DOI: 10.1002/anie.200700879

Molecules That Make Decisions[**]

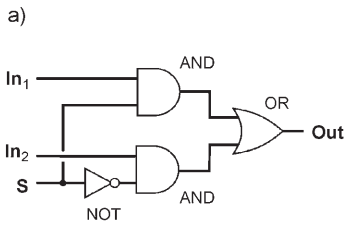
Alberto Credi[*]

Keywords:
binary logic · luminescence · molecular devices · photochemistry · supramolecular chemistry

The realization of computers with very small size, low power consumption, and computing performance that may be hard to reach with silicon-based technology[1] is a strong motivation for the search for information-processing strategies based on molecules. The rational basis for this research stems from the fact that in living organisms information is transported, elaborated, and stored by molecular or ionic substrates.[2] Although the components of a molecular computer will not necessarily have to operate analogously to microelectronic circuits,[3] several efforts have been devoted to the design, synthesis, and characterization of chemical systems that mimic the operation of semiconductor logic gates.[4–15]

As molecular switches convert input stimulations into output signals,[16] the principles of binary (Boolean) logic[17] can be applied to the signal transduction operated by molecules under appropriate conditions.[18] Implementation of the most common Boolean functions (PASS, YES, NOT, AND, NAND, OR, NOR, XOR, XNOR, and INH) with chemical systems is now possible.[4–15,18] A critical issue of molecular logic gates is the interconnection of basic elements to create complex circuits. In contrast, electronic logic gates can be easily interconnected, owing to full input/output homogeneity. However, rather than relying on extensive physical connection of elementary gates, the construction of molecular logic networks can take advantage of functional integration and reconfiguration within a single molecule, which can be achieved by rational chemical design.[4a,19] The fact that a relatively simple, commercially available dye molecule in aqueous solution can perform both the full-adder and full-subtractor functions—which in silicon-based systems require circuits made of five interconnected gates—is a demonstration of this idea.[11c] Recent reports on the first molecular versions of a digital multiplexer[20] and of a keypad access device[21] have taken molecular logic one step further.

A digital multiplexer is a combinational circuit (that is, a circuit whose output value is determined solely by the current values of the inputs) that selects binary information from one of the input channels and directs it to a single output channel.[17] Its function is analogous to that of a mechanical rotary switch that connects any one of several possible inputs to an output. A multiplexer possesses 2^n inputs, one output, and n control channels whose bit combinations determine which one among the different input states is transferred to the output. The simplest device of this type is a 2:1 multiplexer, which possesses two data inputs ($\mathbf{In_1}$ and $\mathbf{In_2}$) and one control input (**S**). Its logic circuit and truth table (that is, a table listing all the possible input/output combinations) are shown in Figure 1a and b, respectively.



b)

In$_1$	In$_2$	S	Out
0	0	0	0
1	0	0	0
0	1	0	1
1	1	0	1
0	0	1	0
1	0	1	1
0	1	1	0
1	1	1	1

Figure 1. a) Combinational logic circuit and b) truth table of a 2:1 digital multiplexer.

Compound **1** (Figure 2a),[22] which comprises a tetraarylporphyrin (P) moiety linked to dihydropyrene (DHP) and dihydroindolizine (DHI) photochromic units, was shown to perform as a 2:1 digital multiplexer in 2-methyltetrahydrofuran.[20] Key to the design of such a system is ensuring both the ability to photoisomerize the two photochromes independently and reversibly,[23] and the ability for each of the photochromes to quench the porphyrin singlet excited state via distinct pathways by electron-transfer processes. Because each photochrome can exist in two forms, **1** may assume any of four isomeric structures, three of which are relevant for multiplexer operation (Figure 2). The two data inputs $\mathbf{In_1}$ and $\mathbf{In_2}$ are represented by heat and red light, respectively, the control input **S** is coded for by green light, and the porphyrin fluorescence (monitored at 720 nm) provides the output signal. The starting state is set as the thermally stable DHP-P-DHI form. When the control input **S** is not applied and the two inputs are off, the molecule remains in the DHP-P-DHI form, which is not fluorescent because of photoinduced electron transfer from the DHP moiety to the porphyrin unit.

