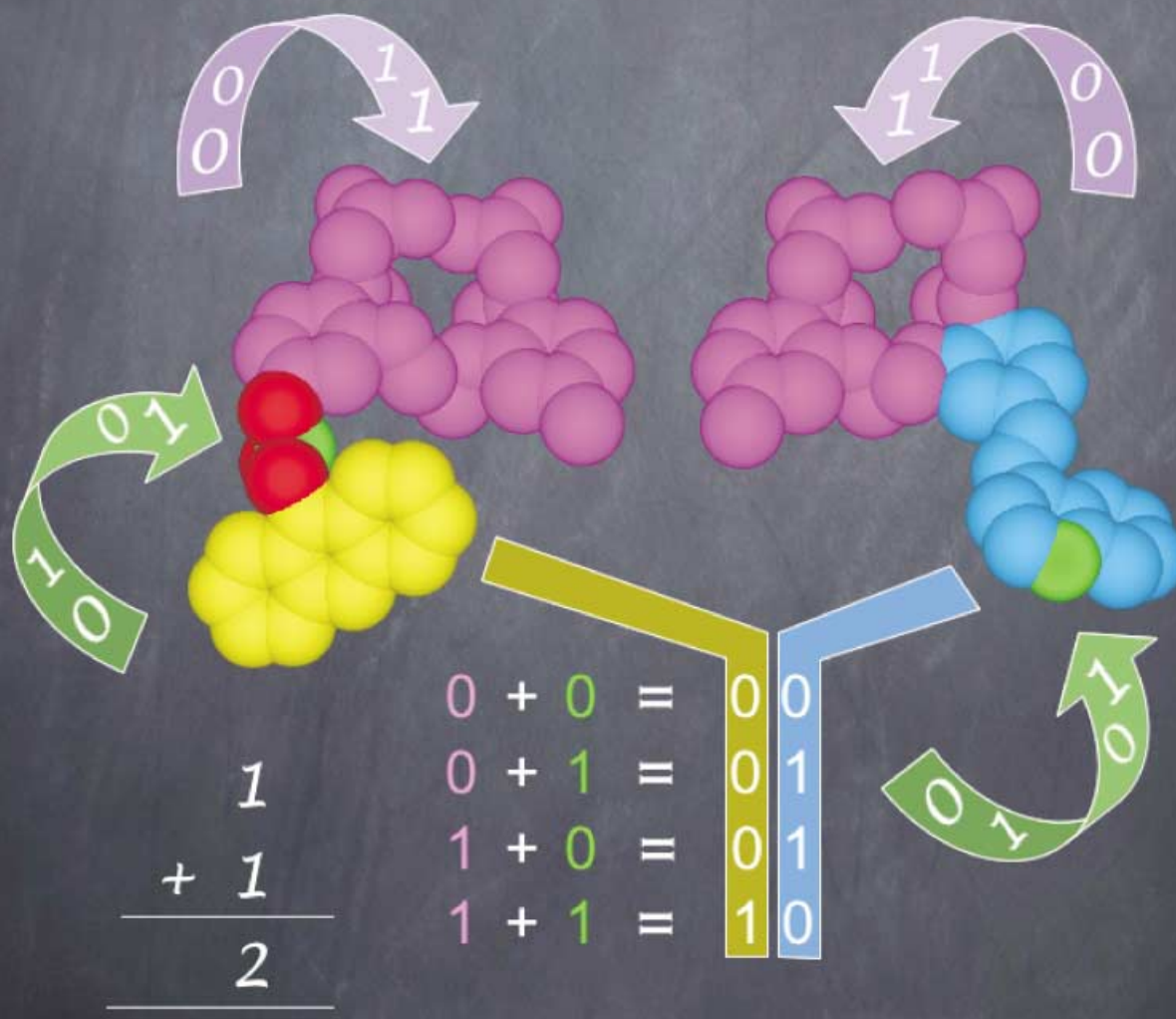
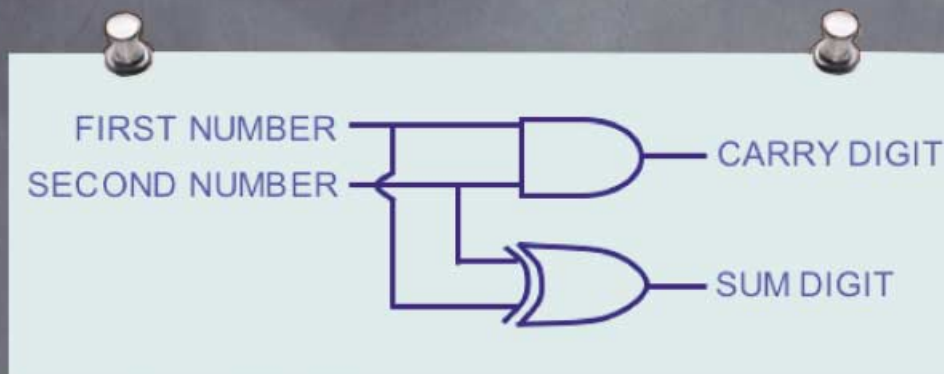


MOLECULAR-SCALE LOGIC GATES



Molecular-Scale Logic Gates

A. Prasanna de Silva*^[a] and Nathan D. McClenaghan*^[b]

Abstract: Currently available approaches to molecular-scale logic gates are summarized and compared. These include: chemically-controlled fluorescent and transmittance-based switches concerned with small molecules, DNA oligonucleotides with fluorescence readout, oligonucleotide reactions with DNA-based catalysts, chemically-gated photochromics, reversibly denaturable proteins, molecular machines with optical and electronic signals, two-photon fluorophores and multichromophoric transient optical switches. The photochemical principles of electron and energy transfer are involved in several of these approaches. More complex molecular logic systems with reconfigurability and superposability provide contrasts with current semiconductor electronics. Integration of simple logic functions to produce more complex ones is also discussed in terms of recent developments.

Keywords: DNA-based logic • fluorescence • logic gates • molecular logic • photochromism • transmittance

Introduction

Our traditional training as chemists usually does not prepare us to face up to one of the crucial technological revolutions from the 20th century—that of information technology (IT). However, now as it contemplates the looming slowdown, the IT industry is entertaining suggestions of how the revolution may be rejuvenated. The slowdown is due to cost issues^[1] as well as fundamental scientific problems arising

when bulk semiconductor features approach dimensions of 100 nm. Among these problems are cross-talk and heat dissipation.

Living things have always processed information for purposes of survival, and more.^[2] Molecular species are the prime movers on this stage. They organize, in a bottom-up fashion, into supramolecular structures that extend up to the cellular level and beyond. The amazing things they do are within and around us all. So it is natural to consider a similar bottom-up approach as a way to brighten the future of the IT industry.^[1,3] In fact, just such an attempt was made during the 1970 s, which in hindsight appears to have been ahead of its time.^[4] However the intervening years have made a re-launch worthwhile and even imperative.

As we will discover below, there is much molecular-scale logic within simple chemical compounds if they are examined from appropriate vantage points.^[5] Such wet chemistry has plenty of inspiration in biology. So on the one hand, the success of wet molecular logic should not be surprising. On the other hand, it should also be natural for such logic devices to find ready application in physiology,^[6] medicine^[7] and biotechnology^[8] as sensors^[9] and diagnostic systems. When such applications target cell interiors, logically enabled molecules leave classical semiconductor devices behind. In such situations size matters, especially when it is small.

