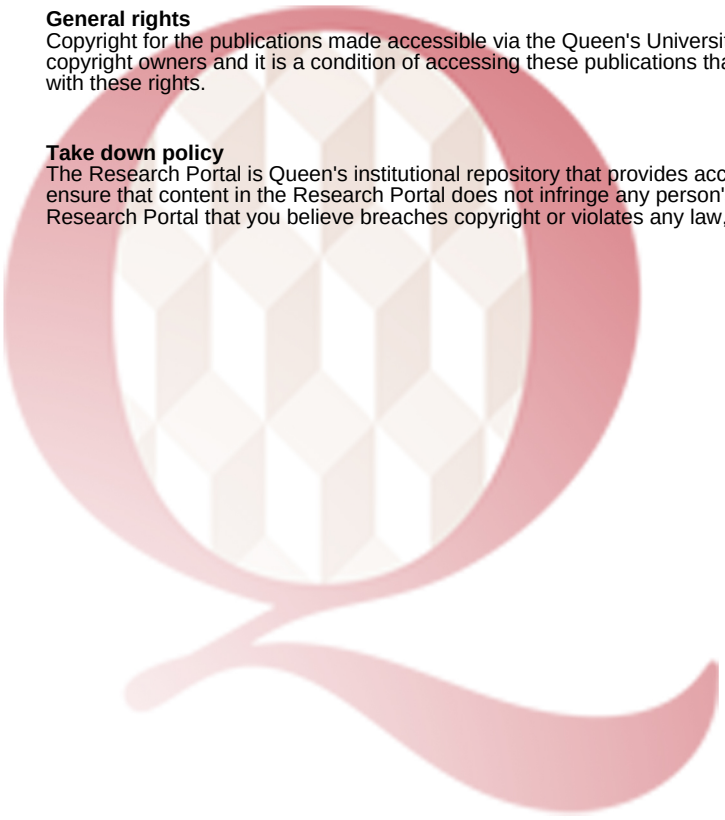
Information Gathering and Processing with Fluorescent Molecules

Daly, B., Ling, J., & de Silva, A. P. (2014). Information Gathering and Processing with Fluorescent Molecules. Frontiers of Chemical Science and Engineering, 8(2), 240-251. DOI: 10.1007/s11705-014-1432-z

Published in:
Frontiers of Chemical Science and Engineering

Document Version:
Peer reviewed version



Information Gathering and Processing with Fluorescent Molecules

Brian Daly, Jue Ling and A. Prasanna de Silva

School of Chemistry and Chemical Engineering, Queen's University, Belfast BT9 5AG, Northern Ireland. E-mail: a.desilva@qub.ac.uk

Abstract: Molecular information gathering and processing – a young field of applied chemistry - is undergoing good growth. The progress is occurring both in terms of conceptual development and in terms of the strengthening of older concepts with new examples. This review critically surveys these two broad avenues. We consider some cases where molecules emulate one of the building blocks of electronic logic gates. We then examine molecular emulation of various Boolean logic gates carrying one, two or three inputs. Some single-input gates are popular information gathering devices. Special systems, such as 'lab-on-a-molecule' and molecular keypad locks, also receive attention. A situation deviating from the Boolean blueprint is also discussed. Some pointers are offered for maintaining the upward curve of the field.

Keywords: molecular logic, molecular computation, molecular sensors, fluorescent molecular devices, fluorescent sensors.

1. Introduction

Since we live in an information age, it is important to realize that we ourselves are information-oriented creatures right down to our constituent cells and molecules. While society is increasingly shaped by the personal information that is gathered and processed for commercial or security purposes, it is becoming increasingly clear that information gathering and processing at the molecular scale is what keeps us alive and well. Therefore researchers need to spend some effort performing information gathering and processing with designed molecules. Such research will enable interventions to bolster human/animal/plant wellness and health.

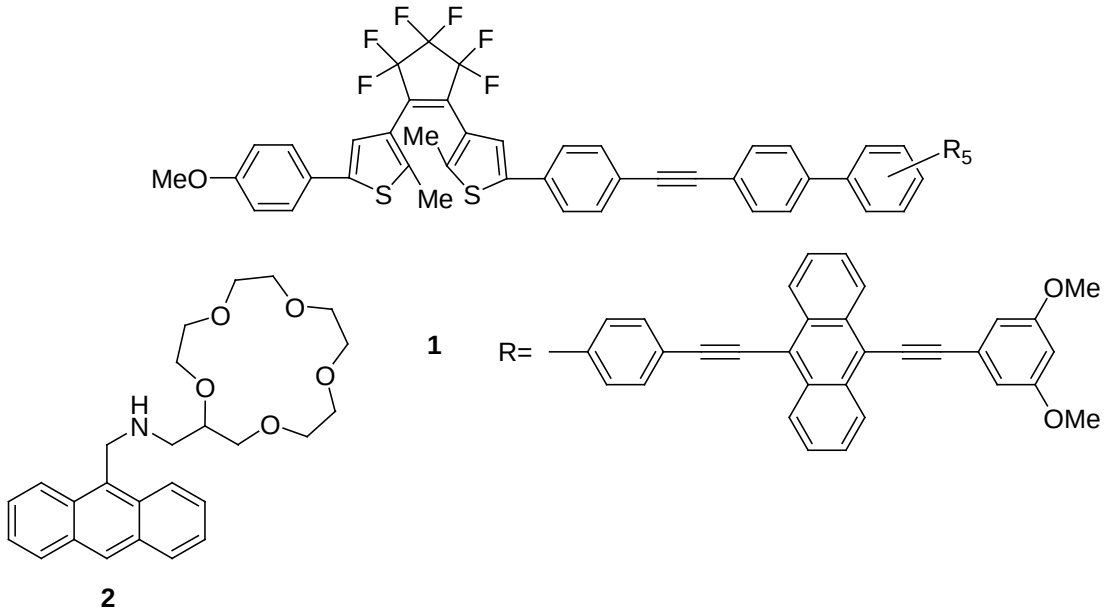
It is now 21 years since the first information-processing molecules were presented.[1] Many laboratories have stepped forward to join in the effort since then.[2-16] However, this review will restrict itself to discussing some recent examples and their historical threads which employ fluorescence as the output channel. We do this because molecular fluorescence, and related emission techniques,[17] can operate in nanospaces of interest to chemists, physicists and biologists,[18] down to the single-molecule level.[19] However, we will also refer to some cases where absorbance is the output channel because of the close relationship between those and emissive examples.

Information processing, at least within modern computers, requires the availability of Boolean logic gates,[20-23] and molecular versions can progress along similar lines. So this review will proceed according to the increasing complexity of the logic. However, electronic logic gates are assembled from smaller components, such as transistors, triodes or diodes.[24] Molecular implementation of these is where our story will begin.

