. Coordination of Zn^{2+} with **1** results in an increased separation of the receptor and fluorophore moieties (from N2–N3 = 2.93 Å in the unbound state to 3.77 Å in the bound state) along with a twisting of the amine lone electron pair ca. 75° away from the π-electrons of the fluorophore. These structural changes suggest that complexation of **1** with the metal ion makes the lone pair of the nitrogen atom unavailable for a PET quenching pathway. This also provides direct evidence that PET between the receptor and the fluorophore moieties is mediated through space. An important aspect to be noted is that the fluorescence quantum yield of the structurally characterized Zn^{2+} complex of **1** is measured to be equal to that observed upon addition of Zn^{2+} salt to the solution of **1** in THF. Thus, interference of residual protons from the hydration

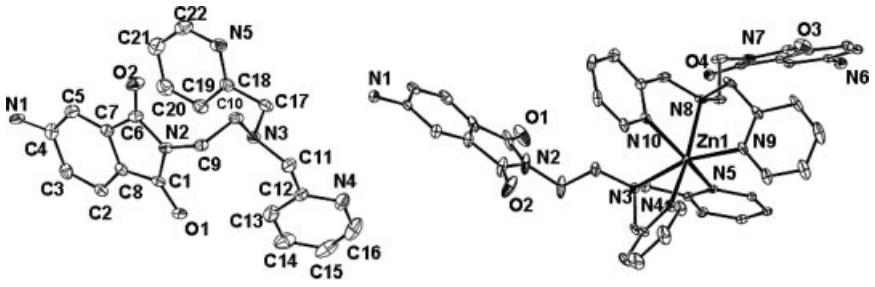
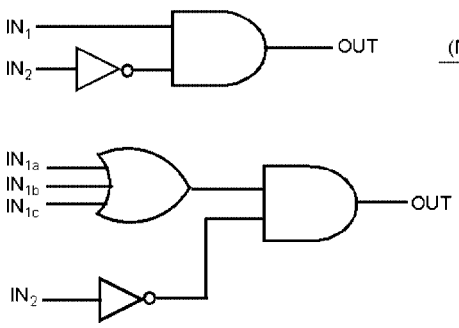


Figure 3. X-ray structure of **1** and its Zn^{2+} complex with atoms represented by thermal ellipsoids at 30% and 10% probability level, respectively. Hydrogen atoms are not shown for clarity and for the same reason the solvent of crystallization and counter anions in the structure of the Zn^{2+} complex of **1** have been omitted.



IN_1 ($M^{2+}/10^{-5}$ M)	IN_2 ($H^+/10^{-3}$ M)	OUT (ϕ_f)
0	0	0
0	1	0
1	0	1
1	1	0

Figure 4. Logic circuit for a fundamental two-input, one-output INH gate. Corresponding truth table. Equivalent four-input, one-output molecular switch: IN_{1a}, IN_{1b} and IN_{1c} correspond to Zn^{2+}, Cd^{2+} and Pb^{2+} and IN_2 corresponds to H^+.

shell of the metal salts, which is a matter of concern in signaling studies, is also completely ruled out.

Another important feature of **1** is its fluorescence response in the presence of protons. Sensor **1** behaves as a typical YES logic up to a certain input level of $[H^+]$ (10^{-5} M). This is due to inhibition of PET upon protonation of the receptor moiety. At high $[H^+]$ (10^{-3} M), quenching of the fluorescence of **1** occurs leading back to the "off" mode.[29] Thus, **1** acts as an "Off-On-Off" switch driven by protons. Interestingly, when we chose a very high $[H^+]$ (10^{-1} M), **1** becomes an H^+ -driven NOT switch (see Supporting Information). When we look across the whole range of H^+ concentrations (Table 1), **1** clearly shows a maximum fluorescence emission at $[H^+] = 10^{-5}$ M. The fluorescence retreats to the original at $[H^+] = 10^{-3}$ M and falls further at $[H^+] = 10^{-1}$ M. An H^+-driven "off-on-off" fluorescent switch leading to a YES and PASS 0 logic by using different input levels of protons is scarcely documented.[18,19] By employing an ICT fluorophore with an amino group as donor, we not only developed a system with lesser excitation energy and output in the visible region but also cross over the YES and PASS 0 logic to achieve a NOT logic. What causes the fall of fluorescence of **1** at high H^+ concentration values? At very high proton concentration, the 4-amino group of the fluorophore is protonated, thereby inhibiting the ICT transition and the system acts as a non-fluorescent molecule. This also enables us to construct an Inhibit (INH) logic gate, which is commonly not encountered.[20–23] An INH logic gate can be interpreted as a particular integration of an AND and a NOT logic gate, where the output signal is inhibited by one of the active inputs.[30] The fluorescence of **1** is "switched on" *only* in the presence of Zn^{2+}, Cd^{2+}, or Pb^{2+} ions and absence of excess protons. Under other circumstances, such as the absence of metal ions, the presence of H^+ ($>10^{-3}$ M), no fluorescence is observed. This behavior can be ascribed to an INH logic function. The corresponding truth table and the logic gate for the INH function is illustrated in Figure 4.