Current IT systems revolve around logic gates sculpted from bulk semiconductors that employ electronic (e.g., voltage) input and output signals.^[10] Their reliability is based on the binary digital (bit) nature of these signals, which protects against noise accumulated from serial operations and transmission over distances. Each type of logic gate has a specific input–output signal correlation pattern. These correlation patterns fall into the truth tables arising from George Boole's classic ideas.^[10,11] Importantly, these ideas were available to mathematicians and other interested parties way before electronic computers happened. So current information technology systems are just one manifestation of Boolean logic employing electronic coding of inputs and outputs. Unsurprisingly, the power supplies are also electronic in this manifestation. One critical feature, which contributes to its undoubted success, is input–output signal homogeneity. The same electronic voltage value emerging as output of one logic gate can be admitted as input of another,

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even identical, gate. This voltage can be simply high or low: digital 1 or 0, respectively, in the positive logic convention, whereas the negative logic convention reverses this relationship. We note that the homogeneity has a quantitative as well as a qualitative aspect. Thus huge arrays can be built up by such a connection of logic gates to achieve selected functions of varying complexity. Very large scale integration (VLSI) arose and the IT revolution was well and truly underway.

Our realization that Boolean logic can have photochemical manifestations allowed molecular logic to become practical.^[12,13] The coding or the language of the inputs, outputs and power supplies need not be all-electronic as in the previous paragraph. Just as the diversity of human languages culturally enriches us all, the different coding of a logic gate's external parameters enriches the practical scope of Boolean ideas as applied to molecules. Naturally, these coding schemes will vary in their direct usefulness to the current IT business, especially if the latter wishes for a straightforward swap of molecular components for bulk semiconductor counterparts. However, it is worth noting that each coding scheme will bring with it a set of advantageous features if we can choose appropriate applications for it. Of course, each of these schemes can result in intrinsically interesting and mind-sharpening science.^[5f,g]

The first coding scheme practical for molecule-based logic switches employed light for the power supply, light (of a different colour) for the output and chemical species for the inputs. Even single molecules can be demonstrated to function in this way.^[14] Clearly, input–output homogeneity is not available here, even at the qualitative level. Nevertheless, as we will see in later sections, small-scale integration of logic is achievable with careful design in spite of the short history of the field. On the other hand, a considerable flexibility of molecular logic, in terms of reconfigurability, has already emerged. Additionally, phenomena apparently unavailable to semiconductor electronics, such as superposed logic, have

been discovered. Various combinations of optical, chemical, electrochemical and electronic signals and supplies have subsequently been used to devise coding schemes for molecular logic, some of which will be featured below.

Single-Input Molecular Logic

Textbooks on computers^[10] or logic^[11] remind us of the four possible output patterns arising from a single input. If the input is 0, the output can be 0 or 1 (two choices). If the input is 1, the output can again be 0 or 1 (two choices). Each one of these four output bit patterns corresponds to a logic type: PASS 0, YES, NOT and PASS 1. PASS 0 always outputs 0, whatever the input. PASS 1 always outputs 1. YES obediently follows the input (e.g., output 1 if input is 1). NOT always opposes the input (e.g., output 0 if input is 1).

For instance, a NOT gate with a chemical input, fluorescence light output and excitation light for the power supply is our **1**^[15] (Figure 1). Any case of chemical-induced fluorescence quenching (of which there are hundreds) would have served in its place, testifying to the generality of this approach. Furthermore, the design of **1** is very general as well, allowing the rational generation of new examples.

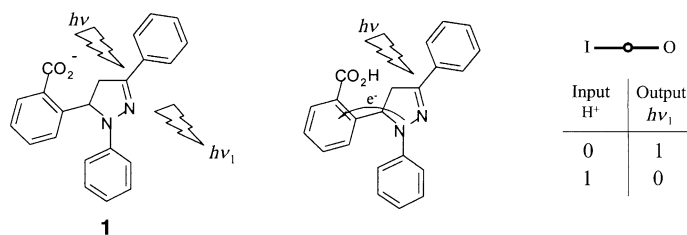


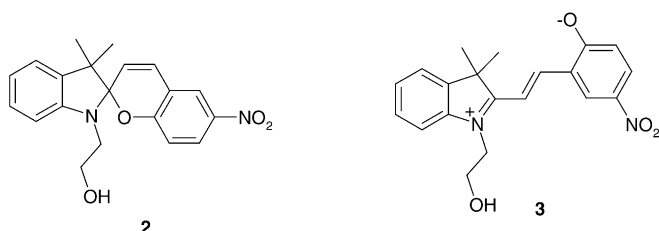
Figure 1. The molecular NOT logic gate **1**: principles of operation and truth table.

Compound **1** contains a fluorophore module (a well-delocalized π -electron system) that receives the excitation light and produces the fluorescence output. It also contains a receptor module (a benzoate) to temporarily bind the input chemical species (H⁺ in this case), provided the latter is available above a threshold level set by the relevant binding constant. These two modules are held together and yet apart by a spacer module composed of several σ -bonds according to the modular “fluorophore–spacer–receptor” format.^[16] The H⁺-induced fluorescence quenching arises as follows. When the H⁺ level is low (input 0), excitation of the fluorophore results in bright fluorescence (output 1) with no substantial photochemistry intervening. However when the H⁺ level is high (input 1), excitation of the fluorophore leads to photochemical intervention and, hence, the fluorescence is quenched (output 0). This intervention is photoinduced electron transfer (PET)^[17–21] from the fluorophore to the protonated benzoate receptor (a rather electron-deficient unit). Of course, PET is the common process underpinning plant photosynthesis, so the generality of the principle is not in doubt. System reset is usually straightfor-

Abstract in French: *Le développement de portes logiques moléculaires fait l'objet de nombreuses approches. Ces dernières qui sont rassemblées et discutées dans le présent article font intervenir entre autres: des interrupteurs chimiquement contrôlés basés sur la fluorescence et/ou la transmittance de petites molécules, des oligonucléotides type ADN à lecture fluorescente, des réactions d'oligonucléotides avec des catalyseurs à base d'ADN, des photochromes à basculement chimique, des protéines dénaturées renversablement, des machines moléculaires à signaux optiques et électroniques, des fluorophores biphotoniques et des interrupteurs multichromophoriques à optique transitoire. Plusieurs de ces approches sont basées sur des processus photochimiques de transfert d'électron et d'énergie. Le fonctionnement de certains systèmes logiques moléculaires plus complexes, reconfigurables et superposables est en contraste avec celui des semi-conducteurs électroniques actuels. Le recours à des fonctions logiques élémentaires pour générer des fonctions plus complexes est également discuté en termes de développements récents.*

ward in small molecules, since thermal back electron transfer is rapid.^[22] Of course, operational reset requires the re-adjustment of the chemical input level as well.

