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Review Article

Supramolecular Chemistry in Water: Self-Assembly of Multi-Component Fluorescent Molecular Logic Gates in Micelles

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Abstract. A recent strategy for developing supramolecular logic gates in water is based on combinations of molecules via self-assembly with surfactants, which eliminates the need for time-consuming synthesis. The self-assembly of surfactants and lumophores and receptors can result in interesting properties providing cooperative effects useful for molecular information processing and other potential applications such as drug delivery systems. This article highlights some of the recent advancements in supramolecular information processing using microheterogeneous media including micelles in aqueous solution.

Keywords: supramolecular chemistry in water, molecular recognition, chemosensors, micelles, molecular logic gates, biomedical diagnostics

1 Introduction

The objective of COST Action CM1005 is the development of supramolecular systems that work in water (Oshovsky, Reinhoudt & Verboom, 2007; Zayed, Nouvel, Rauwald & Scherman, 2010, http://supracheminwater.wordpress.com/). The COST Action is divided into three working groups (i) the molecular recognition of biologically and environmentally relevant species in water (ii) the selective control of reactions in water, and (iii) the self-assembly of organized structures in water that are stimuli responsive and can be used for programming functions in materials and devices. The Action aims to improve the understanding of multiple non-covalent weak bonds (hydrogen bonding, electrostatics, Van der Waals forces, pi-pi interactions etc.) that are collectively powerful interactions for selective recognition of chemical analytes and processes in water.

The majority of molecular receptors for recognition of physiologically important cations, anions and neutral analytes are not readily soluble in water (Magri & Mallia, 2013; Schneider, 2013). One working group within the COST Action is designing and synthesising novel intelligent molecules readily soluble in water, which is not always an easy task even for skilled organic chemists (Magri, 2012). A simple way to circumventing the issue of poor solubility of receptors in water is to incorporate them in micelles to form water-soluble nanoscale supramolecular devices (Pallavicini, Diaz-Fernandez & Pasotti, 2009). Micelles result from the spontaneous association of surfactants to form dynamic spherical conglomerates above the critical micelle concentration (cmc), and other shaped assemblies at higher concentrations, which are representative biomimetic models of biological membranes (Turro, Grätzel & Braun, 1980). In the case of ionic micelles, the micelle interface has an electrical double layer and a potential difference on the order of several hundred millivolts. The electric field can modulate the sensitivity of ion determination due to an amplifying effect on the local ion concentration, Moreover the receptor-micelle nanodevices often show enhanced binding properties as will be discussed.

This article highlights examples of supramolecular multicomponent systems with stimuli-responsive properties that perform molecular computation-based logic (de Silva, 2013; Szaciłowski, 2008). The examples illustrated are presented according to increasing complexity of the logic system (de Silva & Uchiyama, 2007). A common theme throughout is the use of micelle media, which introduces synergistic effects. Examples are included representative of fluorescent sensing devices for various kinds of chemical species as inputs including protons, cations and anions. Readers with a desire for background literature on fluorescent probes can view the cited references (Bissell, Bryan, de Silva & McCoy, 1994; Callan, De Silva & Magri, 2005; de Silva et al., 1997; Valeur & Berberan-Santos, 2012).

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2 Single-input Logic Gates

There are four possible single-input logic gates: PASS 0, PASS 1, YES and NOT. PASS 0 is the simplest of Boolean logic operations and appears trivial. Any molecule that is non-fluorescent remains so independent of the absence or presence of an input. PASS 1 is another trivial logic gate exemplified by a fluorophore that emits fluorescence on excitation independent of the absence or presence of an input. The design of 'fluorophore–spacer–receptor' and 'fluorophore–receptor' molecules allows for YES and NOT logic to be demonstrated. The standard molecular YES logic gate is based on the competition between photoinduced electron transfer (PET) and fluorescence yielding an *off-on* switching action of the fluorescence intensity ideally with no change in the wavelength (de Silva et al. 2009). A NOT gate, also referred to an inverter operates by *on-off* switching.