Thus, a fundamental two-input INH action can be seen for **1** with Zn^{2+}, Cd^{2+}, or Pb^{2+} as $input_1$ and H^+ as $input_2$ and fluorescence as an output. This can be comprehended into a more complex multi-input integrated INH logic gate in which an AND logic provides the output by integrating an OR gate and a NOT gate (Figure 4).

Conclusions

In summary, we have developed a simple molecular system such as **1**, which provides access to multiple logic functions and hence, is unique in some sense as most of the current molecular devices are restricted to one or specific logic operations. System **1** is also the first demonstrated example of an INH logic gate employing HTM ions and H^+ as inputs.

Experimental Section

Synthesis of 1: Compound **1** was prepared in two steps. The first step consisted of the preparation of the 2-bromoethyl derivative of 4-aminophthalimide (AP) according to a published procedure.[24] In the second step, bis(2-picolyl)amine (0.45 mL, 2.5 mmol) and 2-

bromoethyl-4-aminophthalimide (0.269 g, 1 mmol) were taken up in acetonitrile (50 mL) and the reaction mixture was refluxed for 24 h. Subsequently, the solvent was evaporated under vacuum and the residue was purified by column chromatography (neutral alumina; hexane/ethyl acetate). Yield 0.27 g (70%). $C_{22}H_{21}N_5O_2$ (387.44): calcd. C 68.22, H 5.43, N 18.09; found C 68.19, H 5.31, N 17.82. LCMS: *m*/*z* (%) = 388 (100) $[M + 1]^+$. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 2.83 (t, 2 H), 3.81 (t, 2 H), 3.87(s, 4 H), 4.37 (s, 2 H), 6.87 (dd, 1 H), 7.03 (d, 1 H), 7.10 (m, 2 H), 7.39 (m, 2 H), 7.46 (m, 2 H), 7.59 (d, 1 H), 8.47 (d, 2 H) ppm.

X-ray Crystallographic Data. 1: $C_{22}H_{21}N_5O_2$, M = 387.44; monoclinic, space group $P2_1/n$; cell dimensions a = 7.433(3), b = 23.390(10), c = 11.264(5) Å, β = 96.226(7)°, V = 1946.7(14) Å^3, Z = 4, $\rho_{calcd.}$ = 1.322 g cm^3, μ(Mo-K_α radiation) = 0.088 mm^{-1}, λ = 0.71073 Å, T = 100 K. Reflections collected: 21715 (CCD area detector diffractometer), 4619 unique, 283 parameters refined using 2851 reflections with $I > 2\sigma(I)$ to final R indices: $R1$ = 0.0801, $wR2$ = 0.1754, GOF = 1.125. **Zn·1:** $C_{44}H_{42}N_{10}O_4Zn{\cdot}2(ClO_4){\cdot}CH_3CN$, M = 1080.20; triclinic, space group $P\bar{1}$; cell dimensions a = 10.4430(7), b = 12.1265(9), c = 21.2097(15) Å, α = 75.385(1), β = 99.02(2), γ = 65.995(1)°, V = 2370.0(3) Å^3, Z = 2, $\rho_{calcd.}$ = 1.514 g cm^{-3}, μ (Mo-K_α radiation) = 0.707 mm^{-1}, λ = 0.71073 Å, T = 100 K. Reflections collected: 27920 (CCD area detector diffractometer), 11107 unique, 680 parameters refined using 5729 reflections with $I > 2\sigma(I)$ to final R indices: $R1$ = 0.0909, $wR2$ = 0.2450, GOF = 1.030. Hydrogen atoms attached to the amine nitrogen atom were introduced as found on the Fourier difference maps and refined with restraint N–H = 0.87 Å and displacement parameter equal to 1.5 times that of the parent atom. All other hydrogen atoms were introduced geometrically and refined using a riding model. All non-hydrogen atoms were refined anisotropically. During the refinement process of **1**, a disorder of position was observed for the NH_2 group, which was split over two distinct sites, C3 and C4, with occupancy factor of 0.5 each. One hydrogen atom therefore could not be introduced at the C3 site. During the refinement process of Zn·**1**, a disorder of position was observed for one perchlorate group, two of the terminal oxygen atoms were split over two distinct sites with occupancy factor of 0.5 each. CCDC-268266 (Zn·**1**) and -268267 (**1**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information Available (see footnote on the first page of this article): Absorption and fluorescence spectra in the presence of metal ions and protons, representative plot for the determination of the binding constant.