A different example of a NOT logic gate with a light input and transmittance light (of a different wavelength) output is Raymo's **2**.^[23] The light input in this case must be a substantial dose sufficient to photochemically convert **2** into its isomer **3** so that the latter is optically detectable. Compounds **2** and **3** have very different absorption bands so that



the latter can be detected by transmittance of the monitoring light close to its absorption band maximum. Thus ultraviolet irradiation (input 1) of **2** produces **3** so that the transmittance of the monitoring visible light is reduced to a low level (output 0). Again, many classes of photochromic compounds (each containing dozens of examples)^[24,25] are available for exploitation in this way. System reset is quite elegantly achieved by thermal and/or separate photonic stimuli. It is worth noting that some of the computing possibilities of photochromic molecules were mentioned in Hirshberg's classic paper of 1956.^[26]

NOT logic can also be achieved with chemical inputs and outputs, for example, **4**.^[27] Fluorescence and photophysical processes of electronic-energy transfer (EET)^[19–21] are still needed for the readout. Stojanovic and colleagues designed **4** as a DNA-based catalyst, analogous to Cech's ribozymes,^[28] for the hydrolysis of the DNA-type oligonucleo-

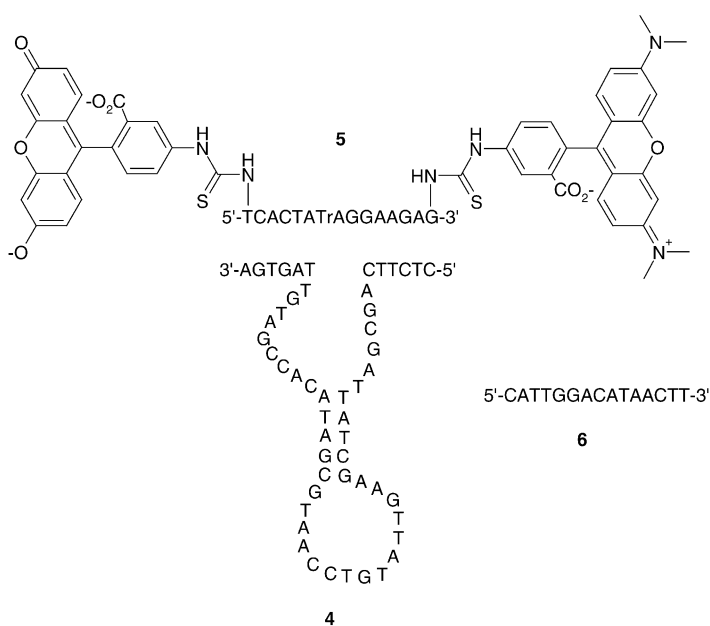
tide substrate **5** which carries a single ribonucleotide (rA) as the cleavage site. Like other DNA-based catalysts, **4** folds into a stem-loop configuration. In the absence of a chosen oligonucleotide **6** (input 0), the stem-loop form of **4** uses its terminal sequences to hybridize with the substrate; this leads to hydrolysis of the latter. This separates the EET donor fluorophore F (a fluorescein derivative) from the EET acceptor fluorophore R (of the rhodamine family). Thus the fluorescence of F shines brightly (output 1). Addition of **6** (input 1) hybridizes with the loop segment of **4** and destroys the catalytic stem-loop configuration. So the substrate **5** survives, with its EET process sucking out the fluorescence potential of F (output 0). System reset requires chemical manipulation, but qualitative input–output homogeneity is nicely available by careful design.^[27] Of course, such hydrolysis reactions take time, from minutes to hours. Some other DNA-based computing schemes take time too, but parallel processing can more than compensate.^[29–30]

Another way of achieving molecular NOT logic is through the all-electronic route as demonstrated by Avouris' team. A single bundle (not a single molecule) of single-walled carbon nanotubes is doped differentially in adjoining regions such that two complementary field effect transistors are created. This, when laid on appropriate metallic contacts (1 μm^2 in area), becomes a NOT logic gate.^[31] It is notable that the spatial saving obtained by employing a molecular device has to be repaid when metallic contacts are used. Nevertheless, such dry molecular gates are more attractive to the current IT industry, since they can substitute for the appropriate semiconductor device without any major change in the infrastructure, especially on the factory floor.

This is an appropriate point to mention the earlier attempt at molecular electronics in the 1970 s, which searched for single molecular equivalents of wires, resistors, capacitors, diodes, transistors and logic gates but without success.^[4] A lot of research investment has finally yielded molecular versions of some of these in recent years, even though single molecule versions remain rare.^[32–36] Some groups of diode-like rotaxane molecules (perhaps a thousand) can be conventionally wired (i.e., with metal conductors) into gates^[37a] in an electronics textbook manner.^[10] Heath, Stoddart and their co-workers find that such gate arrays are irreversibly reconfigured by destroying individual gates (vide infra). These are 1 μm^2 or more in area owing mainly to the metal connectors and electrodes. Interestingly, the same team considers related devices based on [2]catenanes as unimportant for logic purposes.^[37b]

Multiple-Input Molecular Logic

When the number of inputs is increased from 1 to 2, arguments similar to those described in the previous section show the possible number of logic types will rise to 16.^[11] One of these, AND logic, gives an output of 1 only if both inputs are held at 1 each. A molecular-scale example of this, our **7**^[38a] (Figure 2) and its predecessor,^[12] which used a different arrangement of the constituent modules, are designed through the elaboration of the modular “fluorophore–spa-



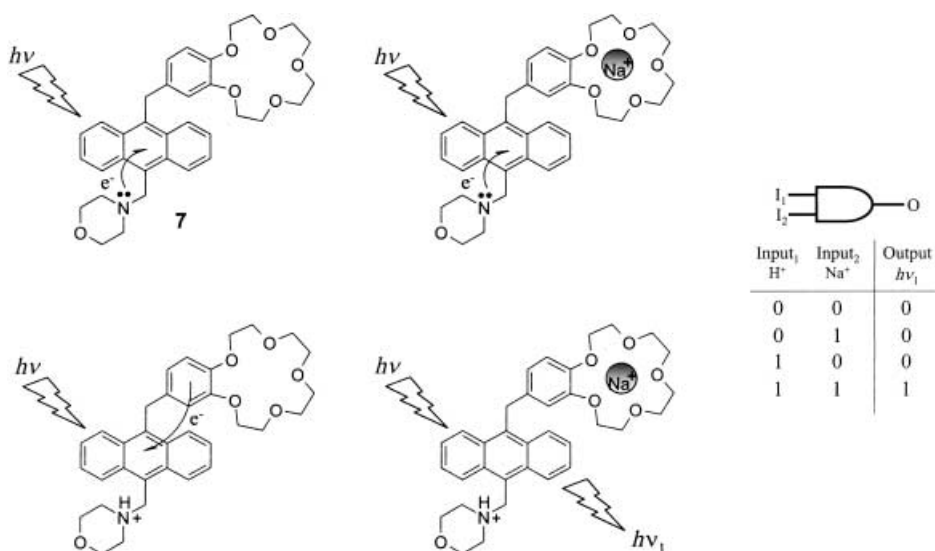
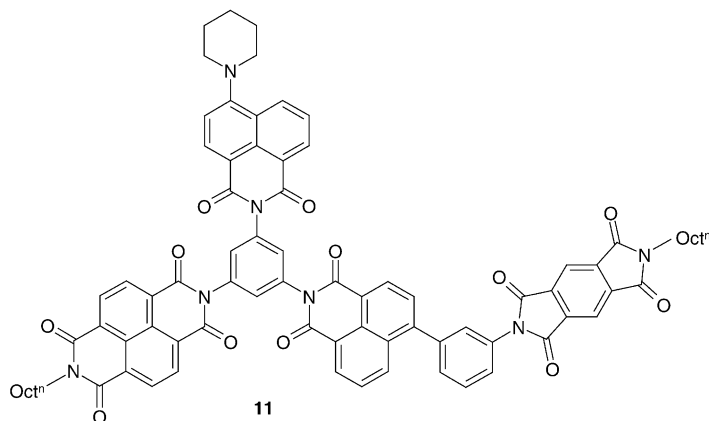
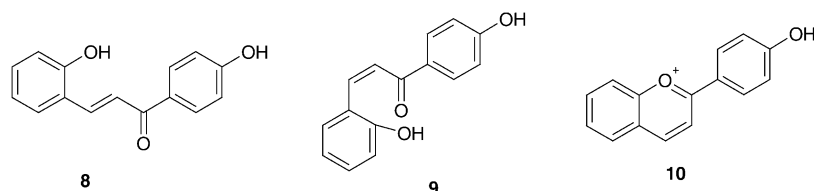


Figure 2. The molecular AND logic gate **7**: principles of operation and truth table.

cer-receptor” format,^[16] described above for **1**. This AND gate is made possible by utilising two discrete, selective binding sites that are weakly coupled to a fluorophore. In this scheme, thermodynamically controlled and guest-modulated PET processes from oxidizable moieties located at each receptor serve to quench the fluorescence from the excited fluorophore, across inert methylene spacers. Only if chemical species (Na⁺ and H⁺) are present at both receptor₁ and receptor₂ are both oxidation potentials raised, such that the electron transfer is abated. Then the fluorescence output is restored (output 1), and the truth table is satisfied. In this implementation, the power supply was provided by excitation light, while inputs are chemical (Na⁺ and H⁺) and the output is fluorescence light. Importantly, the commutative nature of this system is apparent as binding of each guest is truly independent. Such photoionic systems^[12] can be considered wireless, since the inputs are directed to the correct receptor of the gate unaided, while the photons also find their way in and out of the fluorophore component.