2. Molecular mimicry of aspects of triode action

Electronics developed as a field with the advent of the transistor or triode, systems in which the output driven by the principal input can be controlled by a second input. In the triode (composed of a plate and a hot filament with an interspersed grid) the output is the plate current, the principal input is the plate voltage and the second input is the grid voltage. This control feature is exploited in both digital and analog electronics.[24] Moore, Moore and Gust's **1**,[25,26] consisting of a central hexaphenylbenzene surrounded by five bisphenylethynyl-anthracene fluorophores and a single dithienylethene photochrome,[27] is shown to have triode-like behaviour. As is well-known,[27] dithienylethene can be switched cleanly between open and closed forms. The anthracene-based unit absorbs at 430 nm and emits at 520 nm while the open form of dithienylethene absorbs at 350 nm and the closed form absorbs from 500 – 700 nm (the range in which the anthracene-based unit emits.) This crossover means that if the closed dithienylethene is present, emission from the anthracene-based unit will be reduced because of nonradiative electronic energy transfer (EET) to the closed dithienylethene which causes ring-opening. The experimenters shine uv light (350 nm) with constant intensity on **1**, which causes the anthracene-based unit to fluoresce and forces open dithienylethene to isomerise to the closed form. Simultaneously they shine red light (>610 nm) but here the intensity is modulated in the form of a sine wave, the red light has no effect on the anthracene-based unit but causes the closed dithienylethene to isomerise into the open form. At higher intensity of red light more of the dithienylethene is in the open state, resulting in a corresponding rise in the emission from the anthracene-based unit as the dithienylethene unit passes further to the open form. They find that the waveform of the output intensity (at 520 nm) exactly follows that of the modulated red light. Higher frequency modulations introduce a time lag between the two due to the kinetics of the shifting of the photostationary state.

From an electronics viewpoint, the 350 nm uv light intensity can be considered to be analogous to the plate voltage of the triode. The 520 nm fluorescence corresponds to the output plate current, which is sensitively controlled by the red (>610 nm) light intensity which is the grid voltage counterpart.



2

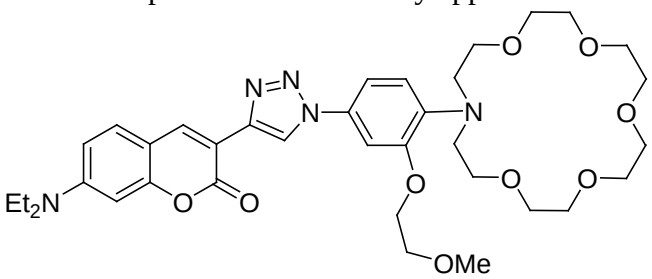
As Moore, Moor and Gust indicate,[26] there needs to be some matching of the current efforts by many laboratories building molecular versions of electronic digital devices by paying attention to analog devices. Our effort in this direction[28] focuses on photoionic emulation of the triode.[24] Triodes and other thermionic devices run on the basis of a hot metal filament, which emits electrons which can be received by another electrode (the plate) but only when it is positive. However, as the plate voltage becomes more and more positive there is a limit to the rate at which electrons can be received, since that is determined by what is emitted by the hot filament. The plate current (output) therefore becomes a quasi-sigmoidal function of the plate voltage (input). During our early efforts at developing photoionic devices of the 'fluorophore-spacer-receptor' type[29-31] based on photoinduced electron transfer (PET), we had learned much from simple pH indicators.[32] One of these lessons was that the optical intensity output varies sigmoidally as the pH input is varied.[33] How can we tune this input/output characteristic with a third parameter? The pK_a value of the indicator, which determines the position of the input/output characteristic on the pH axis, should be adjustable by electrostatic repulsion between the receptor-bound proton and another cation held close-by. Modifying the 'fluorophore-spacer-receptor' structure to a 'fluorophore-spacer$_1$-receptor$_1$-spacer$_2$-receptor$_2$' system,[34] where the second receptor is not capable of engaging in any major interactions with the fluorophore, achieves this purpose. Of course, the receptor$_1$ should target only protons and receptor$_2$ should interact with cations other than protons. Such orthogonality is crucial to the design of **2**,[28] with its amine and 15-crown-5 ether representing receptor$_1$ and receptor$_2$ respectively. Raising the H^+ concentration causes protonation of the amine so that PET from the amine to the fluorophore is prevented. This causes fluorescence to switch 'on'. We note that the H^+ concentration can be considered to represent the plate voltage of the triode. The fluorescence intensity is analogous to the output plate current, which is secondarily controlled by the Na^+ concentration which corresponds to the grid voltage.

It is important to appreciate the corresponding developments in molecular electronic devices based on all-carbon aromatics,[35] including a transistor mimic.[36]

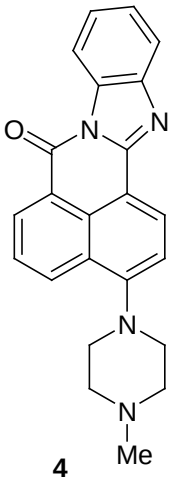
3. Single-input logic

The simplest Boolean logic is the single-input YES gate. This is so simple that it is considered to be a trivial gate in electronics. While this is true for voltage input – voltage output devices, YES gates are non-trivial in photoionic situations since the chemical input and optical output differ in nature. Indeed, these YES gates are ideal for chemical sensing applications[37] when exploited within their analog region.[7] For instance, Ast et al.[38] report the development of a K^+ sensor **3** based on a 1,2,3-triazolyl-coumarin fluorophore attached to a *o*-[2-methoxy(ethoxy)]phenylaza-18-crown-6 lariat ether receptor.[39] High selectivity over Na^+ is shown and, **3** also shows little fluorescence sensitivity to pH (from 6.8 to 7.8). The complexes formed with K^+ are weak (with K_d = 29 mM) but sufficient for monitoring intracellular situations (see below). This complexing is attributed to the ether lariat group as well as the phenylazacrown. In the Boolean sense, the sensor is a K^+-driven YES logic gate[7] with a fluorophore that absorbs at 420 nm and emits at 493 nm. This operates by K^+-induced arrest of PET across a virtual spacer.[31] The non-complexed 'off' state has a quantum yield (Φ_F) = 0.06 while the complexed 'on' state has Φ_F = 0.18. However, the intensity changes with concentration (increases by 3.5% per 1 mM K^+ from 1-10 mM) which, in an analog sense, allows the determination of K^+ concentration. These facts make the sensor suitable for in-vivo use and Ast et al. test it using normal rat kidney cells as well as by building it into a sensor membrane which allows real-time (~200 s) monitoring of flowing samples. **3** is suited to the monitoring of K^+ in the range 5-150 mM, and is an excellent example of a K^+-driven YES gate with fluorescence output..

