Molecular logic gates: Recent advances and perspectives

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The capacity and miniaturization of information storage and processing technology are rapidly approaching a limit. Alternative materials and operating principles for the elaboration and communication of data in electronic circuits and optical networks must be identified. Molecular level computing is predicted as the ultimate solution to overcome the present limitation of computing devices in terms of storage capacity and processing speed. Their attractive features are the miniaturized dimensions and the high degree of control on molecular design through chemical synthesis. In recent years a variety of molecules that respond to various chemical inputs have been synthesized and demonstrated as molecular logic gates. This review covers the recent developments and future perspectives of molecular logic gates with particular emphasis on fluorescent organic molecules.

Keywords: Molecular logic, Molecular switches, Logic gates, Boolean logic, Chemical switches, Fluorescence, Fluorophores

Molecular level information processing is a common feature of numerous biological systems. All of the regulatory processes in living cells, cellular signaling, and neurobiological activities need to process information at the molecular level.1 Every biochemical reaction pathway obeys Boolean logic rules at the molecular level in a sense that every single molecule can follow only one reaction path. For example, processes such as molecular recognition in biological systems, activation of enzymes by small molecules and signal transduction are based on YES-NOT logic schemes.2-4 Although, the collective response of the complex chemical or biochemical system is continuous (or, in other words, highly linear) on a macroscopic level, every single step is a discrete process on a molecular level, and its apparent linearity results from a combination (or averaging) of uncountable individual discrete processes of Boolean characters.5

Generally, information processing at the molecular level is based on two different approaches.6 The first one attempts to mimic the operational principles of solid state computers which are presently in use, at the nanometer scale with molecular systems. This approach is based on molecular electronics, in which both input and output signals are electronic in nature. Molecular photonics based on photon fluxes can be of help for this line of research. The second approach, which takes inspiration from information processing in living organism, is based on chemionics,7 in which molecules and ions can be used as input/output signals to process information by using a molecular substrate. Chemionics usually operates in solution and can be complemented by photonics since chemical and light input/output signals can be easily coupled. Within each aspect of molecular electronics, photonics or chemionics, information processing takes place at logic gates and data manipulation relies on the binary digital (bit) nature of these input and output signals that are elaborated by means of the Boolean logic.

When considering molecules to perform Boolean operations, the entire spectrum of input and output data encoding channels is significant8 (Fig 1). Classical electronic devices use electric input/electric output communication, however molecules can perform operations with a combination of various inputs and outputs.

Among the various recording media for high density data storage, organic materials have been
especially attractive in recent years because of their low cost, simplicity, good stimuli responsive properties, and versatility in molecular design. Therefore, they have been suggested as promising candidates for future application development. In principle, the basic requirements for recording materials are that they should possess at least two distinct stable states via an external stimulus, where each state can represent “0” or “1” of a binary digital mode, and the states can be clearly distinguished during read-out. In principle, any chemical system that can exist in two quasi-stable states of different chemical or physical properties may be regarded as a molecular switch (or molecular logic gate), provided there are some physical or chemical stimuli that can (reversibly) change the state of the system. The simplest examples are colorimetric pH indicators and compounds that change color upon change in proton concentration. They function as “YES” or “NOT” logic gates, depending upon the property of the individual indicator and the assignment of input and output channels (e.g., pH values and colors).

There are four possible combinations of input and output values for one-input one-output logic gates (Fig. 2). The PASS 0 and PASS 1 gates yield outputs “0” and “1” respectively, independent of the input value. The YES gate follows the input value to the output. The gate functions as a simple switch, and in fact is very useful for signal amplification, connecting various devices, and signal transduction. The inverter (NOT gate) performs inversion (complementation) of the input data. It changes one logic level into the opposite; for example, logic 0 (also called the low state, cf. Fig. 2) is converted into logic 1 (the high state) and vice versa. NOT is one of the principal Boolean operation, and very often, it is concatenated with multiple input gates.