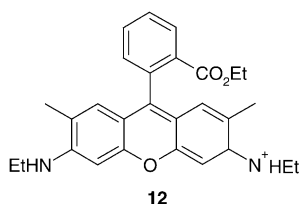
Multi-receptor “fluorophore-spacer-receptor” PET systems showing AND logic can employ chemical species that are more complex than atomic ions. Cooper and James report a system targeting a diol (with a boronic acid) and an ammonium ion (with an azacrown ether). The end-result is a selective sensor for glucosamine at physiological pH.^[38b]

Consequently, previously reported cases which can be switched between different discernible states can be re-examined in a logic context.^[39–41] A different example of an AND logic gate with light and chemical inputs and absorbance/fluorescence output is Balzani and Pina’s **8**.^[42a] Diederich’s work is also related.^[42b] The thermodynamically stable *trans*-form **8** is converted to the *cis*-isomer **9** under irradiation (light input 1). Compound **9** is subsequently cyclized to



output will have a low absorbance. The aminonaphthalimide module is pumped (input₁ 1) to cause PET from it to the naphthalenediimide. Then the naphthalenediimide radical anion is pumped (input₂ 1) to transfer its additional electron to the benzenediimide via the naphthalimide. All this happens on the nanosecond timescale. While there is much elegance in this example, we note that only the qualitative aspect of input–output homogeneity is available here. In fact, the quantitative aspect is still not easy to achieve as far as molecular-scale logic is concerned. No wonder, because the output from a molecular device would then feedback as the input in the absence of wiring.

Elegance again comes to mind when **12**^[44] is considered. Two-photon fluorescence (TPF) is a well-studied phenome-



non in **12** and many other compounds. Of course, this phenomenon is not seen if the compound is only able to absorb one photon at a time, that is, at low irradiation intensities. Thus the provision of two low-power laser beams (the two light inputs both held at 1) are necessary for TPF to occur (output 1), even though the quantum efficiency is quite small. Evidently, the power levels of the low-power beams must be selected with care for the AND gate action to be demonstrable. Now the wavelengths of the two inputs can be the same, but the output wavelength is necessarily different. Thus full input–output homogeneity is not met.

AND logic is only one of the sixteen 2-input logic types that can be achieved in laser experiments featuring bacteriorhodopsin.^[45] The multiple states of this protein that can be accessed photochemically underpins this achievement. Again, the wavelengths of inputs and output are not all the same. The intensities are also deliberately chosen to be different. Nevertheless, this and the other AND gates discussed above demonstrate substantial versatility of design that has emerged already.

Some examples of molecules with intrinsic logic capabilities leading to the implementation of some other 2-input logic gates, which give different output patterns in their truth tables in response to the same set of input conditions, are shown in Figure 3.

Another common 2-input logic type, OR, has been provided recently by Desvergne and Tucker (**13**; Figure 3a), whereby the quantum yield of intramolecular photodimerization (ϕ) of two anthracene moieties is considered as the output.^[46] Quantum yield enhancement originates from the guest-enforced steric changes upon binding ions (Na^+ and Hg^{2+}) at either or both available sites (the 2,2'-bipyridine site or the flexible oligooxyethylene chains), giving an orientation conducive to photodimerization. Reset is possible in this instance by ion sequestration followed by irradiation at a rather short wavelength. Alternative, previously implemented protocols make use of a nonspecific receptor in the “fluorophore–spacer–receptor” design, whereby different guests generate the same high fluorescence response. This ideology, which goes against the flow of normal receptor design in which the emphasis is placed upon more and more selective receptors, gives a fluorescent OR gate in which the number of available input channels are limited only by the number of guests capable of eliciting similar changes in the fluorescence quantum yield.^[47,48]

INHIBIT logic is another type that deserves some attention because it demonstrates noncommutative behaviour. This means that one input has the power to disable the whole system, that is, it holds a veto. Molecules **14** and **15** represent two different approaches using a phosphorescence