---

[*] Prof. A. Credi
Dipartimento di Chimica "G. Ciamician"
Università di Bologna
via Selmi 2, 40126 Bologna (Italy)
Fax: (+39) 051-209-9456
E-mail: alberto.credi@unibo.it

[**] The author thanks V. Balzani, A.P. de Silva, and M. Venturi for useful discussions. Financial support from Università di Bologna (Progetto Strategico CompReNDe) is gratefully acknowledged.

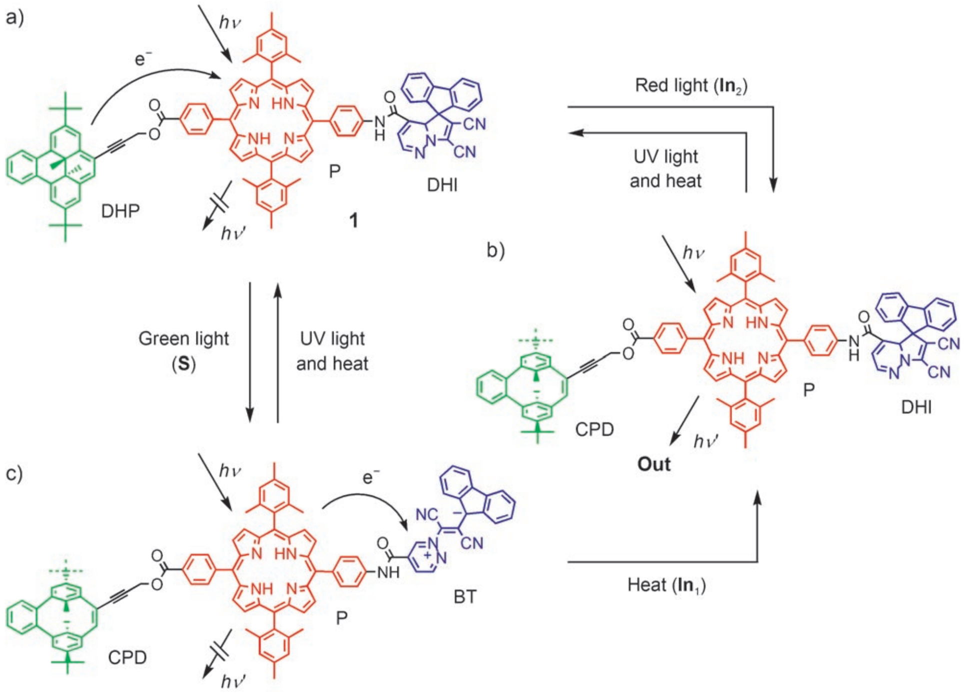


Figure 2. Interconversion of the three isomeric forms of compound **1** (15 μM in 2-methyltetrahydrofuran) that are relevant for its operation as a 2:1 digital multiplexer under the action of heat and light inputs: a) DHP-P-DHI, b) CPD-P-DHI, and c) CPD-P-BT. See text for details.

Switching on $\mathbf{In}_1$ (heat) has no effect, because the system is already in its thermally stable form. Alternatively, switching on $\mathbf{In}_2$ (red light) results in photoisomerization of the DHP unit to the open cyclophanediene (CPD) form, yielding CPD-P-DHI (Figure 2b). The excited state of the porphyrin moiety is no longer quenched, and strong fluorescence is detected, thus, turning the **Out** state to 1. Applying both $\mathbf{In}_1$ and $\mathbf{In}_2$ also leads to a photostationary state containing mainly CPD-P-DHI. Hence, when **S** is 0, the output state mirrors the state of $\mathbf{In}_2$ and ignores that of $\mathbf{In}_1$ (Figure 1b).

