Luminescent sensors and photonic switches*

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Abstract: The principles of photochemistry continue to fuel progress in luminescent sensors and photonic switches. Examples of sensors based on photoinduced electron transfer (PET) are discussed, including those which form the basis of successful systems used in physiology and medicine. More complex formats usually involve multiple receptors. One progression takes us to lanthanide complexes enabled with sensory capabilities. Another path takes us to molecular-scale implementation of logic gates such as AND and INHIBIT. Such luminescent switches can be enriched by combination with nonluminescent cousins. The latter are based on internal charge-transfer excited states (ICT). An example of rudimentary arithmetic at the molecular scale is presented by running a luminescent AND gate in parallel with a nonluminescent XOR gate. Thus, small molecules can process small numbers for the first time outside of our brains.

INTRODUCTION

Over the years, photochemists have expended most of their efforts on exploiting the energy contained in the photon, and a still-growing treasury of chemical conversions has been established [1]. The equally strong ability of the photon to carry information has been co-opted into photochemists' enterprises only occasionally [2]. This imbalance has begun to be redressed in recent times, driven mostly by needs in other areas of scientific endeavor. A growing appreciation of the molecular nature of life has been accompanied by a desire to watch the various molecular/atomic players in as much detail as possible, within and outside living systems. Luminescent molecular sensors rise to this challenge with increasing confidence [3]. One general way of designing such sensors, i.e., according to PET [4,5], is the subject of this account. This design method is strong enough to allow an attack on the current technological problem of miniaturizing information processors. The second half of this account addresses this issue. The strict page limit has meant that a detailed discussion of the relevant current literature can only be offered via several companion reviews [6].

SIMPLE PET SENSORS

As their name suggests, luminescent PET sensors operate by biasing a competition between luminescence emission and PET. In their resting "OFF" state, PET wins out. In the analyte-bound "ON" state, luminescence has its day [3b,4,5]. We start with a simple example. In spite of its simplicity, **1** [7] is now useful enough to be commercial [8]. The emission in this case comes from a textbook lumophore: anthracene [9]. Tertiary amine groups serve as receptors for protons [10]. The thermodynamic feasibility of PET between this lumophore-receptor pair is readily established with a quick look at a handbook containing redox potentials and excited-state energies [11]. As an aside, the presence of two receptors within **1** means that either receptor can spark a PET process, besides other differences from mono-

receptor systems [5,12]. At alkaline pH values, the tertiary amine units quench the anthracene fluorescence essentially completely. Acidification produces a visually dramatic fluorescence enhancement. In fact, fluorescence enhancement factors of 1000 are common for **1** and its congeners [12]. The visual impact accompanying protonation of **1** is a major reason for its use to track acidic lysosomal compartments in living cells [8].
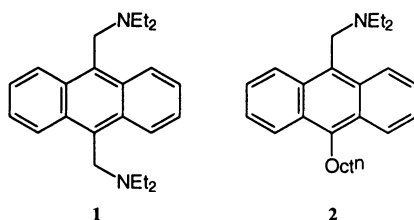
Even this entry-level PET system of an aminomethylanthracene can be put to diverse uses, as the following trio of vignettes will show. When **1** is remodeled into **2** by attaching anchoring/targeting units on the basis of hydrophobicity/hydrophilicity, mapping of the electrical properties of lipid-like membranes becomes possible [13]. The receptor module of **2** behaves like a periscope on a submarine, which can be raised or lowered with respect to the water boundary. The periscope monitors the proton concentration right up against it. The local proton concentration gives information on the local electric field strength and the local dielectric nature [14]. When **1** is transfigured into **3** by its connection to a silica bead, we have a reusable dip-type device for pH monitoring [15]. When a related transformation gives **4** where the connection is to a resin bead, we have a direct visualization of proton build-up in its immediate vicinity [16]. The elegance in this system due to Scott Miller and Gregory Copeland arises from the fact that **4** is not the sole, or even the major, inhabitant on the resin bead. The vast majority of the bead sites are taken up by copies of a member of a combinatorially generated library of potential acyl transferases, with one library member per bead. Active acyl transferases cleave the substrate acetic anhydride offered to them and build up acetic acid in their immediate environment, lighting up the sensor tag **4**. Screening for potential catalyst can hardly be simpler [17].
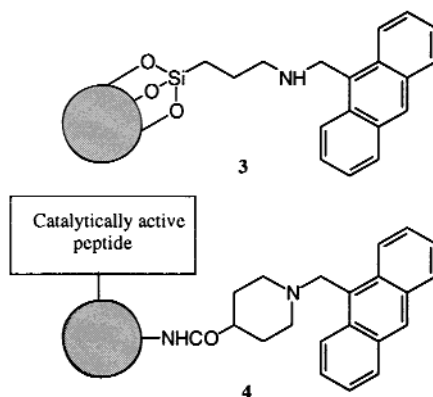
MORE COMPLEX PET SENSORS