Apart from these two single input logic gates there are 16 various combinations of input and output signals for two-input logic gates, eight of which are commonly used in electronics (Table 1): basic OR, AND, and XOR, and, gates concatenated with NOT: NOR, NAND, and XNOR. Usually, INHIBIT (INH) and NINH gates are regarded as simple logic gates as well.

Furthermore, as an ideal recording medium, several important performance parameters are required for a memory device which include: (1) chemical stability; (2) film forming properties; (3) storage capacity; (4) transition time (a short transition time between two states is intrinsically indicative of a fast writing); (5) retention ability (the ability to remain in the stored state is necessary for stable and secure recording); and (6) the on-off ratio (a high on-off ratio is crucial for memory devices in order to realize high-resolution and low-error-rate data storage). In addition, low power consumption, ease of fabrication, and competitive cost are also important for practical application.

Table 1 – Truth tables for two input logic gates

<table>
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<tr>
<th>Input</th>
<th>OR</th>
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Fig. 1 – Schematic representation showing possible input and output channels of molecular logic devices.

Fig. 2 – (a) Truth table for single input logic gates. The simplest electric circuits representing the (b) YES and (c) NOT logic gates. Moving the switch turns on the light in the first system (YES gate), but turns it off in the second one (NOT gate).
Chemically Driven Molecular Logic Gates

Chemically driven molecular switches usually comprise three main building blocks, viz., receptor moiety, linker (spacer) and the reporter moiety. Receptor moieties are specially designed binding sites for triggering ions or molecules. They should exhibit desirable selectivity and sensitivity toward selected triggers. The linker, in turn, should provide electronic communication between the receptor and reported moieties. There are three main ways of providing sufficient electronic communication: (i) bridge providing overlap of $\pi$-systems of both moieties, (ii) short $\sigma$-spacer enabling photoinduced electron transfer, or, (iii) arrangement of receptor and reporter, using supramolecular interactions to provide perturbation of electronic structure of the reporter moiety. The reporter moieties in turn should significantly change their photophysical, electrochemical, magnetic, or chemical properties to yield an easily recognizable signal. The most common are the systems where the interaction between the trigger and the receptor results in the change of photophysical properties such as absorption and/or emission characteristics of the reporter moiety. It may also results in changes of the redox potentials, translocation of molecular fragment within the supramolecular assembly (which may be also associated with changes in optical or electrochemical properties as well), chemical reactivity or magnetic properties.

Chemical switches with optical readout are usually based on photophysical phenomena such as photoinduced electron transfer (PET), photoinduced charge transfer (PCT), electronic energy transfer (EET), excimer/exciplex formation and reorganization of electronic structure of transition-metal based chromophores/fluorophores. PET-based luminescent switches can be triggered by various chemical and physical stimuli such as protons, metal cations, anions, neutral organic molecules, and even nanoparticles. Depending on the desired spectral properties and lifetime of the fluorescent switch, the molecular assembly may include various organic (anthracene, pyrene, naphthalimides, pyromellitimide, coumarins, fluoresceins, pyrazolobenzothiazoles, diphenylpyrazoles) or inorganic fluorophores (polypyridine Ru(II) complexes, lanthanide complexes). Selectivity and sensitivity of these systems are controlled by careful design of the receptor part. The large diversity of possible organic ligands enables the design of fluorophores that respond to a variety of inputs suitable for sensing and logic operations.

Even though a large number of reports were published before 1993 based on analyte induced changes in the properties of organic molecules, it was de Silva and coworkers who exploited the use of Boolean operations to define the relationships between chemical inputs and readable outputs. In Nature magazine in the year 1993, they illustrated the use of a simple PET based anthracene fluorophore to define a molecular photonic two input AND gate with chemical inputs such as H$^+$ and Na$^+$ for the first time (Fig. 3).

After this report, a large number of organic fluorophores have been reported which can perform various Boolean operations independently with respect to chemical inputs. Basic Boolean operations AND, OR, XOR, INH, NOR and NAND were demonstrated in molecules with different inputs including chemical, electrochemical, photochemical and enzyme action, etc. A few selected representative examples of molecules which can perform various Boolean operations with respect to chemical inputs are discussed below.