Akashi's team demonstrated a viable way for detecting barium by using an ether crown-based fluorophore **1** in aqueous solution (Nakahara, Kida, Nakatsuji & Akashi, 2004). The pyrene-functionalised monoaza-18-crown-6 ether derivative is a 'fluorophore-spacer-receptor' system with poor water solubility and Ba^{2+} binding properties in water. Addition of the non-charged detergent Triton X-100 above the cmc allows the chemosensor to position itself in the less polar micellar location, yielding a supramolecular assembly which results in binding of Ba^{2+} by the cryptand. The amino nitrogen atom is involved in the complexation of Ba^{2+}, which cancels the PET from the tertiary amine to the pyrene fluorophore with a high fluorescence output. Although the experiment is conducted at pH 10 due to the sensitivity of **1**, the strategy exemplifies a selective way of detecting barium by YES logic.

Bhattacharya and Gulyani are perhaps the first to develop the concept of multifunctional hydrophobic probe design (Bhattacharya & Gulyani, 2003). The method was demonstrated by detecting for Zn^{2+} in micelles and vesicles with 1-pyrenyl-methyl-*bis*(2-picolyl) amine **2**. In water the chemosensor aggregates as observed by an excimer emission about 500 nm. In micelles, however, aggregation of the probe molecule **2** is prevented such that no excimer emission is observed, while the monomer emission in the presence of Zn^{2+} at 400 nm is substantially enhanced. Large fluorescence enhancements were observed in polyoxyethylene (20) sorbitol monolaurate (Tween 20) micelles and in dipalmitoyl phosphatidylcholine vesicles.

A salophen-UO_2 complex has been demonstrated to exhibit a remarkable increase in binding of fluoride in CTAB micelles (Cametti, Dalla Cort & Bartik, 2008). In water alone, the salophen-UO_2 complex is not soluble. UV-visible titration studies of **3** in 50 mM CTAB

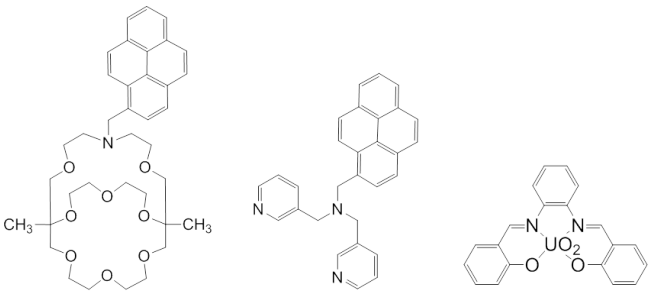

Figure 1: Chemosensors for detection Ba^{2+} **1** and Zn^{2+} **2** and F^- **3** with the assistance of micelles.

were consistent with a 1:1 binding isotherm with fluoride with a binding constant of 10 800 M^{-1}. Sulfate, acetate and phosphate also bind, but one to two orders of magnitude lower. An understanding of the spatial orientation of the salophen-UO_2 receptor **3** in the micelle was determined by NMR paramagnetic relaxation enhancement (PRE) and Nuclear Overhauser Effect (NOE) measurements (Keymeulen, De Bernardin, Dalla Cort & Bartik, 2013). It was discovered that **3** preferentially locates near the micelle interface orientated with the oxygen-linked aromatic rings facing the bulk aqueous solution and the nitrogen-linked phenyl ring backed into the hydrophobic core. The techniques presented by the collaboration of Dalla Cort and Bartik bring a fresh perspective with respect to shedding light on the location and spatial orientation of probes in miceller media. PRE and NOE experiments could be used to complement fluorescent mapping studies near micellar membranes (Bissell et al., 1994; Uchiyama, Iwai & de Silva, 2008).

By self-assembly of a lumophore and receptors with micelles, logic gates can be constructed in a 'plug and play' fashion (de Silva, Dobbin, Vance & Wannalerse, 2009). Triton X-100 is used to solubilize a hydrophobic tris(2,2'-bipyridyl)Ru(II) complex **4**, a lumophore with both a long excitation state lifetime of 200 ns and a long emission wavelength about 625 nm. The elemental PASS 0 and PASS 1 logic gates were mentioned as the micelle alone and the micelle containing **4**. YES logic is demonstrated using a 2-nitrophenyl-*n*-octyl ether receptor **5**, which is emissive on protonation of the aromatic amine at pH 2. Ligand **5** also binds Ca^{2+} at pH of 8 with YES logic behavior by a five-fold emission enhancement. This approach of using separate components for the lumophore and receptors allows for the configuration of new modules enabling new functions in the supramolecular ensemble. To reiterate, the microheterogeneous media is an essential component for enhanced luminescence to be observed.