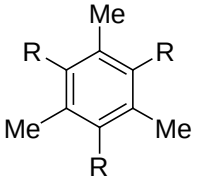
Compound **4** is a recent fluorescent H^+-driven YES logic gate from our laboratory,[40] where the fluorescence switching 'on' is not due to a simple H^+-induced arrest of PET. Rather the cause is an electrostatic destabilization of a non-emissive twisted internal charge transfer (ICT) excited state.[31] This phenomenon is quite closely-related to PET since the thermodynamics of twisted ICT and PET are rather similar.[41] Due to its (justified) popularity, PET is the default assignment of fluorescence switching systems of the YES and NOT logic type in the current literature. However, the lesson concerning **4** suggests that some caution is in order. Either detailed structural variation studies[40] or direct laser photolysis experiments[42] could form part of this cautionary approach.



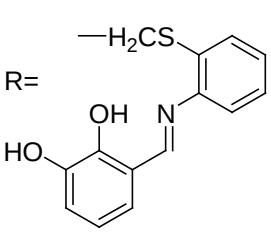
3



4



5



Although there are several commercially successful examples of cation monitoring with fluorescent YES gates based on PET,[43-48] it is worth noting that the sensing of neutral species

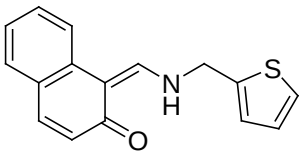
is still restricted to a few classes of molecule, i.e. thiol,[49] NO(N_2O_3)[50,51] and sugars.[52] Here lies a challenge. Another challenge lies in the monitoring of chemical species in biorelevant nanospaces. For instance, even membrane-bounded H^+ can drive fluorescent PET-based YES gates,[53,54] which can be useful for the study of bioenergetics.[55] Mapping of H^+ in such nanospaces is available, at least at the prototype level.[54]

We close this section with an example based on absorbance. **5** is a tripodal phenolic imine[56] which selectively targets F^- through probable hydrogen bonding to, and subsequent H^+-transfer from, the numerous OH groups of catechol units[57] to bring about changes in the absorption spectrum. The pale solution turns yellow. Titration with Bu_4NOH proves that the colour change indeed arises from deprotonation of the catechols. While the acid-base neutralization takes away from the supramolecular functionality of **5**, it nonetheless functions as a F^--driven YES gate in terms of the absorbance output at 433 nm. The H^+-transfer limits **5**'s sensor ability as it means that even small traces of water will prevent its operation.

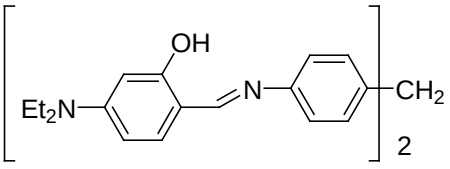
4. Double-input logic

Fluorescent double-input AND logic gates heralded molecular logic-based computation,[1] partly because they are the most widely recognized Boolean gate type. The fact that old societal values of unity, e.g. 'United we stand, divided we fall' can be expressed in terms of AND logic is one reason for this recognition.

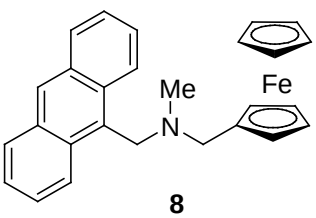
Although several AND gates targeting cation-anion pairs (and zwitterions) are known,[58-62] a new case **6** due to a consortium of Safin, Garcia and Das[63] is featured here. The phenolic imine theme continues with **6**, though x-ray crystallography shows that it crystallizes as the keto amine tautomer. The same tautomer persists in solution as evidenced by ^{1}H-NMR studies. The fluorescence (at 448 nm) of **6** in neutral mixed aqueous solution shows an enhancement factor of 10 in the presence of Zn^{2+} and AcO^-. Both these ion inputs are required to cause this enhancement, i.e. Zn^{2+}, AcO^--driven AND logic. The ^{1}H-NMR experiment in dimethylsulfoxide solution shows that the Zn^{2+}-complex does not form until the basic AcO^- removes the N-H proton of **6**. Since the fluorescence studies are carried out in pH-buffered solution, the basicity of AcO^- should be less critical but the experimental result suggests that this basicity effect persists. As seen in many other cases of this structural type, e.g. **7** (see below), the displacement of the proton from the hydrogen-bonded keto amine/phenolic imine by Zn^{2+} eliminates the ESIPT pathway for fluorescence quenching. The excited state, before and after the displacement, has ICT characteristics, as shown by detailed calculations. Importantly, the fluorescence-based AND logic behaviour of **6** is preserved within *Candida Albicans* cells, which are a common source of human fungal infections.



6



7



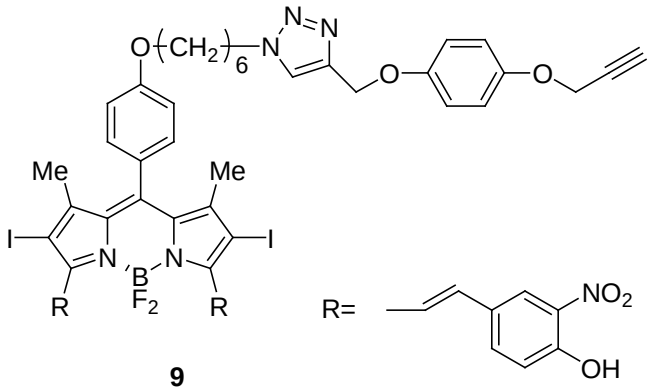
8

Farrugia and Magri's **8**[64] allows monitoring of the simultaneous presence of H^+ and redox potential. They name **8** and its forebears[65] as 'Pourbaix sensors', after the pioneer of H^+- and redox-dependent thermodynamics.[66] **8** is a H^+, redox-driven AND device which contains a tertiary amine which functions as a H^+ receptor. The ferrocene group does not bind Fe^{3+} but is oxidized by it. Protonation of the amine and oxidation of ferrocene to ferricinium stops two separate PET processes and enhances fluorescence. The Φ_F of 0.018 is described as modest by the authors, because of a competing PET process from the excited anthracene to the ferricinium unit, but is easily visible.