The molecular logic gate responds to various inputs based on PET mechanism. The tricarboxylate receptor part can successfully bind magnesium and calcium ions. This nonselectivity constitutes the basis of OR operation. When metal ions bind to the respective sites, the electronic structure of the molecule rearranges and the fluorescence of the fluorophore is switched on. Similarly, in the case of the monomolecular europium(III) complex, a strong fluorescence was observed within the pH range of 4-7. Deprotonation of the ligand or the amide linker results in a change in the photochemical properties of the complex. Instead of efficient electronic energy transfer from the phenanthroline antenna, an

![Fig. 3 – A molecular photonic AND gate (1) and the corresponding logic diagram.](image-url)
electron transfer occurs and a nonfluorescent Eu(II) complex is formed\textsuperscript{22} (Fig. 4).

Perez-Inestrosa et al.\textsuperscript{23} have reported a modified 1-benzylisoquinoline N-oxide (4) that could perform an INHIBIT logic operation with respect to chemical inputs such as H\textsuperscript{+} and K\textsuperscript{+}. Addition of TFA or alkali metal ions generates the on-off control of the emission at 550 nm in INHIBIT relation (Fig. 5).

Performance of arithmetic operation (addition/subtraction) requires the connection of several basic logic gates.\textsuperscript{18,19} Binary addition of digits can be achieved by a combination of XOR and AND gates, usually called as “half-adders”. On the other hand, a combination of XOR and INHIBIT gates can perform subtraction, known as “half-subtractors”. There are numerous reports for the implementation of binary half-adders and half-subtractors using molecules. Two representative examples are included in the following discussion.

A molecular binary half-adder based on photochromic ligand (5) (Fig. 6) was reported by Zhu et al.\textsuperscript{24} On irradiation with UV light (365 nm), the spiropyran undergoes ring opening, yielding colored merocyanine form ($\lambda_{\text{max}} = 590$ nm). It can further react with Fe\textsuperscript{3+} ions to form a stable complex, characterized by a strong absorption at 430 nm. The ligand (5) reacts also with Fe\textsuperscript{3+} in closed spiropyran form which yields a colored cation radical, characterized by a strong absorption at 500 nm. Absorbance at 430 nm thus corresponds to the AND operation with UV light and Fe\textsuperscript{3+} as inputs, while the absorbance at 550 nm (halfway between merocyanine and spiropyran cation radical) corresponds to the XOR function of the same input data.

Akkaya et al.\textsuperscript{25}, have reported the switching of emission from a BODIPY derived system to define a molecular half-subtractor based on the combined effect of emission modulation by PCT and PET (Fig. 7). Half-subtractor is a combination of XOR and INHIBIT operations. The molecule (6) under deprotonation of the phenolic –OH group displays a quenching in the emission maximum at 660 nm. The quenching in emission is due to a PET process from phenolate unit of (6). Addition of TFA (trifluoroacetic acid) generates a hypsochromic shift in the absorption (~40 nm) and emission bands (~100 nm) of (6). This shift is due to the modulation in ICT emission due to the protonation of the dialkyl amino moiety of (6). The three emission responses generated from (6) allow defining a half-subtractor with respect to the chemical inputs such as acid and base.

**Bipyridine Integrated Fluorophores for Logic Operations**

Bipyridyl derivatives are extensively used as ligands in coordination chemistry on account of their
Fig. 6 – (a) Interconversion network of four states of (5). [SP: Spyorpyran, MC: Merocyanin]. (b) Truth table for half-adder derived from (5). [Reproduced from Ref. 24 with permission from American Chemical Society, Washington DC, USA].