Turning on control bit **S** amounts to irradiating the solution of **1** with green light (530 nm). This irradiation leads to a photostationary distribution consisting mainly of CPD-P-BT (Figure 2c), in which the DHI unit has been transformed into the betaine (BT) isomer. If $\mathbf{In}_1$ and $\mathbf{In}_2$ are both 0, the porphyrin emission is quenched by the BT unit, and **Out** is 0. Upon activation of $\mathbf{In}_1$ (heat), without regard to the state of $\mathbf{In}_2$, the molecule is converted into the CPD-P-DHI state (Figure 2b), which displays strong porphyrin fluorescence (**Out** = 1). On the contrary, if only $\mathbf{In}_2$ (red light) is applied, the molecule remains in the CPD-P-BT form, because the photoisomerization of BT to DHI is slow under these conditions, and **Out** remains 0. Therefore, when **S** is set to 1, the output state mirrors the state of $\mathbf{In}_1$ and ignores that of $\mathbf{In}_2$ (Figure 1b). Reset of the molecule to the initial state is accomplished by irradiation at 366 nm, followed by heating.

In principle, operation of **1** at the single-molecule level would be possible, because the switching relies only on intramolecular processes. Single-molecule fluorescence switching in a photochromic compound was observed,[24] indicating that optical output reading of individual molecular multiplexers may be possible. However, the outcome of each excitation event on a single molecule of **1** cannot be predicted with certainty, because the photoinduced processes at the basis of its logic function are not 100% efficient. This uncertainty is an obvious limitation for reliable operation of **1** as a single-molecule logic element. Although the aim of the investigation was not to produce a practical device, the authors discussed some of the factors (for example, fatigue resistance and switching speed) that are expected to be important for real application of this type of system.[20]

Sequential circuits are logic networks whose output depends on both the *current* and *past* values of the inputs.[17] In other words, whereas combinational circuits like adders, subtractors, and multiplexers combine the current input states in some way to produce the output and, hence, have no memory, sequential circuits use the sequence of the input states over time to determine the output. In fact, memory circuits are inherently sequential. In logic design, sequentiality is achieved by introducing feedback loops (that is, the output of a certain logic gate is sent back as one of its inputs or as the input of another upstream gate). This feedback mechanism disrupts the unidirectional information flow that is a fundamental characteristic of combinational circuits. From a chemical point of view, the time variable is put into the game by exploiting the different rates of the processes involved in the gate operation. In chemical terms, one could say that combinational logic can be achieved with molecules by relying on equilibrium states, whereas sequential logic additionally requires the analysis (and possibly the optimization) of the kinetic behavior of the system.

Examples of chemical systems whose properties have been interpreted in terms of sequential logic operation are rare.[23] An important step in this direction is the recent investigation of a molecular species in solution whose fluorescence is switched on only in response to a correct sequence of three input signals.[21] Such a system is reminiscent of an electronic keypad lock, a common security device that can control the opening of a door or a safe. A simplified representation of the corresponding logic circuit is shown in Figure 3. The molecular keypad lock is based on the Fe^{III} complex **2**$^{2+}$ (Figure 4a), which comprises fluorescein (FL) and pyrene (PY) fluorophores connected by a linker that is also a ligand (siderophore) capable of binding ferric ions strongly and selectively.[11a] In ethanol, **2**$^{2+}$ contains the FL moiety in its monoanionic form and probably has a folded structure in which the FL and PY moieties can approach each other. The inputs are coded for by a chelating agent for Fe^{III} (ethylenediaminetetracetic acid (EDTA), **In**$_1$), a basic reactant (sodium acetate, **In**$_2$), and UV radiation (**In**$_3$), whereas the output channel is identified as the FL emission at 525 nm.

In the starting state, the emission of the anionic FL moiety is quenched by the metal ion (Figure 4a). Addition of EDTA extracts the iron ion from the siderophore but also protonates the FL unit, transforming it to the non-emissive neutral state (Figure 4b). Subsequent addition of acetate ions leads to formation of the FL dianion, which is strongly fluorescent (Figure 4c). Alternatively, addition of acetate ions to **2**$^{2+}$ causes the formation of the FL dianion, whose fluorescence is quenched by the still-bound metal ion (Figure 4d). It is clear that inverting the order of the inputs (first base and then EDTA) leads ultimately to the same state, resulting in strong emission at 525 nm (Figure 4c). However, as the extraction of the ferric ion from the siderophore moiety by EDTA is inhibited in a basic environment, a substantial difference in the reaction rate between the two paths (a→b→c and a→d→c) is observed. On the other hand, no photoluminescence can be detected without light excitation: this provides the basis for the third input signal, namely, irradiation at 344 nm.

