Review Article

From Click Chemistry to Fluorescent Molecular Logic Gates
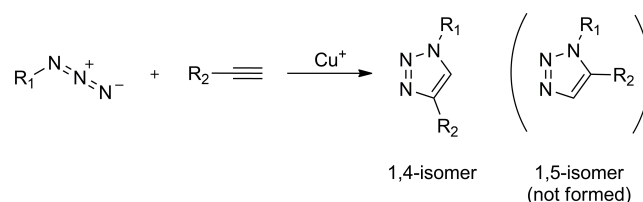
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Abstract. The 2022 Nobel Prize in Chemistry was awarded for the inventions of click chemistry and biorthogonal chemistry, which culminated from trans-disciplinary research in the areas of organic synthesis, fluorescence imaging and chemical biology. In this mini-review, the inventions of the Pourbaix sensor and the lab-on-a-molecule, both examples of purposely designed and synthesised functional molecules with fluorescence properties, are discussed. These intelligent molecules operate on the premise of a competitive tension between non-radiative photoinduced electron transfer (PET), and radiative fluorescence. Redox, acid-base and ion-binding equilibria modulate the states of these molecular devices. Potential applications of these inventions in corrosion detection, cell imaging and health diagnostics for the benefit of society are presented.

Keywords: click chemistry, triazole, molecular logic gates, photoinduced electron transfer, fluorescence, Pourbaix sensor.

1 An Introduction to Click Chemistry

The 2022 Nobel Prize in Chemistry was awarded for the invention of "click chemistry and biorthogonal chemistry" (Kolb et al., 2001; Prescher et al., 2005). It is a class of reaction that joins two molecular entities together in a predictable manner to produce a single product in high yield. This is the gold standard by chemists performing organic reactions. Two of the three winners, Morten Meldal of the University of Copenhagen, and Barry Sharpless of Scripps Research in La Jolla, California, developed the chemistry independently, working away on different problems. Sharpless was thinking about developing more efficient synthetic reactions (Kolb et al., 2001). Meldal was developing organic reactions that could be run on solid-phase peptide synthesis supports for drug discovery (Tornøe et al., 2002; Tornøe et al., 2004). They both

demonstrated an efficient way of reacting an azide (a chemical group with three nitrogen atoms) and an alkyne (a chemical group with two carbon atoms connected by a triple bond) to form a triazole (a five-membered ring of two carbon and three nitrogen atoms). This chemistry was previously known as the Huisgen 1,3-dipolar [2+3] cycloaddition (Huisgen et al., 1967), but the reaction was less than ideal. The reactions required heating, and took hours or days, and the yields were generally poor with a mixture of 1,4 and 1,5 isomers. The Copenhagen and La Jolle teams discovered that the presence of trace copper ions greatly speeds up the reaction without the need for heating and the result is formation of only the 1,4-isomer. The reaction is stereospecific and selective for the formation of a single product.

Figure 1: The 1,3-dipolar Cu(I) catalysed click reaction between an azide and an alkyne forming the 1,4-triazole product (and not the 1,5-triazole).

However, it was the trans-disciplinary aspect, the application of this chemistry to the field of chemical biology, that demonstrated the usefulness of this invention. Within living systems, alkyne and azide groups are not found. It so happens that these functional groups are generally non-reactive and non-toxic to living things. The third award winner, Carolyn Bertozzi of Stanford University, developed a copper-free "click" reaction, as copper(I) is toxic to living cells. The goal of the Bertozzi group was to use fluorescent reporter molecules that could attach to polymeric sugar molecules found on the surface of living cells called glycans, which are large carbohydrate