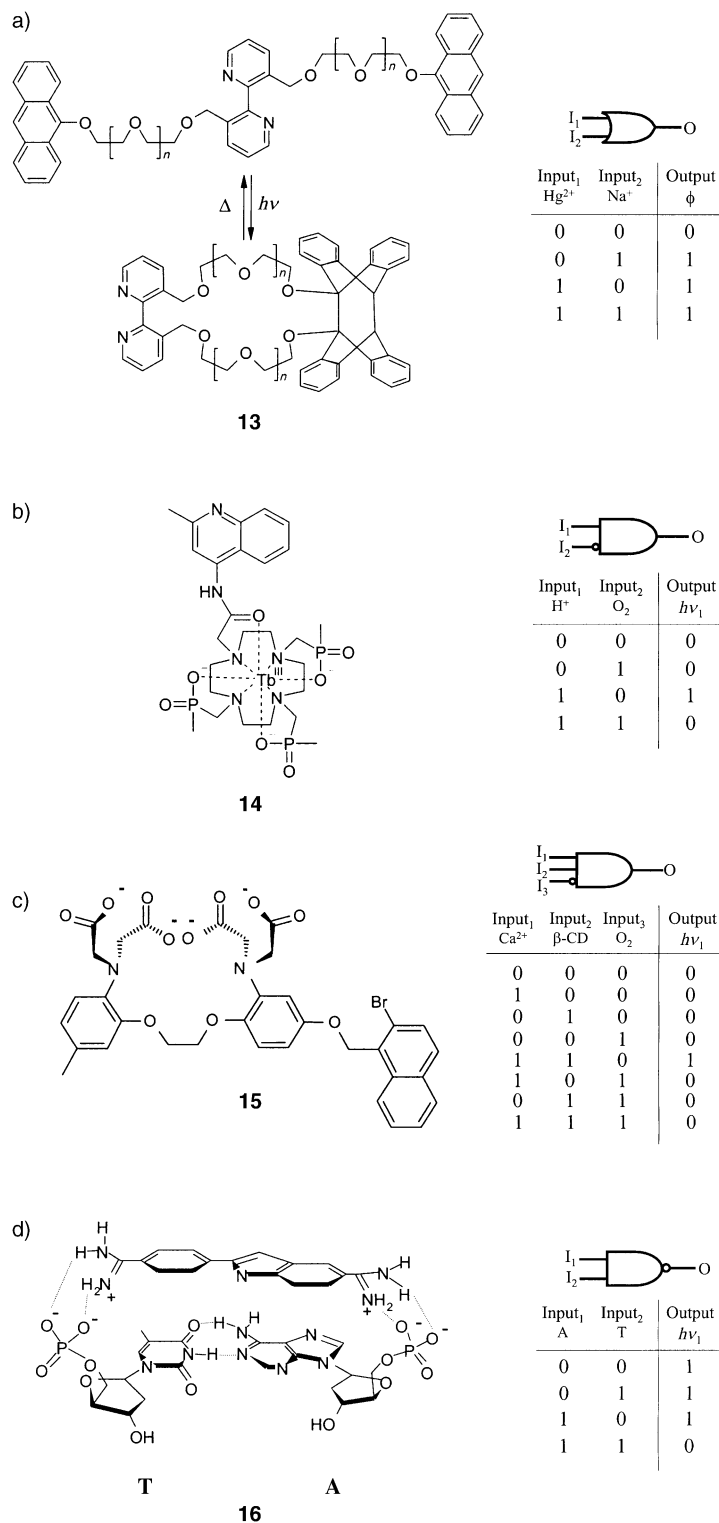


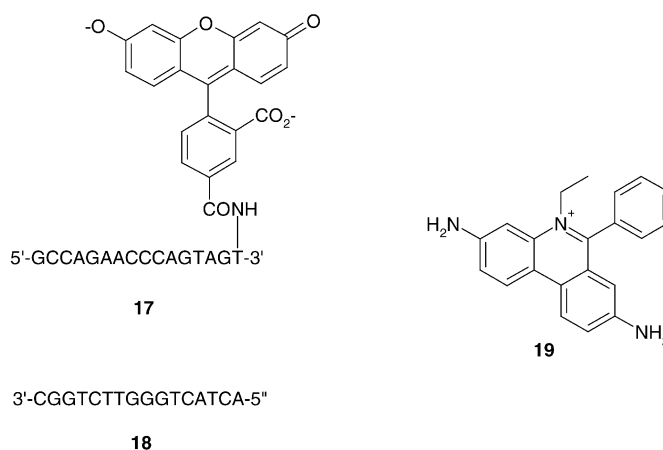
Figure 3. Photoactive molecular systems corresponding to a) OR gate **13**, b) 2-input INHIBIT gate **14**, c) 3-input INHIBIT gate **15** and d) NAND gate **16**.

output. In a 2-input example, Gunnlaugsson et al. use a luminescent Tb^{3+} complex (Figure 3b).^[49] Molecular oxygen is one input that quenches the delayed line-like emission, giving an output 0 regardless of the other inputs. The role of the second input (H^+) is to shift the absorption band of **14**

into the range of the excitation light that provides the power for this device. Luminescence (output 1) is only observed if O₂ is absent (input 0), in the presence of acid (input 1). Gunnlaugsson also contributed to a somewhat different 3-input INHIBIT system a year earlier.^[50] Example **15** (Figure 3c) relies on a number of processes to perform its function and produce bright phosphorescence: 1) a Ca²⁺-arrested PET process from the alkoxyaniline part of the amino acid based receptor to the excited bromonaphthalene, 2) a β-cyclodextrin-blocked bimolecular triplet–triplet annihilation involving two excited molecules and 3) phosphorescence quenching by oxygen. Thus Ca²⁺, β-cyclodextrin and O₂ serve as inputs, with oxygen as the disabling input (as with **14**). A high output is thus only observed with an input string of 110, respectively. The use of phosphorescent systems in molecular logic devices opens up the possibility of operating gates in a controlled sequence. A fluorescent gate and a phosphorescent gate coexisting in solution can be interrogated at will by two different strategies. The first is time-resolved observation following pulse excitation, such that the fluorescent gate responds within nanoseconds and is lost during the “blind” period of observation. The typically millisecond duration of the phosphorescence allows it to be observed without any contamination by the fluorescence signal. Secondly, the phosphorescent gate can be disabled by the addition of oxygen so that its output remains silent, whereas the fluorescent gate loses very little efficiency, especially if short-lived fluorophores are selected. The construction of the 3-input gate, as in the case of **15**, demonstrates that at least small-scale integration of simpler gates is possible within single molecules.

NAND gates have high value in electronics, since multiple copies of these (as well as NOR gates) can be wired up to emulate all the other logic types.^[10] This advantage is only available to molecular logic schemes if full input–output homogeneity is demonstrable. Two systems displaying NAND gate behaviour have been available for a few years.^[51,52] However, Akkaya and Baytekin’s use of a well-known compound (**16**) is of particular interest (Figure 3d).^[53] They use hydrogen-bonding interactions for the first time alongside luminescence ideas for logic design with small molecules. Molecule **16** is known to intercalate into adenine(A)–thymine(T) base-pair regions of DNA. In aqueous/organic solvent mixtures they observe binding between the A–T mononucleotide pair and **16**, with the binding being signalled by luminescence spectral changes. Careful choice of emission wavelength (455 nm) shows significant reduction of luminescence intensity only when both A and T are present, that is, NAND logic.

Earlier we featured DNA-based catalyst **4** functioning in a logic capacity.^[27] Shorter DNA oligomers can also be harnessed in a more direct way by using chemical inputs, fluorescence light output and with excitation light as the power source. This approach by Ghadiri and colleagues can be illustrated by referring to their NAND gate.^[54] This is a single-stranded 16-mer oligonucleotide decorated at the 3'-terminus with a carboxyfluorescein moiety (**17**). The first input is a complementary 16-mer (**18**) and the second input is the common DNA intercaland **19**. Excitation of the fluo-



rescein unit, where **19** does not absorb, gives strong fluorescence emission (output 1) when one or both inputs are absent. When both inputs are applied, **17–18** hybridization occurs and **19** intercalates into the resulting duplex at a position not far from the fluorescein moiety. An efficient EET then occurs from the fluorescein unit to **19**. So the fluorescence emission is quenched (output 0). Oligonucleotide **17** is quite versatile, since it displays different logic types such as AND and 3-input INHIBIT when different inputs are chosen (see reconfigurable gates in the next section).

XOR logic is valuable as a means of comparing the logic state of two signals. As a result of the Stoddart–Balzani collaboration, [2]pseudorotaxanes have been persuaded to participate in this type of molecular logic. Threading/dethreading processes of a macrocyclic host (e.g., naphthocrown ether **20**) and linear guest (e.g., diazapyrenium dication **21**) complex can be influenced by chemical, electrochemical and/or photochemical stimuli with an accompanying recognizable signal.^[55] Figure 4 shows a molecular XOR logic gate based on a [2]pseudorotaxane using chemical inputs (acid and base) and a fluorescence output signal from the 2,3-dialkoxy-naphthalene moiety. In the presence of acid or

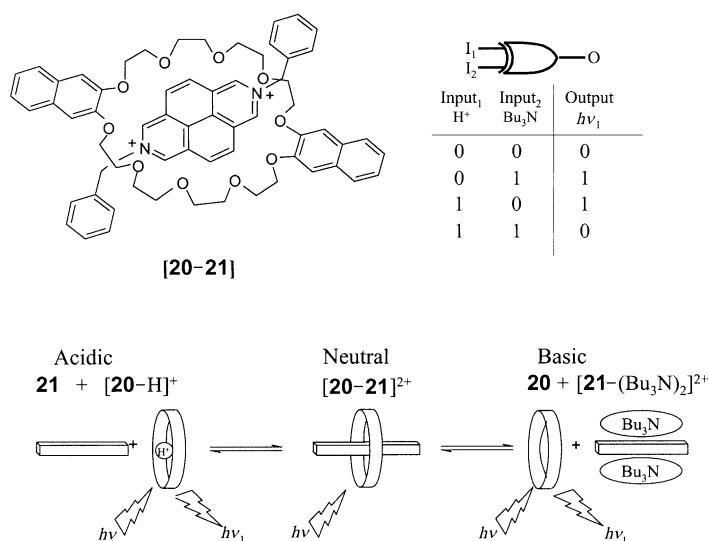


Figure 4. XOR logic with an artificial molecular machine **20–21**.

base the complex threading is not permitted and an output 1 is obtained in the form of emission at 343 nm. In neutral solution (i.e., either no acid or base, or both added simultaneously in stoichiometric amounts) the non-emissive 1:1 complex forms and an output 0 is obtained. Other molecular-machine-based implementations include a XNOR gate with electrochemical inputs and optical absorption as output.^[56] Balzani and Pina's **8**^[42a] can also be nicely persuaded to show XOR logic behaviour when it is combined with $[\text{Co}(\text{CN})_6]^{3-}$. The two inputs are ultraviolet light doses, whereas the output is the optical property of **10**. In the hands of these authors, some principles from the field of artificial intelligence are also displayed by **8**.