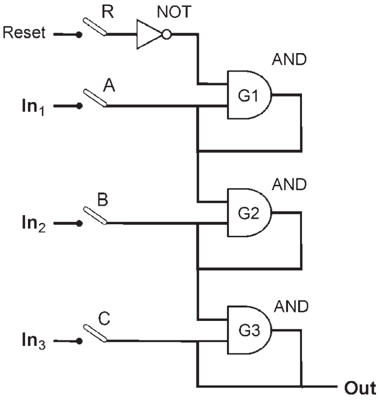


Figure 3. Sequential logic circuit for a device whose output is switched on by three input signals supplied in a defined sequence (**In**$_1$, **In**$_2$, **In**$_3$). The activation of **In**$_1$ by pushing key A locks the output of gate G1 on and enables gate G2. When key B is pressed, **In**$_2$ is activated: the output of gate G2 is locked on, and gate G3 is enabled. Finally, upon activation of **In**$_3$ by pushing key C, the output of gate G3 goes on and **Out** switches to 1. Reset is accomplished by pushing the R key.

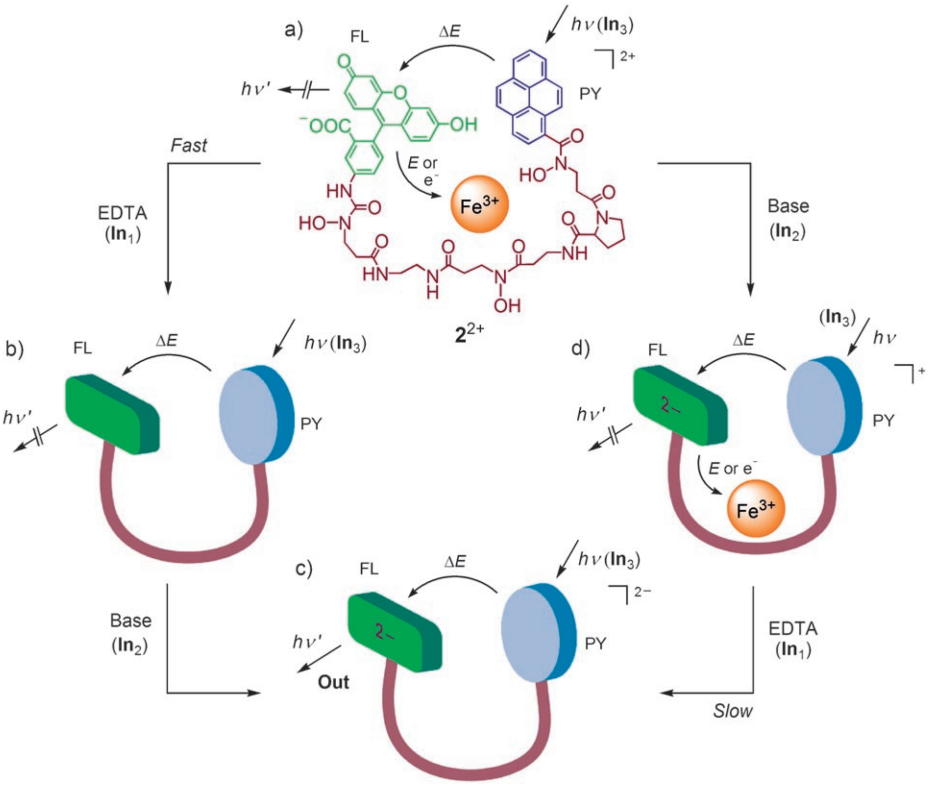


Figure 4. Chemical transformations of a) the Fe^{III} complex **2**$^{2+}$ (0.5 μM in ethanol) to b) the neutral unbound ligand (by the addition of EDTA), c) the dianionic unbound ligand (by the addition of EDTA and base), and d) the Fe^{III} complex of the dianionic ligand (by the addition of base). This molecular device can recognize the correct sequence of three input signals (EDTA, base, and irradiation at 344 nm). See text for details.