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molecules located on the surface of cells. She named her invention biorthogonal chemistry, which refers to any chemical reaction that can occur inside living systems without interfering with the native biochemical cellular processes (Prescher et al., 2005). Then using a fluorescence microscope, the site of the bond formed with the fluorescent reporter can be observed and the target of interest located and quantified. The approach has been expanded to the specific labelling of cellular proteins and studying of drug targets in live cells (Kim et al., 2019). The copper-free click reaction uses a strained alkyne, such as cyclooctyne (Agard et al., 2006). Alkynes favour a linear geometry. However, in cyclooctyne the two single carbon-carbon bonds on either side of the alkyne are bent, turned inward within the eight-membered carbon ring. In this form, the cycloalkyne is under strain. Because of the pent-up strain energy, there is no need for a catalyst. The relieve of the strain energy from the compressed geometry during the chemical transformation from a triple bond (alkyne) to a double bond (alkene) on formation of the triazole ring provides the reaction with the thermodynamic driving force necessary to overcome the activation barrier. Figure 2 illustrates this approach to a click reaction.
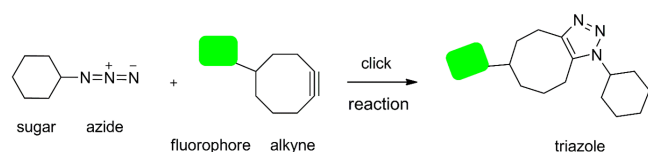

Figure 2: The click reaction between a generic sugar modified with an azide, and a fluorophore-labelled cyclooctyne.

The Bertozzi group applied this chemistry to living cells and animals. Modified sugar molecules with the azide group were fed to the living cells. The cells assimilated the modified sugar molecules as if they were no different than the unmodified sugar molecules and incorporated them into the glycans. Once the modified sugars were stationed on the extremity of the cell within the glycan structure, addition of a (fluoro-labelled) cyclooctyne resulted in the click chemistry on the cell interface. The alkyne reacts with the azide to form two strong chemical bonds resulting in the triazole product figure 2. The location of the glycans are then trackable by a fluorescence signal from the result of the click reaction on irradiation of the cells with light.

2 An Introduction to Fluorescent Indicators and Pourbaix Sensors

The first explicit report of fluorescent pH indicators was with the polyaromatic hydrocarbon anthracene as the fluorescent reporter (de Silva et al., 1985). Fluores-

cent redox (pE) indicators soon followed (Blough, 1988). Numerous reviews on fluorescent chemosensors have appeared at regular intervals to cover the research activity within this busy field (de Silva et al., 1997, 2009, Callan et al., 2005). The coupling of anthracene and pyrene fluorophores with the redox-active ferrocene emerged via 2,3-diaza-1,3-butadiene spacers (Chen-Jie et al., 2008; Martínez et al., 2006). The utility of click chemistry to redox-fluorescent sensors was demonstrated in the Ghosh lab (Thakur, 2013), who reported chromogenic and fluorogenic indicators for Pb(II) figure 3. One such molecule was synthesised from the alkyne-derived anthracene and ferrocene-azide in the presence of copper (I) iodide and 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU) in N,N-dimethylformamide (DMF). The anthracene-triazole-ferrocene product is a dual mode chemosensor in aqueous acetonitrile. In the presence of lead (II) (Pb^{2+}) the solution colour changes from yellow to green, and when irradiated with 363 nm, a blue emission prevails. The Thakur team has since capitalised on azide-alkyne click chemistry to successfully demonstrate ferrocenyl-coumarin INHIBIT combinatorial logic gates (Bhatta et al., 2017; Karmakar et al., 2020). Reviews on chemosensors incorporating click-derived triazoles (Ahmed et al., 2021; Heng Lau et al., 2011) and ferrocene (Sahoo, 2020) are also available.
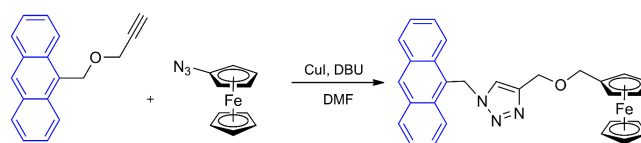
Figure 3: Synthesis of a dual-output colorimetric and fluorimetric sensor (Thakur, 2013).