Table 1: General truth tables for seven two-input logic gates.

$Input_1$	$Input_2$	AND	NAND	OR	NOR	XOR	XNOR	INH
0	0	0	1	0	1	0	1	0
0	1	0	1	1	0	1	0	0
1	0	0	1	1	0	1	0	1
1	1	1	0	1	0	0	1	0

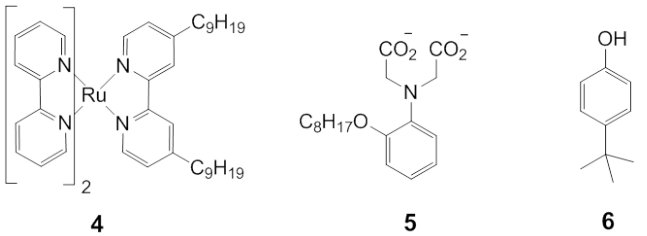

Figure 2: Components **4**–**6** for a supramolecular 'plug and play' logic device.

3 Two-Input Logic Gates

Double input logic gates were also demonstrated in Triton X-100 surfactant with **4** and **5** (de Silva et al., 2009). For referral, Table 1 summarises the two-input logic for seven types of logic gates. When both H^+ and Ca^{2+} are present as inputs, the assembly is an OR logic gate as the presence of either input or both provides a fluorescence output. AND logic is observed when *para-tert*-butylphenol **6** is added as a new module to the assembly. In basic solution, **6** is deprotonated to the negatively charged phenolate, which acts as an electron donor to the excited ruthenium complex rendering the luminescence *off* at pH 12. However, on decreasing the pH to 8, a six-fold luminescence improvement is observed at 625 nm.

A stimuli-responsive polymeric micelle was demonstrated by the Wang group (Wei, Guo & Wang, 2011) as a novel strategy for developing an intelligent drug delivery system (Alvarez-Lorenzo, Bromberg & Concheiro, 2009). Certain tumor cells are known to have characteristically high reductive environments and high proton concentrations. The Wang team developed polymeric crosslinked micelles with Andriamycin **7** conjugated to the micelles. The pH and reduction conditions are the key stimuli-based parameters for an AND logic result. The drug is initially doubly trapped in the micellar system by hydrazone and disulfide bonds. Drug release is achieved at pH 4 and in the presence of 15 mM of the redox agent, dithiothreitol. Addition of acid cleaves the hydrazone bonds while dithiothreitol cleaves the disulfide bonds. When both input chemicals are present, **6** is severed from the polymers, which disperse as smaller fragments. Liberation of the drug by both stimuli allows for selective release of the drug at the target tumor cells.

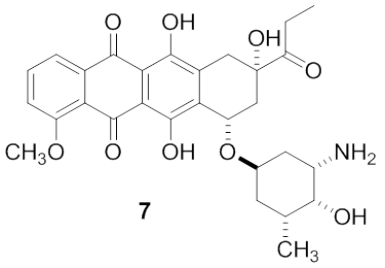

Figure 3: The molecular structure of the anti-cancer drug Adriamycin **7**.

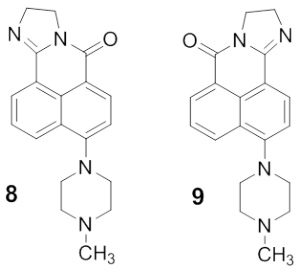

Figure 4: The molecular structures of the naphthalimide regioisomers **8** and **9**.