Light of this wavelength is mainly absorbed by the PY unit, which then sensitizes the FL luminescence by energy transfer. Therefore, by reading the response of the device not later than a few minutes after activation of the inputs, fluorescence at 525 nm is observed only if the correct sequence of **In**$_1$ (EDTA), **In**$_2$ (base), and then **In**$_3$ (UV excitation) is supplied. Any other input combination leads to weak or no fluorescence.[21]

The development of novel computational architectures constitutes the main scientific driving force for the imitation of Boolean logic functions with molecular systems. Aside from futuristic speculations related to the construction of a chemical computer, recent work has shown that molecular logic gates could lead to practical applications in the not-too-distant future. Molecular devices that control protein folding[25] or release a chemical species[26] by processing chemical inputs according to programmed logic functions have been reported. They can be regarded as precursors of systems operating in vivo that are capable of autonomously diagnosing a disease and effecting a therapy. Moreover, a method based on molecular logic gates for tagging and identifying small objects in a large population has been proposed as a ready-to-use application for combinatorial chemistry.[27]

It should be noted that computing devices based on (supra)molecular species and "soft" matter represent a radically different approach to information processing with respect to computers made from solid-state semiconductors. Therefore, comparisons between these types of systems should be made with care and, for certain aspects, may not make much sense. It seems fair to state, however, that the examples mentioned in the previous paragraph are simple computational tasks that molecules can do and silicon cannot. Certainly, the investigation of "intelligent" molecules capable of elaborating signals introduces new concepts in the field of chemistry and stimulates research in the bottom-up approach to nanodevices.

---

[1] *International Technology Roadmap for Semiconductors (ITRS), 2005 Edition and 2006 Update*, available at http://www.itrs.net (accessed June 2007); see also: S. E. Thompson, S. Parthasarathy, *Mater. Today* **2006**, *9*, 20.

[2] a) D. S. Goodsell, *Bionanotechnology: Lessons from Nature*, Wiley, Hoboken, **2004**; b) R. A. L. Jones, *Soft Machines: Nanotechnology and Life*, Oxford University Press, New York, **2004**.

[3] A. Tullo, *Chem. Eng. News* **2006**, *84*, 22.

[4] a) A. P. de Silva, N. D. McClenaghan, *Chem. Eur. J.* **2004**, *10*, 574; b) A. P. de Silva, Y. Leydet, C. Lincheneau, N. D. McClenaghan, *J. Phys. Condens. Matter* **2006**, *18*, S1847.

[5] D. Gust, T. A. Moore, A. L. Moore, *Chem. Commun.* **2006**, 1169.

[6] a) V. Balzani, A. Credi, M. Venturi, *Molecular Devices and Machines: A Journey into the Nanoworld*, Wiley-VCH, Weinheim, **2003**, chap. 9; b) V. Balzani, A. Credi, M. Venturi, *ChemPhysChem* **2003**, *4*, 49; c) R. Ballardini, P. Ceroni, A. Credi, M. T. Gandolfi, M. Maestri, M. Semeraro, M. Venturi, V. Balzani, *Adv. Funct. Mater.* **2007**, *17*, 740.

[7] K. Szacilowski, *Chem. Eur. J.* **2004**, *10*, 2520.

[8] a) F. M. Raymo, *Adv. Mater.* **2002**, *14*, 401; b) F. M. Raymo, M. Tomasulo, *Chem. Eur. J.* **2006**, *12*, 3186.

[9] F. Remacle, R. Weinkauf, R. D. Levine, *J. Phys. Chem. B* **2006**, *110*, 177.

[10] S. J. Langford, T. Yann, *J. Am. Chem. Soc.* **2003**, *125*, 11198; see also: S. J. Langford, T. Yann, *J. Am. Chem. Soc.* **2003**, *125*, 14951.