During the same year of 2013, our research group was also designing a molecule with an anthracene fluorescent reporter and a redox-active ferrocene group. We coined our invention a "Pourbaix sensor" (Farrugia et al., 2013; Magri, 2009). It too works on the concept of orthogonality and uses fluorescence as a means of communication between molecules and human researchers. Orthogonality is used in the context to describe how one photoactivated process occurs independently of another process. Our objective was to design molecules that could detect for two fundamental physicochemical parameters, the acidity and the oxidisability of a solution, and we wanted to detect for both parameters simultaneously. From a logic perspective, this satisfies an AND logic algorithm (de Silva, 2013, Yao, 2020). The reason for our interest in these two conditions is that corrosion of materials, like steel, occurs at condition of high acidity (low pH < 4) and high oxidative conditions near the surface of the material. The stand-

ard industrial method for corrosion detection is the liquid penetrant test using a fluorescent dye and a UV lamp. In logic terms, the fluorescent dye functions as an elementary PASS 1 logic gate. During the corrosion process of steel, iron (III) ions are liberated, which is an oxidant with ferrocene. To detect for the occurrence of these two conditions, we designed a molecule with a fluorophore reporter, blue-emitting anthracene figure 4 and a tertiary amine for detecting protons, and ferrocene for detecting an oxidant, such as ferric Fe^{3+} ion. We employed a reductive amination reaction to bring two components together to form a C-N bond.
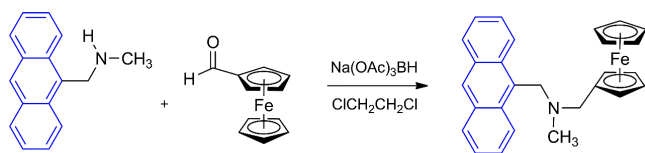

Figure 4: The synthesis of a Pourbaix sensor from an anthracene-containing molecule with an amine group reacting with a ferrocenecarboxaldehyde using sodium triacetoxyborohydride ($Na(OAc)_3BH$).

The molecule functions based on the principles of photoinduced electron transfer (de Silva et al., 2009; Spiteri et al., 2015) Initially, the molecule is not fluorescent. To activate a fluorescence response, the molecule must be irradiated with light, specifically 365 nm light from a UV lamp. However, light activation is not enough to cause the molecule to fluorescence. Within the molecule there are two photoreactions that can occur once the molecule is in the excited state. An electron can pass from the tertiary amine to the excited anthracene fluorophore, or an electron can pass from the ferrocene to the excited anthracene fluorophore. Either photoinduced electron transfer (PET) reaction prevents the sensor molecule from emitting fluorescence. The fluorophore is insulated from the amine proton receptor and ferrocene redox donor by methylene carbon spacers. An enhanced bright fluorescent signal is only observed when the sensor molecule is protonated at the amine and the ferrocene group is oxidised, having met the conditions of high acidity and high oxidisability. Figure 5 illustrates the four states of the molecule and the fluorescence output in each case exemplified as an AND logic gate.

3 Application of Pourbaix Sensors for Corrosion Detection

The cost of corrosion to the world economy is a staggering amount in excess of $2.5 USD trillion per year. Corrosion is initially invisible to the naked eye, but once it is visible, structural damage has already occurred. So what if we could detect the corrosion at an early stage
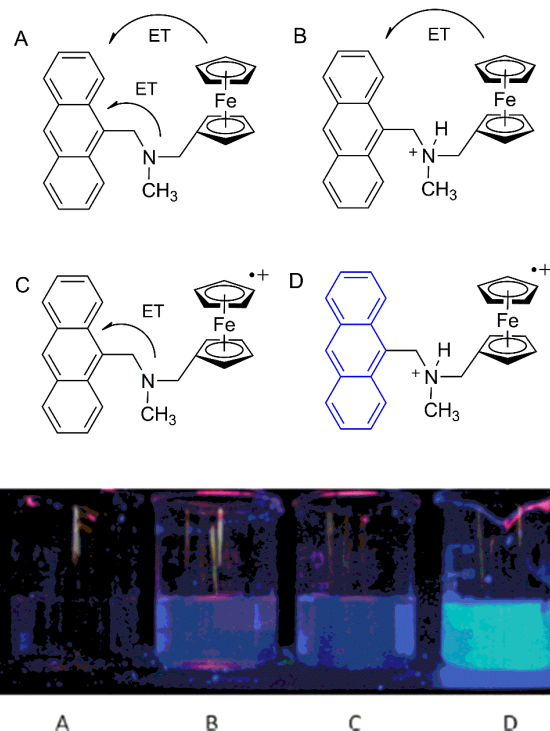