The team of Qian demonstrates up to ten logic functions with the reconfigurable molecules **8** and **9** in water, and extends the use of sodium dodecyl sulphate (SDS) surfactant as an additional input using both absorbance and fluorescence outputs (Qian, Qian, Xu & Zhang, 2008). Six two-input gates are configurable for AND, NAND, OR, NOR, XNOR, INHIBIT logic in additional to the four one-input gates. The versatility of these naphthalimide-based molecules for logic applications is due to the two accessible sites of protonation according to a 'receptor$_1$-fluorophore-spacer-receptor$_2$' design (Zammit, Pappova, Zammit, Gabarretta & Magri, 2015). Though regioisomers, the fluorescence quantum yields of **8** and **9** are significantly different at 0.218 and 0.055 in water; however, implemented as logic devices the characteristics are similar. Addition of anionic SDS (low 0, high 8.2 mM) and hydroxide (pOH of 7 and 4) provides INH and XOR using the absorbance

at 425 nm and negative logic convention for the fluorescence output to form the basis of a half-subtractor. Dual protonation of both compounds provides pathways that change the absorbance and emission spectra, as well as the interaction of SDS below and above the cmc.

The theme of naphthalimides and SDS surfactant and protons is continued with the addition of using the inorganic salt Na_2SO_4 as an alternative input (Qian et al., 2008). With inputs SDS and Na_2SO_4, OR and AND logic are exhibited for **10** and **11**, respectively. XOR and INH logic gates can also be interpreted from the output **11** due to the additional PET pathway from the tertiary amine. Exploiting both the PET and ICT push-pull channels, the authors share their interpretation of a half-adder and half-subtractor functions (Pischel, 2007).

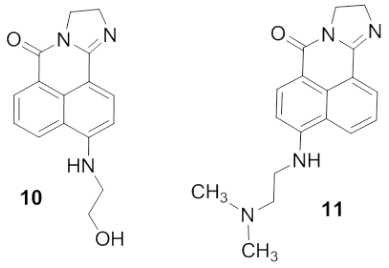

Figure 5: Examples of a two-input OR gate **10** and AND gate **11** with SDS and Na_2SO_4 as inputs.

The team of Uchiyama and de Silva demonstrated the first example of dual-input molecular computation within a small defined nanospace of 3 nm volume (Uchiyama, McClean, Iwai & de Silva, 2005). A lipophilic molecule **12** consisting of a benzo-5-crown-15 ether, an anthracene fluorophore, a tertiary amine and an octyl hydrocarbon chain was used as a probe of the micelle environments. The molecular device contains two classic electron donors used in PET systems. Self-assembly of the molecular probe in cationic and neutral micelles of cetyltrimethylammonium chloride (CTAC), octyl β-D glucopyranoside and Triton X-100 yielded no observable fluorescence response. However, in tetramethylammonium dodecyl sulfate (TMADS) micelles the molecular probe exhibits a ten-fold fluorescent enhancement in the presence of H^+ and Na^+ at elevated concentrations. The reason is the binding constant of benzo-5-crown-15 ether, at only $\log K$ of -0.3 in water, increases by two order of magnitudes ($\log K = 1.9$) due to the local concentration of Na^+ at the micelle interface. At pH 3 and 0.4 M sodium ions, the H^+ and Na^+ input concentrations are high resulting in a substantial fluorescent output due to the sodium ions binding to the benzo-5-crown ether and the protons to the tertiary amine, which in both cases, prevents PET to the anthracene fluorophore reminiscent to a AND logic gate. The strategy illustrates the ability to sense within a nanometer radius (a dimension where silicon-based electronic devices cannot approach) and opens up the possibility of molecular computation in other microheterogeneous (i.e. liposomes and vesicles) and biological systems.

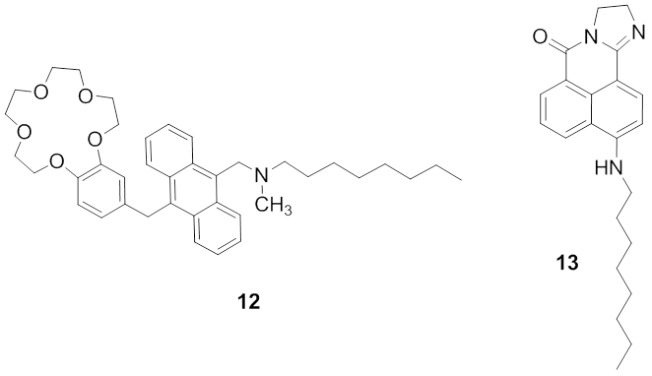

Figure 6: Hydrophobic molecular probes **12** and **13** for information retrieval in nanospaces.