More complex receptors

The previous section concerned itself with a single point receptor—a monoamine, which is remarkably selective in binding protons against all comers. When other analytes are targeted, selectivity of binding

is much harder won. The higher price for adequate selectivity is usually paid by careful geometric disposition of an atom array. Coordination chemistry [18] and supramolecular chemistry [19] provide a continuously growing answer to this issue. For instance, the level of sodium inside many types of resting cells can be picked up without significant interference from most other constituents with certain pseudocryptands. Such pseudocryptands were built into fluorescent ICT sensors [20] by Roger Tsien as part of a powerful program [3a]. We were able to build fluorescent PET sensor **5** from this pseudocryptand receptor, and clear "off-on" signalling is seen as the physiological range of sodium is traversed [21]. It is a pleasure to record that related receptors and lumophores [22] within the PET sensor framework give a successful blood electrolyte diagnostics platform for critical care in hospitals [23]. The N–phenyl tetraazamacrocycle receptor in **6** [24] is not unrelated, especially because **6** is a PET sensor with a virtual spacer [25]. Intracellular levels of zinc cause smooth "off-on" fluorescence signalling, with the added elegance of permitting excitation with visible light. A contemporary report from David Parker's laboratory [26] finds a much smaller (ca. 20%) luminescence modulation of **7** with zinc.

5   6

7; R$_2$ = CO$_2$$^-$

R$_1$ = CONH–
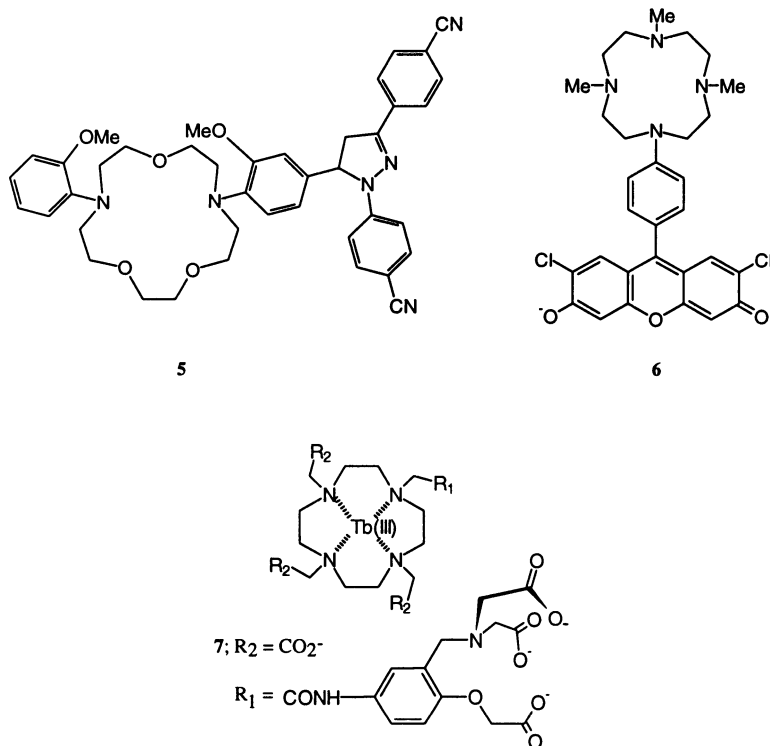
All the receptors considered in the previous paragraph were sufficiently poor binders towards protons to permit effective operation under physiological conditions. However, other applications come to mind where Brønsted basicity of the receptor must be suppressed further. Nitrogen-free receptors can be the solution if the electroactivity required for PET activity is maintained with aryl ether moieties. **8** is the archetype and gives good fluorescence enhancements with sodium [27]. No response is seen even to high acidities. The benzo-15-crown-5-ether within **8** has been cleverly expanded by Reza Dabestani and his colleagues into calixcrowns to give good and excellent selectivities for cesium with **9a** [28] and **9b** [29] respectively. The luminescent monitoring of cesium in highly acidic and highly saline reprocessing waste is looking increasing likely.