Figure 5: Top: The four states of the Pourbaix sensor after activation with light. Bottom: The fluorescent output of the sensor in methanol irradiated with a UV lamp at 365 nm in a dark cabinet. The labels A-D correspond to the four states of the molecule. Beaker D is the 'on' state. Reproduced with permission of the Royal Society of Chemistry and the Centre National de la Recherche Scientifique (Farrugia & Magri, 2013).

before it can be visually observed? Our next generation of Pourbaix sensors were designed to be brighter and and to emit at a longer wavelength with a green fluorescence (Spiteri et al., 2015, 2018; Johnson et al., 2016). Two fundamental changes were made to our next prototypes, which both contributed to increasing the fluorescence brightness. First, we changed the fluorophore to 4-aminonaphthalimide, which has photoinduced charge transfer character (Valeur & Leray, 2000). Second, we placed the fluorophore in the middle of the device so that the ferrocene and amine groups were situated at the extremities to shorten the distance for the PET reactions from ferrocene figure 4. We have succeeded with the incorporation of smart molecules in hydrogels (Scerri et al., 2022) and on polystyrene beads (Vella Refalo et al., 2019, 2018) (figure 6).

The attachment of naphthalimide logic gates to the polystyrene beads (via formation of a peptide bond CO−NH) occurs in an efficient click-like way to yield a single product in quantitative yield.

A third generation of Pourbaix sensors were developed using the perylenediimide (PDI) fluorophore (Scerri et al.,
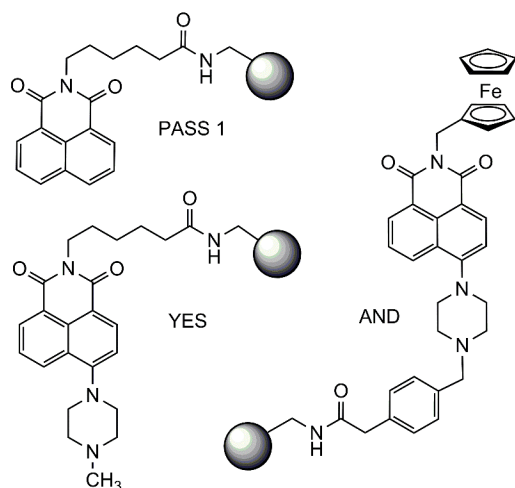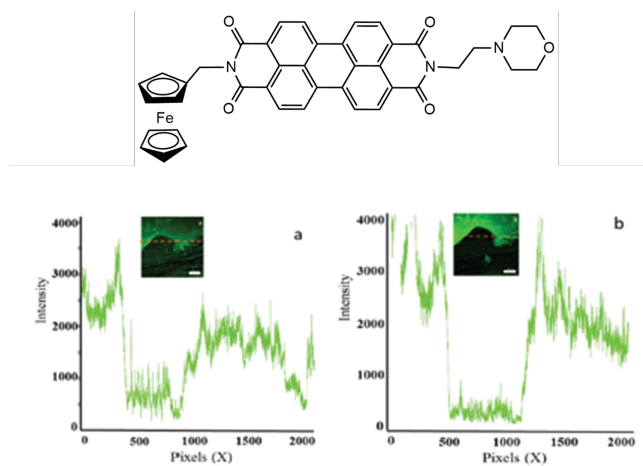
Figure 6: Examples of PASS 1, YES and AND molecular logic gates bound to polystyrene beads. The beads are not drawn to scale and have micrometer dimensions.