4 Three-input Logic Gates

The first reported example of the potential cross-fertilization between Boolean algebra and biomedical sensing was reported for a three-input AND 'lab-on-a-molecule' based on a competition between PET and fluorescence (Magri, Brown, McClean & de Silva, 2006). In this instance, three receptors are incorporated within a single molecule: a benzo-15-crown-5 ether for Na^+, a tertiary amine for H^+, and a phenyliminodiacetate for Zn^{2+}. The modular covalent arrangement of the receptors, spacers and fluorophore facilitates the cooperative sensing algorithm (Magri & de Silva, 2010). Consideration of **12** with the micelle as one of the inputs illustrates a supramolecular system as an example of a 3-input AND logic gate with the inputs Na^+, pH and TMADS.

Three-input IMPLICATION logic is demonstrated using a naphthalimide probe with an octyl hydrocarbon chain **13** (Qian, Xu, Zhang & Qian, 2011). This type of logic is similar to an IF-THEN operation. However, in this example the fluorescence is modulated by the inputs SDS, CTAC and temperature. The molecule is fluorescent in water with a quantum yield of 0.135. Addition of SDS just below the cmc concentration $\sim$ 8.0 mM quenches the fluorescence. Subsequent addition of 100 µM cetyltrimethylammonium bromide (CTAB) causes a 25-fold fluorescence enhancement. The rational for these observations is that the opposite charges of SDS and CTAB in addition to the hydrophobic alkyl chains common to both surfactants results in aggregation between the two micelles, and consequently, liberation of the fluorescence probe. An increase in temperature enhances the fluorescence by making the probe molecule more soluble. The net outcome is that in the

Table 2: Truth table for the supramolecular three-input AND logic gate **12**.

$Input_1$	$Input_2$	$Input_3$	Output
Na^+ [a]	H^+ [b]	TMADS [c]	Fluorescence
0 (low)	0 (low)	0 (low)	0 (low)
0 (low)	0 (high)	1 (low)	0 (low)
0 (low)	1 (low)	0 (high)	0 (low)
0 (low)	1 (high)	1 (high)	0 (low)
1 (high)	0 (low)	0 (low)	0 (low)
1 (high)	0 (low)	1 (high)	0 (low)
1 (high)	1 (high)	0 (low)	0 (low)
1 (high)	1 (high)	1 (high)	1 (high)

[a]High input level of 0.4 M of NaCl. Low input level maintained with no added NaCl. [b]High input level 10^{-3} M acid. Low input level 10^{-11} M acid. [c]High input level of 20 mM TMADS. Low input level no TMADS.

Table 3: Truth table for the supramolecular three-input IMPLICATION logic gate **13**.

$Input_1$	$Input_2$	$Input_3$	Output
SDS [a]	CTAB [b]	T [c]	Fluorescence
0 (low)	0 (low)	0 (low)	1 (high)
0 (low)	0 (high)	1 (low)	1 (high)
0 (low)	1 (low)	0 (high)	1 (high)
0 (low)	1 (high)	1 (high)	1 (high)
1 (high)	0 (low)	0 (low)	0 (low)
1 (high)	0 (low)	1 (high)	1 (high)
1 (high)	1 (high)	0 (low)	1 (high)
1 (high)	1 (high)	1 (high)	1 (high)

[a]High input level of 10 µM of SDS. Low input level maintained with no added SDS. [b]High input level 20 µM CTAB. Low input level with no CTAB added. [c]High input level at 75 °C and low input level at 25 °C.

presence of SDS alone, the fluorescence (and absorbance) is low, while in the other seven combination of SDS, CTAB and temperature, the fluorescence in high (Table 3). We recently reported a colorimetric and fluorimetric inverted enabled OR logic array with CTAC, Triton X-100 and hydroxide as inputs using a rhodamine B probe derivatised with a hexane chain (Caruana, Camilleri Fava & Magri, 2015).