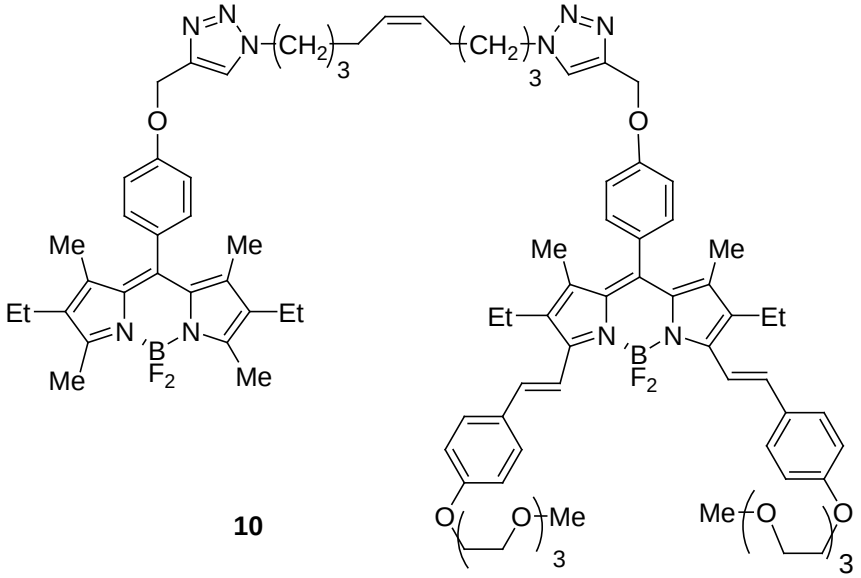
Placing an inverter (NOT gate) in front of one of the two inputs to an AND gate is a direct way to obtain INHIBIT logic action. Thus, one of the inputs acts to disable the output of the gate. A good number of INHIBIT gates which feature fluorescent,[67-70] luminescent[71,72] and absorption[73] outputs are available. However, a recent report by Singh[74] exemplifies an approach to this logic type, which should be rather general. The phenolic imine **7** contains intramolecular hydrogen bonding which gives rise to an excited state intramolecular proton transfer (ESIPT) [75] and which, in turn, produces very weak emission (at 457 and 509 nm) in neutral mixed aqueous media. Several classical analytical reagents are of this type.[76] If a heavy divalent ion such as Zn^{2+} is supplied as input$_1$, fluorescence due to the rigidified π-electron system of the Zn^{2+}-complex emerges strongly at 462 nm with a fluorescence enhancement factor of 8.5. Notably, the source of intramolecular hydrogen bonding is eliminated. If a multivalent anion such as phosphate or adenosine triphosphate (ATP) then arrives on the scene in the role of input$_2$, it would attach strongly to the Zn^{2+} centre to the point of creating the nucleus of a precipitate. The release of the free receptor **7** would be signalled by the drop of fluorescence back to the original low level, suggesting Zn^{2+}, ATP-driven INHIBIT(ATP) logic. The argument of the INHIBIT function (in brackets) identifies the disabling input. If ATP was applied on its own to **7**, no spectral change would be expected.

5. Triple-input logic, including 'lab-on-a-molecule' systems

A major reason for the success of digital electronics is the availability of serial integration.[77] This means that the voltage output from one gate could be fed as the input to the next and so on. Large logic arrays capable of carrying out complex computations arose as a result. Whilst nature is adept at producing concatenated sequences that we can view as logical operations in series (Krebs cycle, for instance) synthetic molecular examples are harder to achieve.[78,79] However with careful design, Akkaya[80] successfully connects an AND gate with an INHIBIT gate to show that molecular switches can pass information from one to another. The first gate in this system is a photosensitizer **9** which generates $^1O_2$ only under acidic conditions when 660 nm light is incident,[81,82] i.e. a H^+, light dose-driven AND gate. Compound **9**, being phenolic, red-shifts its absorption spectrum (from 645 to 720 nm) upon basification. Its heavy atomic nature ensures the easy population of the lowest excited triplet state, which allows formation of $^1O_2$ from ground-state dioxygen via EET. However, the lack of absorption of the incident light in its basic form is the reason why both H^+ and a 660 nm light dose are needed as inputs to generate the $^1O_2$ output from **9**, i.e. AND logic.



9



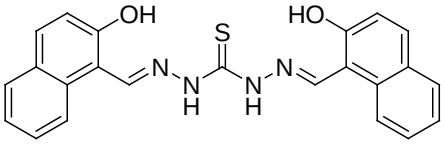
10

The $^1O_2$ produced by **9** acts upon a second gate **10**, which will fluoresce at 537 nm when $^1O_2$ levels are high. Gate **10** contains an EET donor-acceptor pair of fluorophores so that the donor emission at 537 nm is rather low. However, if the donor and acceptor components within **10** could be disconnected the donor emission would recover its high value. Indeed, this is exactly what happens when $^1O_2$ is available to react with the alkene linker within **10**. If a separate input, glutathione, is present the fluorescence intensity at 537 nm is reduced as it reacts preferentially with $^1O_2$, preventing the latter from reaching **10**. Thus we have a glutathione, $^1O_2$ - driven INHIBIT(glutathione) gate where glutathione is the disabling input. Although the irreversibility of this reaction means that this gate can only be used once, the underlying concept is an important one.

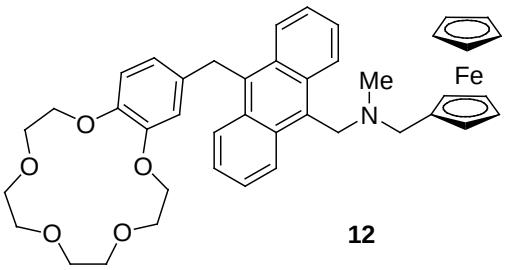
It is worth mentioning that the $^1O_2$ communication between the output from AND gate **9** and the input to INHIBIT gate **10** is facilitated by embedding the pair of gates in a detergent micelle solution in D_2O. It is also relevant to note that H^+ [83] and light[84] have been employed as means of serial integration of molecular logic gates. The general problem of serial connection is widely addressed by the method of functional integration,[7,85] where a relatively complex input-output pattern emerging from a molecule is analysed in terms of a minimized array of AND, OR and NOT gates.

A new example of functional integration can be found in Li's **11**[86] whose fluorescence at 520 nm displays a Cu^{2+}-disabled, Zn^{2+}, F^--driven OR logic. This gate array is composed of an OR

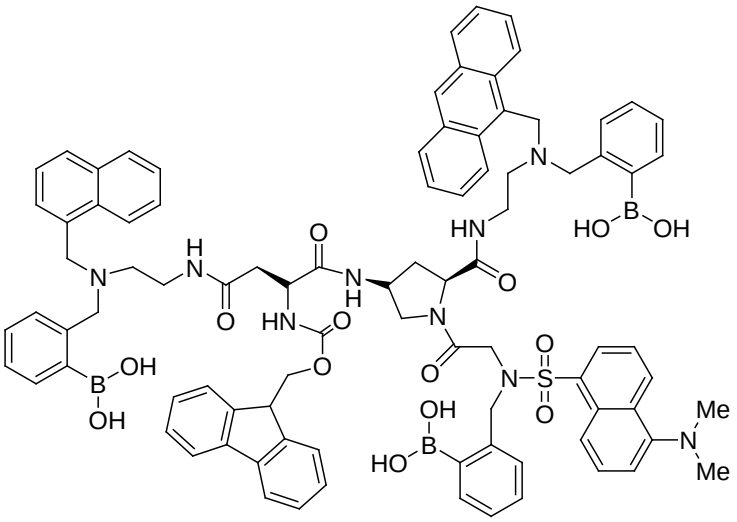
gate feeding an AND gate whose other input line contains a NOT gate (which receives Cu^{2+}). **11** contains a phenolic imine, as found in **7**, to receive Zn^{2+} or Cu^{2+} and a thiourea to receive F^-, even in mixed aqueous solution. Given the variety of heteroatoms within the π-system, the ICT nature of its excited state is to be expected. Zn^{2+} binding to the phenolic imine would increase the ICT nature by deprotonating the phenol and by augmenting the electron withdrawing imine nitrogen. Experimental evidence for this comes from the red shift of the absorption spectrum from 381 nm to around 450 nm. A similar red shift of the emission spectrum from 430 nm to around 520 nm (with enhanced emission) adds to the evidence. Unusually, Cu^{2+} produces a fluorescence enhancement at 375 nm, which is even blue-shifted compared to the absorption of the ion-free compound. Nevertheless, there is almost no intensity at 520 nm. F^- binding to the thiourea would enhance the electron density of the thiourea nitrogen which also increase the ICT nature of **11**'s excited state. A red-shifted and enhanced emission at 520 nm is seen again. Thus the emission output at 520 nm is 'high' in the presence of Zn^{2+} or F^- or both, but 'low' if Cu^{2+} is admitted. Since Cu^{2+} has a reputation for the strongest binding to classical receptors like phenolic imines,[87] it displaces Zn^{2+} from the receptor site if the latter happens to be present. Related K^+-disabled, H^+, Zn^{2+}-driven OR logic is available.[88]