Figure 7: Confocal fluorescence microscope images (λ_{ex} = 488 nm) of a scratched edge of a polyurethane coating with a PDI Pourbaix sensor after exposure to a 0.5 M NaCl solution at (a) 0 min and (b) 90 min. Inset: The orange dotted line shows the cross section being viewed. Reproduced with permission of the Royal Society of Chemistry (Scerri et al., 2021).

2021) as shown in figure 7. PDIs are used as pigments in paints and protective coatings in the automotive industry because of their excellent thermal stability and high temperature tolerances. We incorporated a PDI molecule into a polyurethane coating on mild steel (Scerri et al., 2021). The molecule was irradiated with a 488 nm laser and observed through the eyepiece of the fluorescence microscope before and after treatment. Coated mild steel coupons were dipped into a 0.5 M NaCl solution or deionised water as a control. No discernible rust was visible to the naked eye after exposure to the 0.5 M NaCl solution after 90 minutes. However, through the eyepiece of the fluorescent microscope, the onset of corrosion was apparent. The polyurethane edge of the scratch become a bright green and a cross section image highlights a deeper 'moat' along the coating edge (figure 7). The result exemplifies the possibility of using logic-based molecules as part of the preventive maintenance protocol for vital transport such as airplanes and space vessels and infrastructure such as bridges and towers.

4 Application of Pourbaix Sensors in Living Cells

Naphthalimides are a class of molecule with proven anti-proliferation activity (Tandon et al., 2017). They intercalate with topoisomerase (Topo) II enzyme and DNA to induce apoptosis by blocking the binding of the Topo enzyme to double strand DNA. We explored the possibility of using Pourbaix sensors as potential multi-targeted anticancer and fluorescent cellular imaging agents (Johnson et al., 2021). The compounds were studied *in vitro* against MCF-7 and K562 cancer cell lines. Most of the

compounds did not display any cytotoxicity even after 72 hours. We therefore examined the cellular uptake and fluorescence imaging. A vibrant green emission was observed in the nucleus of the live cells within minutes, confirming the internalisation within the MCF-7 cells (figure 8).
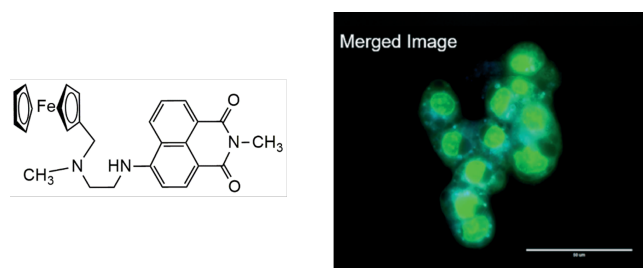
Figure 8: Fluorescent image of a Pourbaix sensor in MCF-7 cells after 24 hours incubation period. Scale bar of 50 μM. Images were captured on an EVOS FL fluorescent microscope. Reproduced with permission of the Royal Society of Chemistry (Johnson et al., 2021).

5 Application of Pourbaix Sensors for Multi-Analyte Detection

Another invention based on the concept of orthogonality and fluorescence is the concept of a 'lab-on-a-molecule' (Magri et al., 2006). Rather than detecting for two parameters, could we detect for three or more parameters including solvents, metal ions, anions, saccharides, polarity and medications (Rout et al., 2012, 2014)? It may seem trivial counting from two to three, but adding a third dimension in geometry changes the perspective from

the concept of area to volume. In medicine, detection of three targets simultaneously even better confirms a disease condition. A molecule with this enhanced capability would be a three-input AND logic gate.