5 Multi-level Logic

In the previous section supramolecular systems were illustrated that detect for three input conditions and with only two output results of either a low fluorescence or a high fluorescence. Now we demonstrate systems with three output levels. Traditionally, the design principle for these systems is based on 'fluorophore-spacer$_1$-receptor$_1$-spacer$_2$-receptor$_2$' and 'receptor$_1$-spacer$_2$-fluorophore-spacer$_2$-receptor$_2$' strategies to develop *off-on-off* ternary systems (de Silva, Gunaratne & McCoy, 1996). At a low input level the switch is *off*, at a medium input level the switch is *on*, and at a high input level the switch is *off* again (Pais et al., 2013). The regulation of analytes in living things is governed by ternary logic. Too little or too much of analyte results in illness, and in extreme situation even death. Thus, good health requires the right balance of each analyte within a specific concentration range (Burtis & Ashwood, 2001).

Off-on-off systems were first demonstrated with **14** based on a fluorophore-spacer$_1$-receptor$_1$-spacer$_2$-receptor$_2$' design consisting of an anthracene fluorophore, a tertiary amine and pyridine as the receptors (de Silva et al., 1996). Pallavicini also demonstrates an easy-to-assemble approach with no synthetic effort in a 'plug and plug' fashion (Pallavicini et al., 2009). In the analogous supramolecular version, the fluorophore is pyrene **15** and the two receptors are the lipophilic bases *N*,*N*-dimethyl-*N*-dodecylamine **16** and 2-dodecylpyridine **17**. Assembled in Triton X-100 as the surfactant, and anionic SDS as the co-surfactant (at various concentrations), the multicomponent system is a tuneable *off-on-off* micellar sensor device with the capability of shifting the *on* window along the pH axis with the curve apex ranging between pH 5 to 10. In another *off-on-off* example from the Pallavicini group, the polyaspartamide based co-polymer, PHEA-PEG$_{5000}$C$_{16}$ is used as the surfactant and SDS and CTAC as the co-surfactants (Diaz-Fernandez et al., 2010).

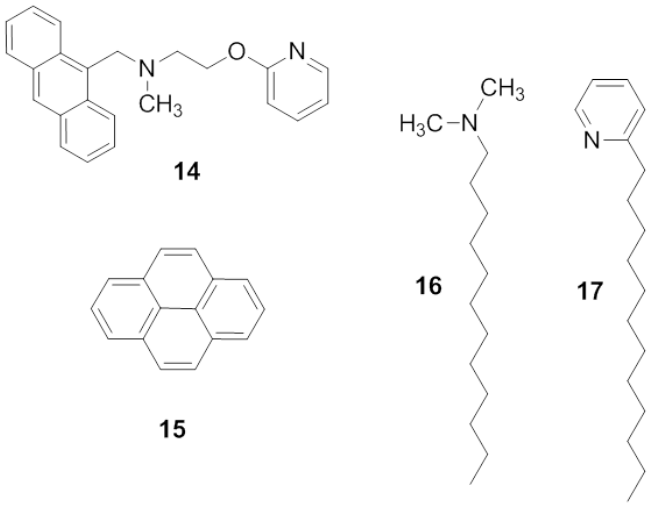

Figure 7: An *off-on-off* molecular device **14** and the components of a supramolecular device consisting of pyrene **15**, *N*,*N*-dimethyl-*N*-dodecylamine **16** and 2-dodecylpyridine **17**.

Das reported pH dependent fluorescence switching of salicylideneaniline in micelles according to *on-off*, *off-on*, and *off-on-off*. pH profiles (Das & Dutta, 2014). Salicylideneaniline **18** behaves as an *off-on* switch in 1:1 acetonitrile/H_2O and 3% negatively charged SDS aqueous solution. At pH 6 or lower, the fluorescence is *off* while at pH 10 the fluorescent is *on*. However, in CTAB and Triton X-100 ternary *off-on-off* behaviour is admirably observed with the fluorescence turning *off* pH 10. In CTAB a distinct *on* pH window is observed between pH 7–11. The differing chemistry is attributed to the equilibrium between the keto (fluorescent) form **18** and the enol form (non-fluorescent) **19** by acid and base catalysis.