8

9a; R = O-Allyl
9b; R = H

X =
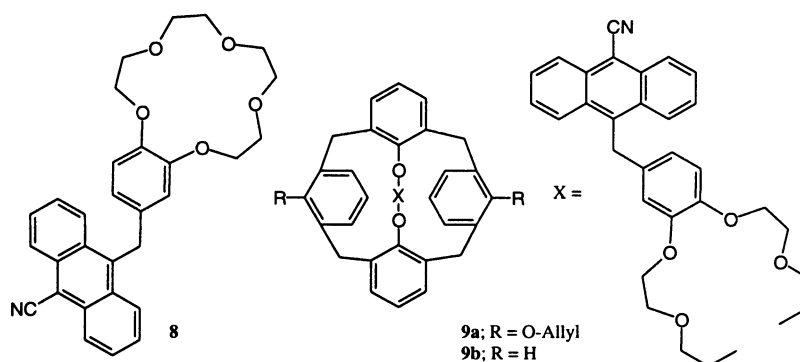
More complex lumophores

It might be surprising to discover that the "more complex lumophores" actually are lanthanide ions. The actual emission from lanthanide coordination compounds are centered on the metal ion. So where is the complexity? As they are, simple (aqua) lanthanide ions such as europium or terbium are poor at absorbing or emitting light owing to their atomic nature. To be useful, these ions need to be embedded in receptors with organic π-electron systems. Then the organic π-system can efficiently serve as the light-absorbing chromophore. If the excited state of the antenna organic π-system is energetically high enough, the gathered energy can be transferred to the lanthanide ions held closeby. Further down the line, strong emission will occur if the metal center is adequately shielded from relatively energetic vibrations such as O–H [30]. The necessity of this long process is why the title of this section was chosen. Additional manifestations of the complexity are the multiple paths available for PET (to the metal or to the antenna?) and the very small luminescence enhancements sometimes reported (e.g., concerning **7**).

The first example of this genre, **10** [31], employs the reliable tertiary-aminomethyl motif as the "spacer-receptor" section within the "lumophore-spacer-receptor" format. The lumophore is a composite of a terpyridyldicarboxylate receptor and a terbium metal ion. The substantial proton-induced luminescence enhancement could be attributed to efficient PET concerning a rather long-lived triplet excited state of the terpyridyldicarboxylate π-system. The underlying cause could be traced to the energetic


10
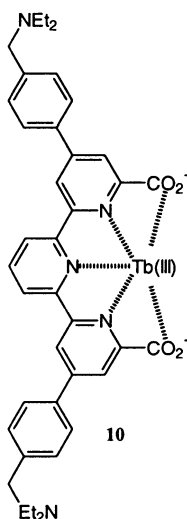
closeness of this triplet state and the terbium-centered excited state. **10** introduced the special features of delayed luminescence of lanthanides to sensor research. This thesis is being carried forward with PET and non-PET systems in David Parker's [32] and our [33] laboratories.

MOLECULAR LOGIC GATES

Most sensors, and certainly all of those discussed in the previous paragraphs, aim to respond to only one analyte. But now we deliberately plan for the response of our molecular system to be caused by some combination of a small set of chemical species. Furthermore, the objective of the inquiry changes around. With sensors, our question is "What is the concentration of the chemical analyte species?" Now our question becomes "What is the luminescence response pattern as the different combinations of chemical species are provided at saturating concentrations?" General answers to the latter query will only arrive if we design systems with multiple receptors, each essentially specific for its target.

AND logic

We introduced the subject of molecular-scale logic gates with **11** [34] which clearly combines modules from the proton-sensitive **1** and the sodium-sensitive **9**. The input protons and sodium ions find their way to their respective receptors without cross-talk. The device is powered by ultraviolet light absorbed into the 9-cyanoanthracene lumophore. The output blue fluorescence reaches us easily. However, fluorescence is seen only when both sodium and protons have occupied their respective receptor to block both PET processes. Simple system **11** therefore performs the AND logic operation, while taking care of the IN/OUT communication issues between the human domain and the molecule. Laboratories from Japan, Switzerland, Italy, and Portugal have joined us in this effort [35].
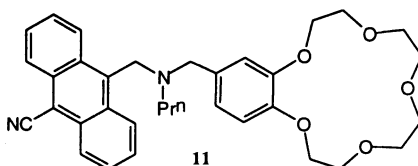

INHIBIT logic

Logic gates with chemical input and light output are naturally difficult to chain one to another, unlike conventional all-electronic semiconductor devices. Nevertheless, we have successfully tackled the integration problem at least on a very small scale. **12** [36] performs the three-input INHIBIT logic operation. This is actually a two-input AND gate (using calcium ions and β-cyclodextrin inputs) which has a third input (dioxygen) capable of disabling the entire system. The emission from 1-bromonaphthalene phosphor cannot survive aerated conditions. The binding of calcium into the diaminotetraacid receptor [3a] blocks a PET process as usual. The wrap-around binding of β-cyclodextrin to the 1-bromonaphthalene unit prevents triplet excited states of the phosphor from destructively colliding with one another. Thorfinnur Gunnlaugsson *et al.* describe the two-input INHIBIT function of **13** [37]. Here, protons form one input, and dioxygen serves as the disabling input. The atom-centered emission output is time-delayed and sharply line-like in the wavelength domain. The availability of gates with quenchable delayed emission like **12** and **13** alongside fluorescent gates like **11** allows us to operate molecular logic components serially. Either type can be selected in the presence of the other: a) delayed observation only picks gates with delayed output, and b) aeration only allows observation of fluorescent gates.
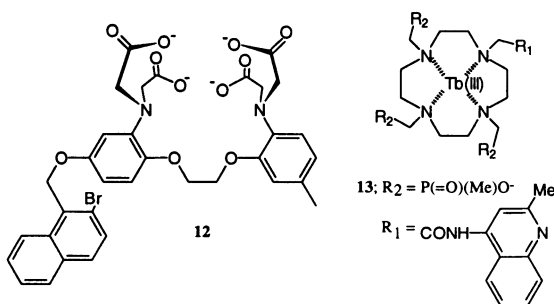
MOLECULAR ARITHMETIC