For the first lab-on-a-molecule, three receptors were selected, each specific for an individual analyte. A benzo-15-crown-5 ether binds Na^+, a tertiary amine binds H^+, and a phenyliminodiacetate binds Zn^{2+}. The fluorescence reporter is the planar blue-emitting anthracene fluorophore. These four components, the three receptors and the fluorophore, are covalently attached and separated by methylene CH_2 spacers. In a solution of water with Na^+, H^+, and Zn^{2+} present at high concentration levels, the molecule glows blue. The absence of just one of these three analytes prevents the molecule from emitting a blue emission, similar to the image in figure 5.

The latest prototype of this genre is a green-emitting aminonaphthalimide lab-on-a-molecule (Scerri et al., 2019) figure 9. The sodium receptor was modified with the stronger binding N-(2-methoxyphenyl)aza-15-crown-5 ether for binding Na^+, a piperazine ring for binding H^+, and a ferrocene group for sensing Fe^{3+}. The significance of this combo of three analytes is of relevance to corrosion detection. As already discussed, high Fe^{3+} and H^+ levels are diagnostic for eroding conditions for steel objects. The presence of Na^+ accelerates the rate of corrosion.

This same trio of analytes is also of consequence to cancer. Cancerous cells have a tendency to grow much more rapidly than health cells. There is evidence that the analyte levels are often higher in cancer cells. Free Fe^{3+} is redox active and is known to contribute to various cancers including colorectal and liver cancer. The intracellular vacuoles of tumour cells are more acidic and the intracellular Na^+ levels of cancer cells can be up to three times higher than in normal tissue. Hence, the simultaneous detection of high Na^+, H^+ and Fe^{3+} could not only serve as an early warning method for corrosion of steel (Magri et al., 2014), it could also be a test for diagnosing a patient with cancer. The alternative is three separate tests and consideration of the results of the three tests by a practitioner, which will lengthen the time for the analysis. However, lab-on-a-molecule systems can perform a 'yes' or 'no' decision quickly and intelligently. It is envisioned that perhaps one day we may have a lab-on-molecule that could perform a CHEM-7 analysis, for example, for Na^+, K^+, Cl^-, HCO^-, blood urea nitrogen, creatinine and glucose from a tiny drop of blood (Scerri et al., 2019).

6 Conclusion

Chemical reactions that are fast, selective and high yielding are desirable to the chemist. Within living systems, reactions that are biorthogonal, that is, those that do
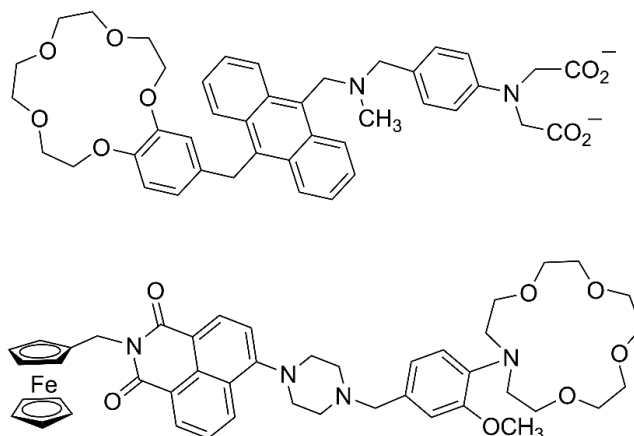
Figure 9: The molecular structures of three-input lab-on-a-molecules.

not react with the complex biochemistry, are desirable to the cellular biologist for probing the cellular environment in a controlled manner. Some possible steps forward for the field of molecular logic gates is the development of molecules in more synthetically efficient ways, and the incorporation of fluorescence sensing molecules within living systems that can detect multiple analytes in an orthogonal and cooperative way. The amalgamation of the concepts of click chemistry and biorthogonal chemistry with molecular logic-based computation should yield new discoveries and inventions going forward.

7 Conflicts of Interest

The author declares no conflicts of interests in the preparation this manuscript.

8 Acknowledgements

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