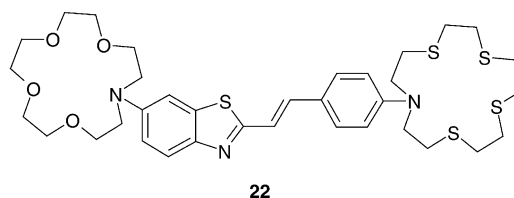
A more recent, but more general approach to XOR gate molecules will be discussed later in a later section on number processing.

Structurally simple **12**^[44] shows another logical face (see next section). While two-photon fluorescence (TPF) conferred the AND logic property upon **12**, conventional one-photon fluorescence output fits XOR behaviour. Either of the two low-power laser beams (either input 1) produces normal fluorescence emission (output 1). Of course, no emission results (output 0) if both laser beams are switched off (both inputs 0). When both laser beams are switched on (both inputs 1), TPF is produced at the expense of normal fluorescence that is under observation (output 0). Careful selection of conditions will probably be needed for a good demonstration of the XOR truth table.

Reconfigurable and Superposed Molecular Logic

The examples highlighted above serve as representatives for some of the important logic expressions that have succumbed to implementation at the molecular scale. While each species was attributed one specific logic label, in certain circumstances one can change the coding involved to define different logic expressions from the same molecule, that is, reconfigurable logic. For example, a convenient method to change the logic expression for molecular logic gates with an optical expression is to monitor the gate at a different wavelength when significant input-induced spectral shifts are present—in other words, wavelength-reconfigurable logic. For example, system **16** was presented as a NAND gate when the output is taken at 455 nm.^[53] However, considering the output at 411.5 nm the TRANSFER logic truth table is satisfied. This gives an output 1 if we have input₁ as 1 for either value of input₂. TRANSFER logic is equivalent to a YES (referring to input₁), whereby input₂ is not involved with the output. A simpler 1-input YES logic gate whose receptor accepts input₁ and refuses input₂ should also produce the same logical result.

Reconfiguring of molecular logic gates can equally be achieved by considering different types of output. A photoionic system **22** presented by Rurack et al. has four states (due to two different binding sites coupled to a chromophore/fluorophore) that are distinguishable by means of absorption and emission maxima as well as emission quantum yield and lifetime.^[57] Therefore this species defies classifica-

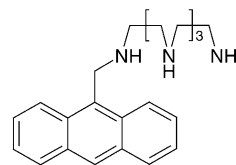


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tion until operating conditions are restricted. For instance, if the absorbance at 440 nm is taken as the output a NAND logic classification can be attributed. If emission is taken as the output a 2-input INHIBIT gate is obtained.

Different types of input can also be a means of reconfiguring gates. This was briefly mentioned concerning Ghadiri's **17**^[54] in the previous section. While proteins have been viewed as logic gates for some time,^[58] Konermann now shows that cytochrome c is a logic gate that is reversibly reconfigurable by choosing different input sets.^[59] In its native state cytochrome c has quenched fluorescence (output 0), since the tryptophan fluorophore is held close to the heme quencher unit. Chemical denaturants (the inputs) unfold the protein so that the tryptophan fluorophore is able to distance itself from the heme unit and thus emit strongly (output 1). For instance, when H^+ and OH^- are employed as the two inputs individually, the fluorescence output becomes 1. When both are simultaneously applied in stoichiometric amounts, they annihilate one another to give no net effect, that is, the protein remains in its native poorly fluorescent state (output 0). This is XOR logic. We mentioned a similar annihilation strategy concerning **20–21** complex^[55] for the same end result. Cytochrome c can now be reconfigured to produce AND logic by changing the inputs to urea and H^+ , but at carefully selected low concentrations such that both must be present simultaneously if denaturing is to occur and the fluorescence is to shine out. It is important to note that removal of the inputs by dialysis returns the protein to its native form.

An earlier approach towards this goal comes from Pina, Garcia-Espana and colleagues who introduced pH-controlled reconfiguring of logic behaviour of an anthrylmethylpolyamine PET system **23**.^[60] Like many anthrylmethylamines,^[61] **23** begins to switch off its fluorescence at basic pH



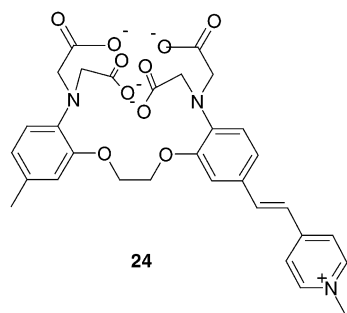
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values around pH 7 in this case. Co-existence of quencher d-block ions in this solution causes switch off to begin at lower pH values, near pH 4 in the case of Ni^{2+} and near pH 3 for the more avidly bound Cu^{2+} . Then at pH 7, either Cu^{2+} or Ni^{2+} or both would cause fluorescence quenching (output 0), that is, NOR logic. At pH 4.5, however, Cu^{2+} alone achieves output 0, whereas Ni^{2+} has no effect. This is

a NOT logic operation on the Cu^{2+} input only. This paper also has nice examples of logic being reconfigured by changing the inputs to other metal ions.

Reconfiguring of logic in the semiconductor electronics field is conducted by physically destroying particular connections in gate arrays,^[10] though field-programmable versions are gaining in popularity.^[62] Irreversibly reconfigurable molecular electronics systems based on rotaxane-like machines are now available from the Heath–Stoddart collaboration in which the gate itself, rather than the connection, is destroyed by altering the applied voltage.^[37a]

An extension of the concept of wavelength-reconfigurable logic leads us to the idea of superposition of logic gates.^[63] This facet afforded by certain photo-active compounds such as **24**, and which is unattainable with solid-state electronic



versions, relies on the ability of molecules to exploit the inherent multi-channel nature of polychromatic light to obtain different, simultaneous logic expressions from the same species. Indeed, while only sequential electrical signals can travel along a wire, multiple optical signals can travel along a fibre optic cable, which is the basis for modern communication networks. An interesting comparison can be made with quantum computation, whereby simultaneous occurrence (or superposition) of strings of input bits is important.^[64] However, while quantum computers are thought to operate simultaneously on all possible combinations of a quantum bit (qubit) string, these seemingly simple molecules show superposition of logic gates.

As mentioned previously, the simplest 1-input gates YES, NOT, PASS 0 and PASS 1. All of these four are demonstrable with a non-modular “chromophore-receptor” system **24**^[63] by using a chemical input (H^+) and a light transmittance output at carefully chosen wavelengths, because of the large H^+ -induced displacement of the absorption band. These four wavelengths can be observed simultaneously. Although transmittance output is a less sensitive means of molecular detection than fluorescence, modulation techniques can approach the single-molecule regime.^[65] It is notable that **24** is by no means the only compound to have the feature of superposed logic. Almost any chemically-perturbed dye, such as a simple pH indicator,^[66] will share this property. The larger the chemically induced spectral shift, the better. Example **16**^[53] shows aspects of this as well.