11



12



13

Ferrocene derivative **12**, also from the Magri stable,[88] is more elaborate than **8** since it incorporates a benzo-15-crown-5 ether receptor for Na^+ so as to produce a H^+, redox, Na^+-driven AND gate. Na^+-induced suppression of PET from the crown receptor to the anthracene fluorophore is the extra pathway when compared to **8**. The Φ_F of 0.072 of **12** in the presence of all three inputs at 'high' levels is much higher than that of the corresponding state of **8** and is at least partially due to the Na^+-bound crown electrostatically retarding the PET process from the excited anthracene to the ferricinium unit. This progression from two- to three-input

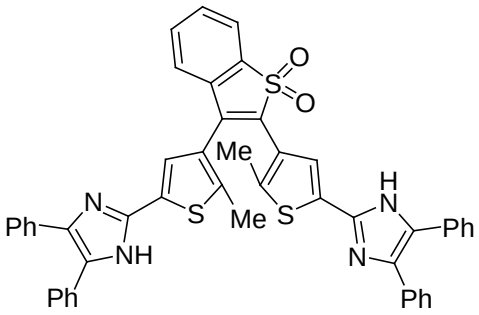
AND logic, as we go from **8** to **12**, is an important step since elevated Na^+, H^+ and free iron are simultaneously present within certain specific cancers. Such simultaneous detection and analytics by means of a single fluorescent output enables this 'lab-on-a-molecule'[89] to highlight the increased risk of cancer development. In a separate context, these inputs are also associated with steel corrosion and thus **12** could provide an early warning to engineers that sea defences or underwater turbines are at risk.

A nice development in the 'lab-on-a-molecule' tradition[89] is the monomolecular combinatorial sensor **13** due to Margulies.[90] Sensor **13** is an oligopeptide based on multiply chiral aminoproline and aspartic acid, which has four pendant fluorophores and three phenylboronic acid units. The latter units permit binding to sugar-based drugs, especially those carrying chiral centres. π-stacking and hydrogen-bonding are also involved. Additional amine groups located near some fluorophores permits PET to occur as long as the amine units are unprotonated and unbound to sugars via the neighbouring boronic acids.[52] Dipolar exciplex states are also possible.[31] One of the fluorophores also has an ICT excited state,[31] whose dipole will respond to local polarity changes during drug capture. EET occurring among the different fluorophores will be similarly controlled by drug binding, leading to different emission intensities of the four fluorophores. Overall, each drug will elicit a different fluorescence signature[91] (across a wide wavelength range) from **13** when excited at 270 nm where all four fluorophores absorb to a greater or lesser extent. The fluorescence spectral intensity patterns are subjected to the chemometric technique of principal component analysis[92] for added distinction so that several commonplace drugs could be clearly distinguished one from another, even within the real-life environment of human urine. A cautionary note would be that the signatures need to be assured as thermodynamically stable states (by waiting for a sufficiently long time, for instance). The multivalencies exhibited by **13** and its prospective guests are known to cause kinetic traps[93] which could deceive the analyst.

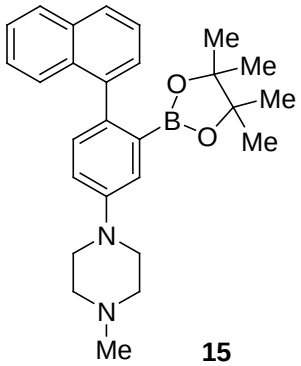
6. Molecular keypad locks

A keypad lock, which carries a 'low' output signal in its resting 'locked' state, accepts particular specified sequences of inputs in order to elicit a 'high' output signal (which corresponds to the opening of the lock). Many molecular versions of these are reviewed in section 11.4 of reference 7. Most only achieve this discrimination within carefully-defined time periods. Zhu's **14**[94] is a dithienylethene photochrome,[27] which is outfitted with imidazole units such that chelation possibilities exist. The thiaphilic ion, Ag^+, not only binds strongly to **14** but it retards the colour (absorbing at 610 nm) development normally induced by uv (366 nm) light irradiation. A PET process from the receptor to the bound Ag^+ could be responsible for this sluggishness. H^+ also binds to the imidazole nitrogens but does not hinder the photochromism. The application of the three inputs of Ag^+, uv light dose and H^+ in that particular sequence to **14** produces a poor coloration. This is due to the Ag^+-induced retardation of photochromism. The last addition of H^+, though it can strip the Ag^+ off **14** in both its colourless and coloured states, can do nothing to correct the lost opportunity of full coloration. Any of the other five possible sequences of three-input strings produce full coloration. For instance, the input sequence of Ag^+, H^+ and uv light dose would find the uv light dose hitting protonated **14** (with the Ag^+ stripped off) to cause smooth and full coloration. If we define poor coloration as the 'open' state of the lock and full coloration as the 'closed' state, we see that the lock would be open only if the specific input sequence of Ag^+, uv light dose and H^+ is applied to **14**. However, we note that a certain two-input string (Ag^+ and uv light dose only, in that order) would also open the lock, i.e. this would be another correct password. Additionally, the fully colourless starting state of **14** in the absence

of any inputs will separately need to be specified as being a ‘closed’ state of the lock for the correct operation of this system. Although this is a weakness and a step away from the Boolean binary principle, there is no difficulty to experimentally distinguish between states with full, poor and no coloration.