[11] a) D. Margulies, G. Melman, C. E. Felder, R. Arad-Yellin, A. Shanzer, *J. Am. Chem. Soc.* **2004**, *126*, 15400; b) D. Margulies, G. Melman, A. Shanzer, *Nat. Mater.* **2005**, *4*, 768; c) D. Margulies, G. Melman, A. Shanzer, *J. Am. Chem. Soc.* **2006**, *128*, 4865.

[12] a) R. Baron, O. Lioubashevski, E. Katz, T. Niazov, I. Willner, *Angew. Chem.* **2006**, *118*, 1602; *Angew. Chem. Int. Ed.* **2006**, *45*, 1572; b) R. Baron, O. Lioubashevski, E. Katz, T. Niazov, I. Willner, *J. Phys. Chem. A* **2006**, *110*, 8548; c) T. Niazov, R. Baron, E. Katz, O. Lioubashevski, I. Willner, *Proc. Natl. Acad. Sci. USA* **2006**, *103*, 17160.

[13] H. Tian, Q.-C. Wang, *Chem. Soc. Rev.* **2006**, *35*, 361.

[14] a) M. N. Stojanovic, T. E. Mitchell, D. Stefanovic, *J. Am. Chem. Soc.* **2002**, *124*, 3555; b) H. Lederman, J. Macdonald, D. Stefanovic, M. N. Stojanovic, *Biochemistry* **2006**, *45*, 1194.

[15] G. Seelig, D. Soloveichnik, D. Y. Zhang, E. Winfree, *Science* **2006**, *314*, 1585.

[16] *Molecular Switches* (Ed.: B. L. Feringa), Wiley-VCH, Weinheim, **2001**.

[17] J. R. Gregg, *Ones and Zeros: Understanding Boolean Algebra, Digital Circuits, and the Logic of Sets*, Wiley, New York, **1998**.

[18] A large number of chemical switches exhibiting interesting properties, from a binary-logic viewpoint, have been reported in the literature. In many cases, the authors were either not aware of such behavior in their systems or published the work before the notion of molecular logic gates became popular. For the first explicit description of the analogy between molecular switches and logic gates, see: A. P. de Silva, H. Q. N. Gunaratne, C. P. McCoy, *Nature* **1993**, *364*, 42.

[19] A. P. de Silva, *Nat. Mater.* **2005**, *4*, 15.

[20] J. Andréasson, S. D. Straight, S. Bandyopadhyay, R. H. Mitchell, T. A. Moore, A. L. Moore, D. Gust, *Angew. Chem.* **2007**, *119*, 976; *Angew. Chem. Int. Ed.* **2007**, *46*, 958.

[21] D. Margulies, C. E. Felder, G. Melman, A. Shanzer, *J. Am. Chem. Soc.* **2007**, *129*, 347.

[22] S. D. Straight, J. Andréasson, G. Kodis, S. Bandyopadhyay, R. H. Mitchell, T. A. Moore, A. L. Moore, D. Gust, *J. Am. Chem. Soc.* **2005**, *127*, 9403.

[23] It is well-known that photochromic compounds exhibit a memory effect. When they are employed in combinational logic systems, suitable experimental conditions (for example, long-enough time scales) need to be chosen to remove this effect. The behavior of photochromes at short time scales can yield sequential logic. See, for example: F. M. Raymo, R. J. Alvarado, S. Giordani, M. E. Cejas, *J. Am. Chem. Soc.* **2003**, *125*, 2361.

[24] T. Fukaminato, T. Sasaki, T. Kawai, N. Tamai, M. Irie, *J. Am. Chem. Soc.* **2004**, *126*, 14843.

[25] S. Muramatsu, K. Kinbara, H. Taguchi, N. Ishii, T. Aida, *J. Am. Chem. Soc.* **2006**, *128*, 3764.

[26] R. J. Amir, M. Popkov, R. A. Lerner, C. F. Barbas III, D. Shabat, *Angew. Chem.* **2005**, *117*, 4452; *Angew. Chem. Int. Ed.* **2005**, *44*, 4378.

[27] a) A. Prasanna de Silva, M. R. James, B. O. F. McKinney, D. A. Pears, S. M. Weir, *Nat. Mater.* **2006**, *5*, 787; b) R. Webb, *Nature* **2006**, *443*, 39.