Fig. 7 – (a) Structure of the BODIPY derivative (6). (b) Emission spectrum of (6) in THF in presence of various chemical inputs. Inset shows the truth table for a half-subtractor; outputs are borrow (B) and difference (D). (c) Logic diagram of a half-subtractor. The difference and borrow outputs were collected at two different wavelengths at 660 nm and 565 nm. [Reproduced from Ref. 25 with permission from American Chemical Society, Washington DC, USA].
facile preparation/functionionalization possibilities, and the ability to bind a wide array of d- and f-block elements. Conjugated fluorophores based on a D-π-A-π-D design with 2, 2'-bipyridine as the acceptor core are known to exhibit good photophysical properties owing to the electron deficiency of the pyridine ring and the possibility of enhanced conjugation in the fluorophore backbone by changing from a non-planar to a planar conformation.26-28 There are several reports of bipyridyl-based fluorophores as chemosensors29-32 and logic gates.33-35 In majority of the reported cases, photoinduced electron transfer (PET) has been used for the modulation of the fluorescence emission of molecular logic systems.5,10,17,36,37 Examples of the use of excited-state charge transfer (ESCT) are very few.

Desvergne et al.33, have reported a 2, 2'-bipyridine appended photochromic system (7), which can perform OR logic operation with respect to Hg\(^{2+}\) and Na\(^+\) ions as inputs and fluorescence as the readable output. (Fig. 8).

de Silva and co-workers34 have reported a molecular logic gate based on an anthracene appended bipyridine derivative (3). The cation bound receptor is sufficiently electron deficient and planar so as to allow rapid PET process from the anthracene fluorophore. Therefore, significant quenching of the anthracene emission is observed. A NOR operation was followed with respect to changes in fluorescence from (3) based on the chemical input such as Zn\(^{2+}\) and H\(^+\) (Fig. 9).

In contrast to PET based switches, the PCT (photoinduced charge transfer) systems has several advantages.14,38 In PCT-based molecular switches, the receptor and fluorophore (chromophore) moieties are connected in a way that provides extensive orbital delocalization between two parts, for which one end of the molecule needs to be electron rich and the other electron poor. Upon interaction with a suitable input, the electron distribution may change significantly, thus varying the optical properties of the molecule. In conjugated donor (D)–acceptor (A)-based push/pull systems, excitation leads to the redistribution of electron density and the generation of an excited-state dipole moment. When the receptor responds to an input, the additional charge interacts with the photo-generated dipole, thus modifying the fluorescence...
spectrum. One end of such a molecule needs to be electron rich, and the other side, electron poor. For example, interaction of a charged species to the donor moiety (D) will result in the hypsochromic shift of the spectral properties (absorption/emission bands), while interaction with acceptor moiety (A) results in a bathochromic shift of absorption and emission bands (Fig. 10). Recently, Das and coworkers have demonstrated a half-subtractor based on the emission response from 1-aminopyrene and 2-aminoanthracence moieties. In this case, the intramolecular charge transfer (ICT) generated fluorescence outputs were interrupted and controlled by protonation and deprotonation of the donor moiety (-NH₂ group).

Fig. 10 – Principle of the PCT driven luminescent molecular switch based on the donor-spacer-acceptor architecture. Binding of a cationic trigger to the donor (green) moiety results in the hypsochromic shift of the absorption (emission) band (a), and binding of the same trigger to the acceptor moiety (red) results in a bathochromic shift of the corresponding transition (b). The multi-receptor system may exhibit both bathochromic and hypsochromic shifts upon binding with different trigger ions (c), which results in a multistate molecular switch. [Reproduced from Ref. 14 with permission from American Chemical Society, Washington DC, USA].

We have reported recently a bipyridine based D-A-D system (9) (Fig. 11) which can perform multiple logic operations. The tunable excited-state charge transfer exhibits reversible modulation of its emission response to multiple chemical inputs, thus resulting in different fluorescent signals. The intraligand charge-transfer (ILCT) emission of 9 at 574 nm has been modulated to three emission outputs by using chemical inputs such as Zn²⁺, H⁺ and EDTA. The optical response of 9 could be demonstrated by using a microchannel technique on a filter paper. To visualize the different optical outputs from 9 with respect to various chemical inputs, the microchannel device was illuminated with 365 nm UV light (Fig. 11b). Thus, different logic operations such as AND, INHIBIT, 3 input INHIBIT, IMPLICATION and combination of these logic operations could be achieved.