14



15

Margulies develops a second use for **13**[93,95] by producing a molecular keypad lock with improved security features. Margulies was also involved in the pioneering work on molecular keypad locks,[96] where a relatively complicated molecular structure was used to bind Fe^{3+} with multipoint interactions. These multipoint interactions allow the relatively complicated molecular structure to achieve kinetically stable states which are different from the thermodynamically stable state so that history-dependent logic could arise. **13** also fits the bill when it binds sugars and sugar-containing drugs. Notably, both **13** and the sugars are intrinsically multipoint binders owing to their numerous functional groups. Unlike the older systems, **13** allows coded passwords such as 111 or 119 where certain inputs are repeated. This is achieved because the wide-spectral fluorescence response of **13**, especially after processing by principal component analysis, is significantly dependent on the concentration of the input. The coding here is; 111 represents three consecutive additions (to give a trebled original concentration) of input 1. Furthermore, **13** allows the use of multiple passwords by outputting distinguishable fluorescence signatures for each of them. Therefore **13** is closer in operation to the electronic keypad locks of everyday life in the above aspects. However, it is notable that **13** exploits its combinatorial response ability rather than Boolean features. It is only the Boolean versions which result in clear ‘open’ and ‘closed’ states for the locks.[7] The current combinatorial system would require a separate declaration of such ‘open’ and ‘closed’ states, according to chosen features of the fluorescence signature for instance.

7. Multi-level logic

We have already seen how a ‘fluorophore-spacer$_1$-receptor$_1$-spacer$_2$-receptor$_2$’ system **2** where the receptor$_2$ is redox-inactive can emulate the tunability aspect of a triode.[28] ‘Fluorophore-spacer$_1$-receptor$_1$-spacer$_2$-receptor$_2$’ systems where both receptors are redox-active can emulate AND logic gates, as was the case with the very first gate of all.[1] ‘Fluorophore-spacer$_1$-receptor$_1$-spacer$_2$-receptor$_2$’ systems have another trick up their sleeves if both receptors target the same input but with different strengths and with widely different emission enhancement factors. For instance, protonation of receptor$_1$ gives a large fluorescence enhancement whereas protonation of receptor$_2$ at significantly lower pH values gives a large fluorescence quenching. This is fluorescence ‘off-on-off’ switching[97,98] as the H^+ concentration steps from ‘low’ to ‘medium’ to ‘high’. It is clear that we have left the Boolean road at this point, since the input is being described with three levels rather than two. Notably, the output remains Boolean. A nice new case of this general type, **15**, which actually has the format ‘receptor$_1$- spacer$_1$-fluorophore-receptor$_2$’ is described by Pischel, Ros and

their collaborators.[99] A closely related format 'receptor$_1$-spacer$_1$-receptor$_2$-fluorophore' is known.[100] Viewed simplistically, **15** contains a tertiary amine to serve as receptor$_1$ and an isoquinoline to serve as receptor$_2$. In fact, the isoquinoline receptor$_2$ is part of an integrated ICT fluorophore in spite of a biaryl twisting. In acetonitrile solution, **15** steps through fluorescence quantum yields of 0.07, 0.45 and 0.01 as 0, 1 and 2 equivalents, respectively, of H^+ are supplied. The emission remains in the 530-560 nm region throughout. The result in this non-aqueous medium can also be described as a double-input XOR logic gate with degenerate H^+ inputs.[5] More benzannellated derivatives of **15** show multi-valued outputs as well,[99] adding further to the usefulness of this study.

8. Conclusions and outlook

The molecular emulation of larger and larger logic gate arrays, especially those serving useful purposes within small spaces for instance, needs to remain as the focus of workers in the field. Two keys to developing larger logic gate arrays, i.e. functional integration and deliberate gate-to-gate communication, are featured in this review. Now their generality needs to be established by the presentation of more examples.

However, attention also needs to be given to the equally applicable small arrays. Indeed, the smallest of them all – the gate components – can profitably be constructed in the molecular domain. These will also have their uses. Many uses of logic gates arise in the area of fluorescent sensing. The continuing commercial success with the monitoring of electrolytes and gases in blood needs to be followed up with similar applications in other contexts. The targeting of each of the principal atomic and molecular players in bioprocesses with fluorescent sensors would be very worthwhile. Some promising examples are contained in this review. A particular point worth bearing in mind is that semiconductor devices, especially those with wireless function, cannot be miniaturized to the level of intracellular operation in a cost-effective and biocompatible manner. Molecular designers have far less competition in this area than they might imagine.

It is notable that even this short review covered a wide range of inputs: light dose, H^+, Na^+, K^+, F^-, AcO^-, ATP, redox, $^1O_2$, glutathione, Cu^{2+} and various sugars/sugar-based drugs. This is merely a glimpse of the diversity that chemistry offers to device designers. In contrast, semiconductor electronics works with electric voltage only. If semiconductor electronics engineers built a world-altering industry starting with a diversity of 1, what can't chemical designers do with a diversity of 10^n?

'Lab-on-a-molecule' systems and molecular keypad locks give a taste of what can be achieved when multiple inputs are brought to bear on relatively complex molecular devices. Many of our molecular device designs, e.g. the fluorescent PET switching principle,[31] were established for small molecules but they can serve as starting points. If these designs fail in the larger systems, we will only stand to be educated about the new prevailing conditions. If these designs even succeed minimally, much new ground would be broken. We can take heart from the fact that the emergent behaviour of polymers, when compared to small molecules, has spawned industries since the time of Staudinger.[101]

The scope of this review was limited mainly to the fluorescent signalling aspects of molecular logic. Readers who are interested in non-fluorescent aspects of molecular logic will find many examples within a recent book.[7] Similarly, this book also discusses non-fluorescent non-Boolean aspects such as the encoding of alphanumeric characters (in terms of their ASCII symbols) via ^{1}H-NMR of chemical mixtures.[102] A recent reference achieves similar

encoding with a photochromic compound possessing excellent thermal stability.[103] Photo-optical modulation becomes possible as a result.

Overall, this review shows that molecular information gathering and processing[7] is in good health. Designed fluorescent molecules play leading roles. As more and more mental resources are applied to the effort, the outputs are bound to be bountiful. Applied chemistry will be the beneficiary.