Acknowledgments

The authors thank Prof. S. Pal for his help and suggestions in solving the crystal structure of the compounds. This work was supported by the Department of Science and Technology (DST), Government of India; Council of Scientific and Industrial Research (CSIR) and UPE Program of the University Grants Commission (UGC). S. B. thanks CSIR for a fellowship.

[1] A. P. de Silva, N. D. McClenaghan, *Chem. Eur. J.* **2004**, *10*, 574.
[2] V. Balzani, M. Venturi, A. Credi, *Molecular Devices and Machines*, Wiley-VCH, Weinheim **2003**.
[3] F. M. Raymo, *Adv. Mater.* **2002**, *14*, 401.
[4] A. P. de Silva, N. D. McClenaghan, C. P. McCoy, *Molecular Switches*, Wiley-VCH, Weinheim, **2000**.
[5] P. D. Beer, P. A. Gale, G. Z. Cheng, *Coord. Chem. Rev.* **1999**, *185–186*, 3.
[6] L. Fabbrizzi, M. Lichelli, P. Pallavicini, *Acc. Chem. Res.* **1999**, *32*, 846.
[7] J. P. Desvergene, A. W. Czarnik, *NATO ASI Series*, Kluwer Academic, Dordrecht, **1997**, vol. C492.
[8] A. P. de Silva, H. Q. N. Gunaratne, T. Gunnlaugsson, A. J. M. Huxley, C. P. McCoy, J. T. Rademacher, T. E. Rice, *Chem. Rev.* **1997**, *97*, 1515.
[9] S. C. Burdette, C. J. Frederickson, W. Bu, S. J. Lippard, *J. Am. Chem. Soc.* **2003**, *125*, 1778.
[10] C.-T. Chen, W.-P. Huang, *J. Am. Chem. Soc.* **2002**, *124*, 6246.
[11] T. Hirano, K. Kikuchi, Y. Urano, T. Higuchi, T. Nagano, *Angew. Chem. Int. Ed.* **2000**, *39*, 1052.
[12] R. B. Thompson, B. P. Maliwal, C. A. Fierke, *Anal. Chem.* **1998**, *70*, 1749.
[13] G. K. Walkup, B. Imperiali, *J. Org. Chem.* **1998**, *63*, 6727.
[14] A. W. Czarnik, *Acc. Chem. Res.* **1994**, *27*, 302.
[15] P. Ghosh, P. K. Bharadwaj, J. Roy, S. Ghosh, *J. Am. Chem. Soc.* **1997**, *119*, 11903.
[16] A. P. de Silva, H. Q. N. Gunaratne, G. E. M. Maguire, *Chem. Commun.* **1994**, 1213.
[17] L. Fabbrizzi, M. Licchelli, A. Poggi, A. Taglietti, *Eur. J. Inorg. Chem.* **1999**, 35.
[18] S. A. de Silva, A. Zaveleta, D. E. Baron, O. Allam, E. V. Isidor, N. Kashimura, J. M. Percarpio, *Tetrahedron Lett.* **1997**, *38*, 2237.
[19] A. P. de Silva, H. Q. N. Gunaratne, C. P. McCoy, *Chem. Commun.* **1996**, 2399.
[20] J.-M. Montenegro, E. Perez-Inestrosa, D. Collado, Y. Vida, R. Suau, *Org. Lett.* **2004**, *6*, 2353.
[21] T. Gunnlaugsson, D. A. Mac Donail, D. Parker, *Chem. Commun.* **2000**, 93.
[22] A. P. de Silva, I. M. Dixon, H. Q. N. Gunaratne, T. Gunnlaugsson, P. R. S. Maxwell, T. E. Rice, *J. Am. Chem. Soc.* **1999**, *121*, 1393.
[23] T. Gunnlaugsson, D. A. Mac Donaill, D. Parker, *J. Am. Chem. Soc.* **2001**, *123*, 12866.
[24] S. Banthia, A. Samanta, *J. Phys. Chem. B* **2002**, *106*, 5572.
[25] T. Soujanya, R. W. Fessenden, A. Samanta, *J. Phys. Chem.* **1996**, *100*, 3507.
[26] S. A. McFarland, N. S. Finney, *J. Am. Chem. Soc.* **2002**, *124*, 1178.
[27] N. B. Sankaran, S. Banthia, A. Das, A. Samanta, *New J. Chem.* **2002**, *26*, 1529.
[28] A. P. de Silva, H. Q. N. Gunaratne, C. P. McCoy, *Nature* **1993**, *364*, 42.
[29] The pK_a values for the protonation equilibria of the tertiary amine and the pyridine moiety are 7.5 and 4.4, respectively; see ref.[18]
[30] The INH function, A Λ B′, should not be confused with the NAND function, (A Λ B)′.

Received: August 14, 2005
Published Online: October 13, 2005