Fig. 11 – (a) Mechanism of multiple fluorescence expressions through excited-state charge transfer (ESCT) in (9) with respect to Zn²⁺ and H⁺ inputs. b) A paper microchannel fluorescence-response device that uses (9) for the detection of various analytes. The photograph shows the emission outputs of (9) from the four display chambers (DR1-4) and the main reservoir (MR) with respect to the interaction of (9) during the flow of chemical inputs through the open microchannels. “On” and “off” indicates open and closed channels, respectively. DR1: λem = 574 nm, DR2: λem = 488 nm, DR3: no emission, DR4: λem = 464 nm. [Adapted from Ref. 37].
Signal Communication, Write-Read-Erase-Read and All Photonic Gates

The recent promising developments in the field of molecular data processing includes the achievement of communicating signals between gates, method for write-erase heads and the demonstration of all in one photonic logic gate. Zhu et al.\textsuperscript{39} have reported a FRET (fluorescence resonance energy transfer) based multianalyte chemosensor for signal transfer from a combination of logic gates to a switch. The fluorescence intensity of independent fluorophores was able to tune by controlling FRET process between BODIPY and Rhodamine B, with respect to external stimuli such as Ba\textsuperscript{2+} and Hg\textsuperscript{2+} in combination with the isomerization of two states of rhodamines. This could be achieved by attaching both donor (BODIPY) and acceptor (Rhodamine B) in the same calix[4]arene ring. Similarly, a thiacalix[4]arene based chemosensor (11), bearing two pyrene groups showed distinct fluorescence responses with Ag\textsuperscript{+}, Fe\textsuperscript{3+} and cysteine\textsuperscript{40}. The control of monomer and excimer emission with respect to these inputs allows the generation of a reversible and reconfigurable sequence which demonstrates a ‘Write-Read-Erase-Read’ function (Fig. 12c).

![Fig. 12](image)

![Fig. 13](image)
Combination of several photochromes in a single molecule opens the possibility for modulating internal interactions such as energy and electron transfer. Exploring this concept, Gust and coworkers\textsuperscript{41} have recently demonstrated an all-photonic multifunctional logic device. The photonic inputs as well as the output signals were controlled by the isomerization of individual chromophores using light of different wavelengths. This in fact allows a remote control of logic operations from outside. Three photochromes were covalently linked to get a molecular triad (\textsuperscript{12}), consisting of dithienylethene (DTE) and two fulgimides (FG). Using different wavelengths, independent photoisomerization were achieved between open forms \textsuperscript{12} (DTE\textsubscript{o} and FG\textsubscript{o}) and closed forms \textsuperscript{13} (DTE\textsubscript{c} and FG\textsubscript{c}), thus allowing formation of six constitutional isomeric forms (Fig. 13). This in turn allows the system to perform AND, XOR, INH, half adder, half subtractor, multiplexer, demultiplexer, encoder, decoder, keypad lock and reversible transfer gate operations.

**Conclusions and Perspectives**

A survey of the recent literature reveals that a variety of fluorophores have been synthesized and used as either probes for analyte detection or as logic gates. Analyte detection and logic operation are therefore the two sides of the same coin. Depending upon the requirements and nature of the fluorophores, one can use them as chemosensors or molecular switches for logic operations. This area continues to be interesting for chemists and as a result, a large number of new molecules are being synthesized and studied. Even though the initial reports on molecular logic gates have attracted significant interests and enthusiasm among scientists, this research topic is still at the premature stage in terms of a practical application. Nevertheless, it is important to explore the possibilities of developing new molecular entities and the ways and means to integrate them with practical devices. Since biological systems can do information storage and processing at molecular level with high storage capacity and processing speed using DNA genetic code, the days of mimicking such process through artificial systems may not be too far. The necessity for ultra power computing in small space will drive scientists to eventually succeed in achieving the challenge.

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**References**