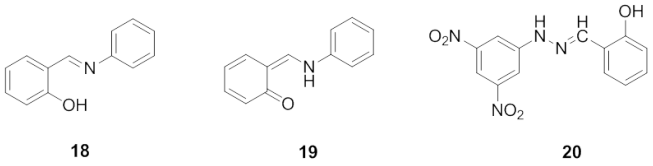

Figure 8: Examples of hydrazones **18** and **20** with *off-on-off* behaviour in micelles.

In another recent study, Goswami and Das also report the dinitrophenolhydrazone derivative **20** in 1:1 CH_3OH:H_2O, SDS, CTAB and Triton X-100 (Goswami & Das, 2011). In 1:1 CH_3OH:H_2O, a broad pH window from 5 to 12 is observed with *off-on-off* behaviour, while with CTAB a much narrow pH window is observed between 4 and 7. In SDS a *low-medium-high* response is observed on increasing pH. The sites of protonation are thought to be the phenol and the secondary amine. At pH 12 fluorescence quenching results from the phenolate to the 2,4-dinitrophenyl moiety. Below pH 6, fluorescence quenching is postulated to result from protonation of the dinitroanilic nitrogen, which lowers the oxidation further allowing for excited electron transfer from the phenol.

Pallavicini have both independently demonstrated *on-off-on* pH window sensing molecular devices (Denat, Diaz-Fernandez, Pasotti, Sok & Pallavicini, 2010). A multicomponent approach consisting of Coumarin 343 **21**, Cu^{2+} ions and *N*-dodecylated trimethylcyclen **22** are self-assembled in Triton X-100 micelles. At low pH the two organic components do not interact, and the fluorescence from 21 is high. At intermediate pH, 21 is deprotonated and coordinates to Cu^{2+} ions resulting in fluorescence quenching. At high pH, the carboxy end of **21** is displaced from Cu^{2+} by the formation of complex with hydroxide reviving the fluorescence. In both examples, the *off* window is between pH 6 and 8, which is the physiological pH sweet spot of 6.8 to 7.4. The lipophilicity of nonsteroidal anti-inflammatory drugs (NSAIDs) is also measurable by expressing an *off-on* fluorescent signal correlating the fluorescence increase with the logarithmic water/octanol partition coefficient ($\log P$).

The emissive and absorptive properties of **13** and other related members of the naphthalimide-based fluorescence sensors were investigated as chromogenic and fluorogenic sensors for anionic surfactants (Qian, Qian & Xu, 2009). The probe **13** is an *on-off-on* fluorescence sensor for SDS. Interpretation of the spectroscopic output provided for multiple output readouts at 430 nm by UV-visible absorption and 525 nm by fluorescence spectroscopy with SDS, CTAB and Triton X-100 allowing for a sensor array, which also discriminates SDS at different concentration ranges. The octyl hydrocarbon chain was found to be an important parameter as other model probes with butyl and dodeceyl hydrocarbon chains exhibited inferior emission switching properties.

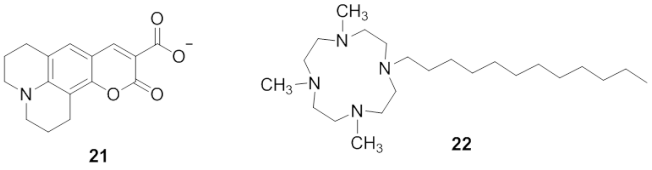

Figure 9: The components Coumarin 343 **21** and *N*-dodecylated trimethylcyclen **22** as part of an *on-off-on* supramolecular nanodevice for gauging drug lipophilicity.

6 Conclusion

The self-assembly of surfactants provides an alternative strategy for information processing applications at the molecular level. Supramolecular systems can be designed that respond to various chemical inputs such as cations, anions, pH as well as physiochemical parameters. Advantageously, supramolecular assemblies require minimal synthetic effort. Most of the one- and two- inputs logic gates have been demonstrated in micellar media as well as examples of supramolecular systems that exhibit *off-on-off* and *on-off-on* profiles within narrow pH windows and *low-medium-high* ternary pH profiles on sequential addition of proton inputs. Applications in drug delivery and smart materials are just a sliver of potential uses.

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