Parallel operation of molecular logic components lets us introduce molecular arithmetic. Most current computers and calculators achieve arithmetic via half-adders. These are AND and XOR gates wired in parallel which allow manipulation of the decimal number series 0, 1, and 2. Since AND gates like **11** were available, molecular-scale emulation of the half-adder needed XOR gates. The latter were known since 1997 when the laboratories of Vincenzo Balzani and Fraser Stoddart put **14** and **15** together [38]. **14** and **15** form a pseudorotaxane which collapses if protons or a tertiary amine arrive to complex out one of the components. On the other hand, application of stoichiometric amounts of protons and the tertiary amine cause mutual neutralization, which lets the pseudorotaxane **14.15** survive. The fluorescence output of **14** clearly shows XOR logic. Another clever approach to XOR logic has been unveiled recently [39]. Alberto Credi, in Vincenzo Balzani's laboratory, has outlined a workable scheme by which XOR gates like **14.15** can be a component of half-adders [40]. This scheme deserves to be carried forward to its conclusion.
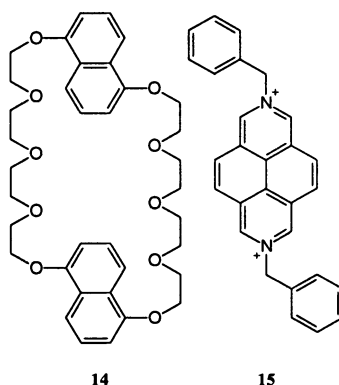
In general, however, we felt the use of molecular logic gates will be more flexible if their inputs are not governed by mutual reactivities and stoichiometries thereof. We looked to ionic perturbations of ICT excited states in electronic push-pull systems like **16** to develop XOR logic which can be easily operated in parallel with AND logic cousins [41]. The present incarnation of this type of XOR gate is only weakly luminescent, so **16** is used in transmittance mode. Importantly, **16** has two receptors selective for the two inputs (protons and calcium ions) at opposite ends of its chromophore. Thus, application of either input leads to the shifting of **16**'s absorption band away from the monitoring wavelength, i.e., transmittance digital 1. Application of both inputs causes mutual cancellation of the band shifting. Thus, **16**'s absorption band remains at the monitoring wavelength, essentially the same situation pertaining to the absence of both inputs, i.e., transmittance digital 0.

16 **17**
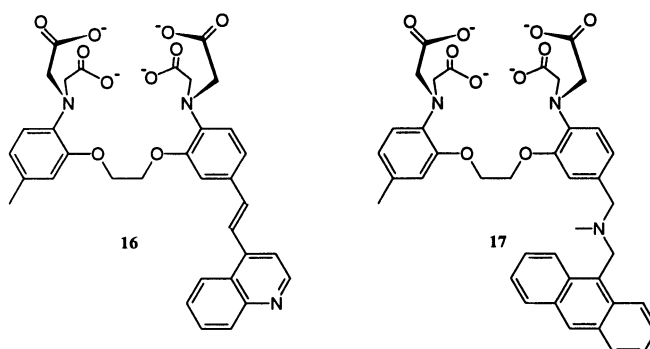
The best AND gate to partner XOR gate **16** in this numerical relationship is **17**. The genealogical relationship between **11** and **17** is clear, with a calcium ion receptor being employed within **17** rather than the sodium ion receptor found in **11**. **17** produces a fluorescence output only when protons and calcium ions are both present. The near-perfect identity of the calcium ion receptors in **16** and **17** is a great aid to their parallel operation. While the two proton receptors do not enjoy such a perfect relationship, their proton binding constants are near enough to be useful for our purpose. Optical compatibility of **16** and **17**, while being nowhere near perfect, is good enough to clearly demonstrate molecules being numerate at least up to the decimal number 2.

CONCLUSION

The foregoing pages have illustrated the thesis that photochemical design principles are key to molecular-scale gathering and processing of information—issues of mounting significance in the world at large. Whatever challenges that remain in the way of wider exploitation of this thesis would surely be overcome if the resources of the photochemistry community were to be focused thereon.

ACKNOWLEDGMENTS

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