References

1. A.P. de Silva, H.Q.N. Gunaratne and C.P. McCoy, *Nature* 1993, **364**, 42.
2. V. Balzani, M. Venturi and A. Credi, *Molecular Devices and Machines, 2nd Ed.* Wiley-VCH, Weinheim, 2008.
3. *Molecular and Supramolecular Information Processing*, (Ed: E. Katz), Wiley-VCH, Weinheim, 2012.
4. *Biomolecular Information Processing*, (Ed: E. Katz), Wiley-VCH, Weinheim, 2012.
5. K. Szacilowski, *Infochemistry*, Wiley, Chichester, 2012.
6. *Molecular Switches, 2nd Ed.*, (Eds: B. Feringa and W. S. Browne), Wiley-VCH, Weinheim, 2012.
7. A.P. de Silva, *Molecular Logic-based Computation*, RSC, Cambridge, 2013.
8. A.P. de Silva, N.D. McClenaghan and C.P. McCoy, in *Electron Transfer in Chemistry, Vol. 5* (Ed. V. Balzani) Wiley-VCH, Weinheim, 2001, p 156.
9. F.M. Raymo, *Adv. Mater.* 2002, **14**, 401.
10. A.P. de Silva and N.D. McClenaghan, *Chem. Eur. J.* 2004, **10**, 574.
11. A.P. de Silva, Y. Leydet, C. Lincheneau and N.D. McClenaghan, *J. Phys. Condensed Matter* 2006, **18**, S1847.
12. A.P. de Silva and S. Uchiyama, *Nature Nanotechnol.* 2007, **2**, 399.
13. Y. Benenson, *Mol. Biosyst.* 2009, **5**, 675.
14. E. Katz and V. Privman, *Chem. Soc. Rev.* 2010, **39**, 1835.
15. H. Tian, *Angew. Chem. Int. Ed.* 2010, **49**, 4710.
16. U. Pischel, J. Andreasson, D. Gust and V. F. Pais, *ChemPhysChem* 2013, **14**, 28.
17. R.A. Bissell and A.P. de Silva, *J. Chem. Soc. Chem. Commun*. 199**1**, 1148.
18. A.J. Bryan, A.P. de Silva, S.A. de Silva, R.A.D.D. Rupasinghe and K.R.A.S. Sandanayake, *Biosensors* 1989, **4**, 169.
19. C. Gell, D. Brockwell and D. A. Smith, *Handbook of Single Molecule Spectroscopy* Oxford University Press, Oxford, 2006.
20. J.R. Gregg, *Ones and Zeros* IEEE Press, New York, 1998.
21. A.P. Malvino and J.A. Brown, *Digital Computer Electronics 3rd Ed*. Glencoe, Lake Forest, 1993.
22. C. Maxfield, *From Bebop to Boolean Boogie* Newnes, Oxford, 2009.
23. M. Ben-Ari, *Mathematical Logic for Computer Science* Prentice-Hall, Hemel Hempstead, 1993.
24. E. Hughes, *Electrical Technology, 6th Ed.* Longman, Burnt Mill, 1990.
25. A.E. Keirstead, J.W. Bridgewater, Y. Terazono, G. Kodis, S. Straight, P.A. Liddell, A.L. Moore, T.A. Moore and D. Gust, *J. Am. Chem. Soc.* 2010, **132**, 6588.
26. G. Copley, T.A. Moore, A.L. Moore and D. Gust, *Adv. Mater*. 2013, **25**, 456.
27. M. Irie, *Chem. Rev*. 2000, **100**, 1685.
28. A.J.M. Huxley, M. Schroeder, H.Q.N. Gunaratne and A.P. de Silva, *Angew. Chem. Int. Ed*. 2014, **53**, 3622.
29. J.F. Callan, A.P. de Silva, J. Ferguson, A.J.M. Huxley and A.M. O'Brien, *Tetrahedron* 2004, **60**, 11125.

30. A.P. de Silva, H.Q.N. Gunaratne and K.R.A.S. Sandanayake, *Tetrahedron Lett.* 1990, **31**, 5193.
31. A.P. de Silva, H.Q.N. Gunaratne, T. Gunnlaugsson, A.J.M. Huxley, C.P. McCoy, J.T. Rademacher and T.E. Rice, *Chem. Rev.* 1997, **97**, 1515.
32. *Indicators* (Ed. E. Bishop) Pergamon, Oxford, 1972.
33. A.P. de Silva, H.Q.N. Gunaratne, P.L.M. Lynch, A.L. Patty and G.L. Spence, *J. Chem. Soc. Perkin Trans. 2* 1993, 1611.
34. A.P. de Silva, T.P. Vance, M.E.S. West and G.D. Wright, *Org. Biomol. Chem.* 2008, **6**, 2468.
35. P. Avouris, Z.H. Chen and V. Perebeinos, *Nature Nanotechnol*. 2007, **2**, 605.
36. A. Bachtold, P. Hadley, T. Nakanishi and C. Dekker, *Science* 2001, **294**, 1317.
37. *Chemosensors* (Eds: B.H. Wang and E.V. Anslyn), Wiley, Hoboken, 2011.
38. S. Ast, T. Schwarze, H. Müller, A. Sukhanov, S. Michaelis, J. Wegener, O.S. Wolfbeis, T. Körzdörfer, A. Dürkop, and H.-J. Holdt, *Chem. Eur. J*. 2013, **19**, 14911.
39. R.A. Schultz, B.D. White, D.M. Dishong, K.A. Arnold, G.W. Gokel, *J. Am. Chem. Soc*. 1985, **107**, 6659.
40. S. Zheng, T.S. Moody, P.L.M. Lynch, H.Q.N. Gunaratne, T.E. Rice and A.P. de Silva, *Photochem. Photobiol. Sci.* 2012, **11**, 1675.
41. Z.R. Grabowski and J. Dobkowski, *Pure Appl. Chem*. 1983, **55**, 245.
42. P. Batat, G. Vives, R. Bofinger, R.-W. Chang, B. Kauffmann, R. Oda, G. Jonusauskas, N.D. McClenaghan, *Photochem. Photobiol. Sci*. 2012, **11**, 1666.
43. H. He, M. Mortellaro, M.J.P. Leiner, S.T. Young, R.J. Fraatz and J. Tusa, *Anal. Chem.* 2003, **75**, 549.
44. H. He, M. Mortellaro, M.J.P. Leiner, R.J. Fraatz and J. Tusa, *J. Am. Chem. Soc*. 2003, **125**, 1468.
45. J.K. Tusa and H. He, *J. Mater. Chem.* 2005, **15**, 2640.
46. H.R. He, K. Jenkins and C. Lin, *Anal. Chim. Acta* 2008, **611**, 197.
47. A.P. de Silva, H.Q.N. Gunaratne, J.-L. Habib-Jiwan, C.P. McCoy, T.E. Rice, and J.-P. Soumillion, *Angew. Chem. Int. Ed. Engl.* 1995, **34**, 1728.
48. www.optimedical.com.
49. A.P. de Silva, H.Q.N. Gunaratne and T. Gunnlaugsson, *Tetrahedron Lett.* 1998, **39**, 5077.
50. H. Kojima and T. Nagano, *Adv. Mater.* 2000, **12**, 763.
51. M.J. Plater, I. Greig, M.H. Helfrich and S.H. Ralston, *J. Chem. Soc. Perkin Trans. 1* 2001, 2553.
52. T.D. James, M.D. Phillips and S. Shinkai, *Boronic Acids in Saccharide Recognition*, RSC, Cambridge, 2006.
53. R.A. Bissell, A.J. Bryan, A.P. de Silva and C.P. McCoy, *J. Chem. Soc. Chem. Commun.* 1994, 405.
54. S. Uchiyama, K. Iwai and A.P. de Silva, *Angew. Chem. Int. Ed. Engl.* 2008, **47**, 4667.
55. F.M. Harold, *The Vital Force–A Study of Bioenergetics*, Freeman, New York, 1986.
56. V.K. Bhardwaj, M.S. Hundal and G. Hundal, *Tetrahedron* 2009, **65**, 8556.
57. K.J. Winstanley, A.M. Sayer and D.K. Smith, *Org. Biomol. Chem*. 2006, **4**, 1760.
58. A.P. de Silva, G.D. McClean and S. Pagliari, *Chem. Commun*. 2003, 2010.
59. S.J.M. Koskela, T.M. Fyles and T.D. James, *Chem. Commun*. 2005, 945.
60. M. Alfonso, A. Espinosa, A. Tàrraga and P. Molina, *Org. Lett*. 2011, **13**, 2078.
61. A.J. Moro, P.J. Cywinski, S. Korsten and G.J. Mohr, *Chem. Commun*. 2010, **46**, 1085.
62. A. P. de Silva, H. Q. N. Gunaratne, C. McVeigh, G. E. M. Maguire, P. R. S. Maxwell and E. O'Hanlon, *Chem. Commun.* 1996, 2191.
63. D. Karak, S. Das, S. Lohar, A. Banerjee, A. Sahana, I. Hauli, S.K. Mukhopadhyay, D.A. Safin, M.G. Babashkina, M. Bolte, Y. Garcia and D. Das, *Dalton Trans*. 2013, **42**, 6708.