Integrated Molecular Logic

The construction of integrated molecular logic gates faces considerable hurdles, so it is good to be able to report substantial progress. In 1999 very small scale functional integration of logic operations was achieved through rational design without physical integration of simpler gate molecules.^[50] This last option still remains difficult for single-molecule studies. As an example of functional integration, in the framework of Boolean algebra, NOR logic can be deliberately targeted in a photoionic system in the following way. NOT logic implies chemical-induced luminescence quenching and OR logic suggests nonselective luminescence enhancement. NOT–OR logic therefore requires nonselective luminescence quenching induced by two chemical species. This is illustrated in Figure 5a with **25**, in which the 1,3-diaryl- Δ^2 -pyrazoline fluorescence is quenched by H^+ (when the imine nitrogen lone electron pair interacts with hydrogen centres^[67]) or Hg^{2+} (due to population of a nonemissive ligand-to-metal charge-transfer state^[68]) guests. In the same vein of combinational logic, NAND is equivalent to a NOT gate working on an AND output; while an INHIBIT function is equivalent to the output of a NOT gate serving as an input to an AND gate. Thus these and several other basic examples of functional integration can be obtained. Other recent examples of small-scale integration include the enabled OR, whereby the output of an OR gate serves as an input for an AND gate,^[69] and the integration of XOR and OR gates.^[63] The 3-input systems can also produce truth tables that can be analyzed by rules of combinational logic^[10,11] in terms of arrays of simpler 2-input AND, 2-input OR and 1-input NOT gates. For instance, Dabestani, Ji and co-workers built on the structural and mechanistic operation of AND gate **7** by replacing the simple tertiary amine group with an azacrown ether, which is responsive to K^+ in addition to H^+ . A calixarene was used in place of the benzocrown ether to host a Cs^+ .^[70] In acid media, Cs^+ causes fluorescence enhancement of **26**, while K^+ has no effect. In basic media, K^+ causes fluorescence enhancement while Cs^+ has no effect. These observations can be recast into a truth table format illustrating how this simple elaboration makes possible a 4-gate, 8-wire array featuring two 2-input AND gates, a 2-input OR gate and a 1-input NOT gate (Figure 5b). An analogous case involving Na^+ instead of Cs^+ is also available.^[71]

Raymo and Giordani report another 3-input approach to equally complex logic arrays. Their systems rely on the well-known spiropyran photochromic **2**,^[26] showing an additional state **27** in the presence of H^+ .^[72] This important discovery is shown in Figure 5c.^[5d] Absorption of ultraviolet light changes **2** to the coloured merocyanine form **3**, the protonation of which to give **27** changes the colour again. The three inputs are thus ultraviolet light, visible light and H^+ . Two outputs can be monitored, namely the absorption band of **27** at 401 nm (output₁) and the absorption band of **3** at 563 nm (output₂). A logic array can thus be generated in which several simpler logic gates, including 2-input AND, 2-input OR and 1-input NOT, are necessary to reproduce the functions performed by a single-molecular system. The size of the

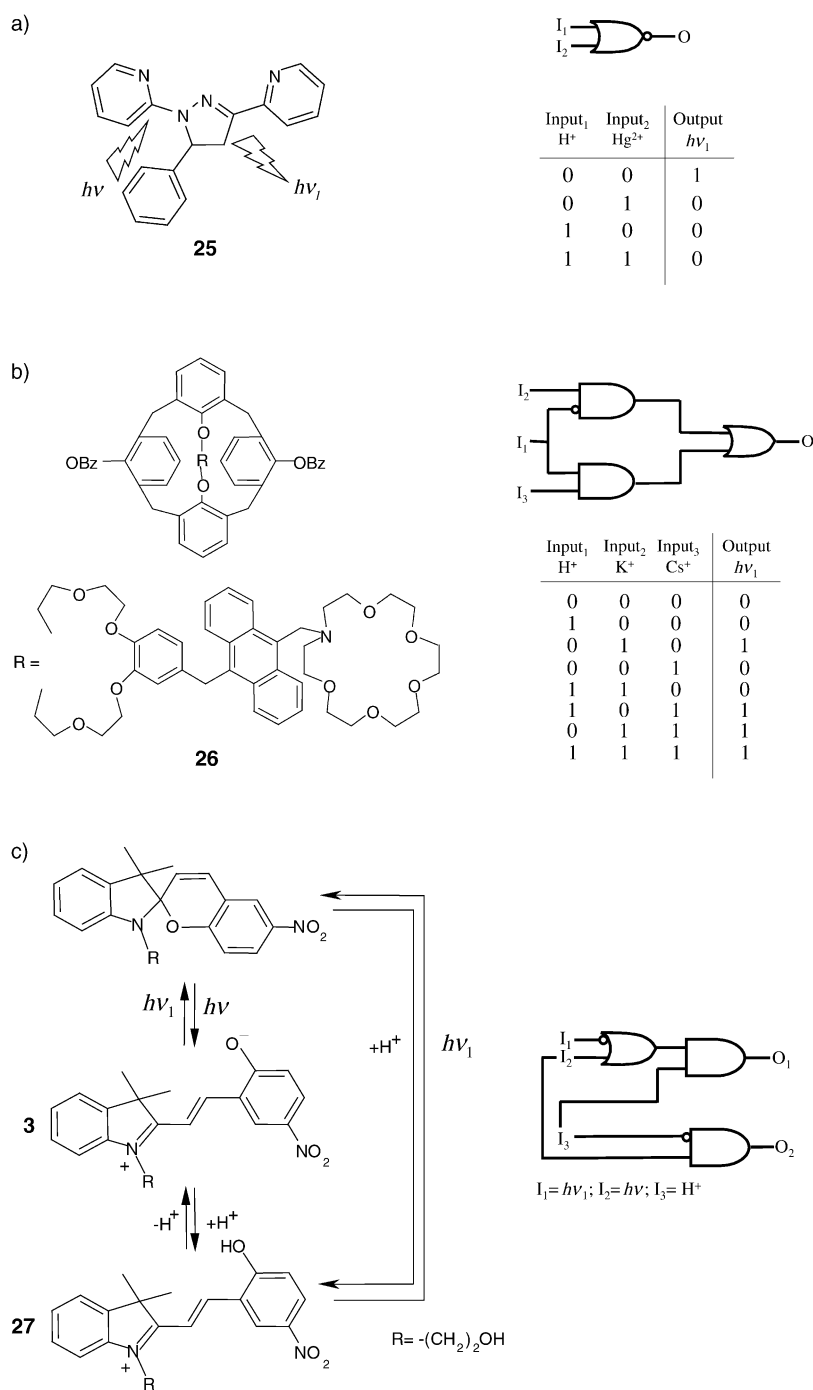


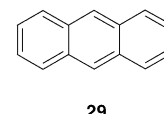
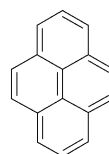
Figure 5. Molecular logic gates showing functional integration: a) **25**, b) **26** and c) the set **2**, **3** and **27**.

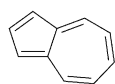
gate array originally published^[72] has been subsequently revised downwards.^[5d] Nevertheless, this system demonstrates integration as well as wavelength-reconfigurability.