64. T.J. Farrugia and D.C. Magri, *New J. Chem*. 2013, **37**, 148.
65. D.C. Magri, *New J. Chem*. 2009, **33**, 457.
66. M. Pourbaix, *Atlas of Electrochemical Equilibria in Aqueous Solutions* Pergamon Press, Oxford, 1966.
67. J.H. Bu, Q.Y. Zheng, C.F. Chen and Z.T. Huang, *Org. Lett*. 2004, **6**, 3301.
68. G. Nishimura, K. Ishizumi, Y. Shiraishi and T. Hirai, *J. Phys. Chem. B*, 2006, **110**, 21596.
69. J.M. Montenegro, E. Perez-Inestrosa, D. Collado, Y. Vida and R. Suau, *Org. Lett*. 2004, **6**, 2353.
70. S. Banthia and A. Samanta, *Eur. J. Org. Chem*. 2005, 4967.
71. T. Gunnlaugsson, D.A. Mac Donaill and D. Parker, *J. Am. Chem. Soc*. 2001, **123**, 12866.
72. M. de Sousa, M. Kluciar, S. Abad, M.A. Miranda, B. de Castro and U. Pischel, *Photochem. Photobiol. Sci.* 2004, **3**, 639.
73. J.S. Park, E. Karnas, K. Ohkubo, P. Chen, K.M. Kadish, S. Fukuzumi, C.W. Bielawski, T.W. Hudnall, V.M. Lynch and J.L. Sessler, *Science* 2010, **329**, 1324.
74. K. Kaur, V.K. Bhardwaj, N. Kaur and N. Singh, *Inorg. Chim. Acta* 2013, **399**, 1.
75. W. Kloppfer, *Adv. Photochem*. 1977, **10**, 311.
76. V.T. Lieu and C.A. Handy, *Anal. Lett*. 1974, **7**, 267.
77. J.S. Kilby, *ChemPhysChem* 2001, **2**, 483.
78. R. Guliyev, S. Ozturk, Z. Kostereli and E.U. Akkaya, *Angew. Chem. Int. Ed.* 2011, **50**, 9826.
79. A.P. de Silva, *Chem. Asian J*. 2011, **6**, 750.
80. S. Erbas-Cakmak and E.U. Akkaya, *Angew. Chem. Int. Ed.* 2013, **52**, 11364.
81. S.O. McDonnell, M.J. Hall, L.T. Allen, A. Byrne, W.M. Gallagher and D.F. O'Shea, *J. Am. Chem. Soc.* 2005, **127**, 16360.
82. S. Ozlem and E.U. Akkaya, *J. Am. Chem. Soc.* 2009, **131**, 48.
83. F. M. Raymo and S. Giordani, *Org. Lett*. 2001, **3**, 3475.
84. F. M. Raymo and S. Giordani, *Org. Lett*. 2001, **3**, 1833.
85. A. P. de Silva, I. M. Dixon, H. Q. N. Gunaratne, T. Gunnlaugsson, P. R. S. Maxwell and T. E. Rice, *J. Am. Chem. Soc*. 1999, **121**, 1393.
86. L.L. Wang, B. Li, L.M. Zhang and Y.S. Luo, *Dalton Trans*. 2013, **42**, 459.
87. K. Rurack, *Spectrochim. Acta A. Mol. Biomol. Spectrosc*.2001, **57**, 2161.
88. D.C. Magri, M. Camilleri Fava and C.J. Mallia, *Chem. Commun.* 2014, **50**, 1009.
89. D.C. Magri, G.J. Brown, G.D. McClean and A.P. de Silva, *J. Am. Chem. Soc*. 2006, **128**, 4950.
90. B. Rout, L. Unger, G. Armony, M.A. Iron and D. Margulies, *Angew. Chem. Int. Ed.* 2012, **124**, 12645.
91. A.T. Wright and E.V. Anslyn, *Chem. Soc. Rev*. 2006, **35**, 14.
92. *Chemometrics* (Eds. M.A. Sharaf, D.L. Illman and B.R. Kowalski) Wiley, New York, 1986.
93. B. Rout, P. Milko, M.A. Iron, L. Motiei and D. Margulies, *J. Am. Chem. Soc.* 2013, **135**, 15330.
94. S.J. Chen, Z.Q. Guo, S.Q. Zhu, W.E. Shi and W.H. Zhu, *ACS Appl. Mater. Interfac*. 2013, **5**, 5623.
95. B. Rout, L. Motiei and D. Margulies, *Synlett* 2014, **xx**, xx. DOI: 10.1055/s-0033-1340639
96. D. Margulies, C. E. Felder, G. Melman and A. Shanzer, *J. Am. Chem. Soc.* 2007, **129**, 347.
97. A.P. de Silva, H.Q.N. Gunaratne and C.P. McCoy, *Chem. Commun.* 1996, 2399.
98. S.A. de Silva, A. Zavaleta, D.E. Baron, O. Allam, E. Isidor, N. Kashimura and J.M. Percarpio, *Tetrahedron Lett.* 1997, **38**, 2237.

99. V.F. Pais, M. Lineros, R. López-Rodríguez, H.S. El-Sheshtawy, R. Fernández, J.M. Lassaletta, A. Ros and U. Pischel, *J. Org. Chem*. 2013, **78**, 7949.
100. J.F. Callan, A.P. de Silva, J. Ferguson, A.J.M. Huxley and A.M. O'Brien, *Tetrahedron* 2004, **60**, 11125.
101. H. Morawetz, *Angew. Chem. Int. Ed. Engl*. 1987, **26**, 93.
102. T. Ratner, O. Reany and E. Keinan, *ChemPhysChem* 2009, **10**, 3303.
103. Y. Wu, Y. Xie, Q. Zhang, H. Tian, W. Zhu and A.D.Q. Li, *Angew. Chem. Int. Ed.* 2014, **53**, 2090.