The controllable composition of the system of **2**, **3** and **27**, each with its distinct absorption spectrum allows its combination with an external fluorophore **28**.^[73] The characteristic fluorescence spectrum emitted from the latter is sent through the system **2/3/27**, so the 3-state system effectively serves as a custom light filter. This therefore represents the concatenation of a fluorophore (interpretable as a PASS 1 logic gate), through its fluorescence output, with the 3-state

system containing its wavelength-reconfigurable logic array. Naturally, the overall combinational logic array is rather similar^[74] to that seen for the absorbance output of **2/3/27** alone.^[72] Again, the size of the gate array originally published for this case including **28**^[72] has been subsequently revised downwards whereby **29** replaces **28**, but operates at a similar wavelength.^[74] So the rich absorption spectra of **2/3/27** are being monitored at chosen wavelengths as before,^[72] though now the wavelengths are defined by other molecular fluorophores. The simultaneous use of several fluorophores in the same solution^[74] can allow progress towards another nice case of superposed logic.^[63]

Raymo and Giordani's coupling of the fluorescence output of a fluorophore to the absorption capabilities of another molecule employs the EET mechanism of emission–reabsorption,^[73,74] which dominates at large distances of separation between the two species, from 10 nm to astronomical scales. Dipole–dipole or Förster transfer takes over as the main EET mechanism at molecular-scale distances of approximately 5 nm. Remacle, Levine and Speiser^[44] exploit this to couple **12** to **30**. In this instance, both **12** and **30** are equally complex logic arrays made up of XOR and AND gates. So the result of the concatenation is significantly more complex logically. Since the XOR function can be represented as a set of two 2-input AND, one 2-input OR and two 1-input NOT gates,^[10] the final array possesses six 2-input AND, two 2-input OR and four 1-input NOT logic





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modules—the largest scale irreducible integration that we are aware of on the molecular scale.

Just as the light output from one gate can serve as the input of a second gate, chemical species can also serve to link molecular logic units. Chemical signal transfer is likely to be rather versatile because 1) EET usually runs downhill, thus limiting the number of possible concatenations of photo-driven molecular devices; 2) chemical messengers control entire cascades of biochemical reactions and 3) the large diversity of chemical species permits unique links between chosen gate pairs within large sets. Stojanovic and colleagues^[27] consider this possibility with various oligonucleotides as the transfer agents. Raymo and Giordani^[75,76] consider H^+ as the transfer agent, so that variety is lost but interesting logic integrations are possible.

Logic systems driven by up to five inputs are available in some delightful work from Szacilowski and Stasicka^[77] on the equilibrium reaction of thiols with a text-book metal complex $[Fe(CN)_5NO]^{2-}$. Though it must be noted that some of these are irreversible transformations. The nitroprusside ion is known to first-year undergraduates as a colour test for sulfide. So the absorbance at a chosen wavelength in the visible region (526 nm) is the output. Szacilowski and Stasicka now find this reaction is controllable by several variables such as thiol, protons, light, metal and other cations and anions as well as temperature and pressure. The last two physical properties produce moderate and gradual absorbance changes rather than the sharp sigmoidal changes that are suited to switching action. Nevertheless, this is a nice use of physical properties in a logical context. All these variables are nicely used as the logical inputs to result in some rather complex molecular-scale logic integrations with such a simple compound. Several examples of reconfigurable logic as well as some analogue computing illustrations are included.

Molecular Number Processing

Parallel operation of molecular logic gates can achieve a universally recognisable form of elementary computation, that is, arithmetic. Primary arithmetic operations, which herald an entry to numeracy for humans, require the addition of simple integers. In the simplest cases this corresponds to the sums: $0+0=0$, $0+1=1$ (or $1+0=1$) and $1+1=2$ (or a binary “10”). To achieve the addition of binary numbers, in an analogous fashion to solid-state devices, requires the implementation of a molecular half-adder. This can be achieved through combination of two compatible logic gates (XOR and AND), whose outputs code for the SUM and CARRY digits, respectively (see Figure 6). Compatibility in the present instance concerns chemical inputs,

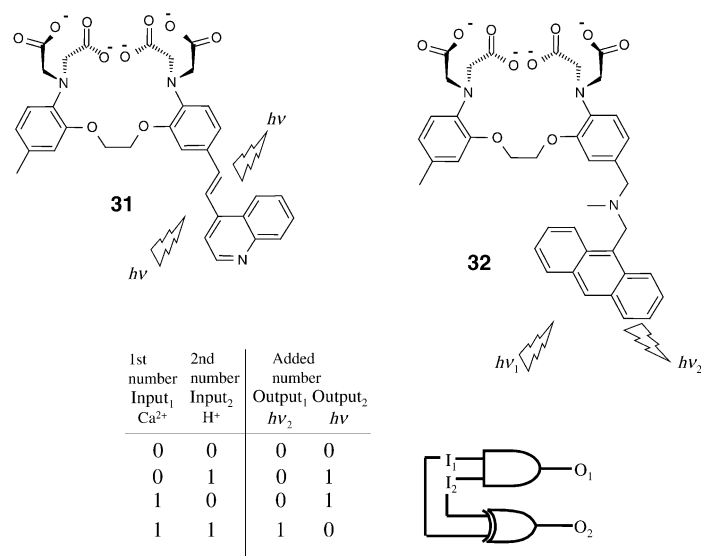


Figure 6. Arithmetic with molecules through parallel operation of XOR (**31**) and AND (**32**) gates.

optical outputs and power supplies, with minimal inter-gate interference.^[78] Light is the output from both types of gate, transmitted light for XOR gate (**31**) and fluorescence from AND gate (**32**), which operates on the same principles as **7**, but uniquely with inputs Ca^{2+} and H^+ . Molecule **31** acts as an XOR gate due the input-dependent perturbations on the energy of the Franck–Condon excited state, which is manifested in a significant displacement of the absorption band in the presence of only one high input. This approach to XOR logic promises to be rather general, as well as being free of inter-input annihilation as used in **20–21**.^[55] When two ion inputs are present, the antagonistic effects (destabilization with Ca^{2+} , and stabilization with H^+) effectively cancel each other out making the absorption (and transmittance) properties at 390 nm the same as the ion-free case, while with only one high input the shifted absorption band results in a much smaller absorbance (and hence high transmittance value) at this wavelength. The first bit of the two-bit number “output₁,output₂” comes from the bright fluorescence output from **32**, which is observed only in the presence of two high inputs. Thus the truth table shown in Figure 6 is satisfied. Therefore, by operating two carefully designed molecules in parallel, rudimentary arithmetic is performed on two binary numbers. Molecules have performed related acts of computation inside our brains. Now it happens outside too, with small molecules at that. It is notable that larger DNA-type oligonucleotides can also be persuaded to be numerate, even concerning larger numbers.^[79]

Remacle, Levine and Speiser’s **12** and **30**^[44] can potentially perform molecular number operations more complex than those achieved by our half-adder system of **31** and **32**, when certain technical issues are overcome. In fact, both **12** and **30** are half-adders in their own right according their integrated logic arrays described in the previous section. The one-photon fluorescence emission of **12** (which is the first XOR output) can feed **30** as mentioned there. Another light input is needed to pump **30**, but this is easily supplied. How-

ever, a separate OR gate is needed to collect the outputs from the AND outputs of **12** and **30**, so that a full-adder is created. We await further work from these authors on this front.

Outlook

In ten short years, molecular-scale logic has gone from its identification through to rudimentary demonstrations of molecular numeracy. Nevertheless, many issues have to be satisfactorily addressed if progress is to be made in line with computer tradition. Perhaps most importantly, issues of component integration have to be further addressed. Small-scale functional integration is available. Physical integration with photonic or chemical links has already led to somewhat larger-scale logic arrays. So we believe there is movement in this direction. However, we must not forget that other directions also beckon. Applying synthetic molecular logic in the biological world is one such. Identification of logic operations in oligonucleotides and proteins are reminders of this opportunity. Adaptation of logic switches for use in analogue regimes as sensors^[7,19] will be another growth area. Given all this activity, the second decade of molecular-scale logic awaits new adventurers.

Acknowledgement

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