Molecular Sensors

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Sensing on a Molecular Level—Chemistry at the Interface of Information Technology**

*Oliver Trapp**

analytical methods · micelles · molecular devices · sensors · signal modulation

Dedicated to Prof. Helmut Schwarz on the occasion of his 65th birthday

The combination of molecular devices capable of processing information regarding their environment and mechanisms to efficiently encode the information is of great potential in many fields of chemistry and beyond. Molecular computers based on networks of interacting molecules that perform logic operations or organized as neurons in a neural network can be envisaged.[1] Molecular computers could overcome the size limitations of currently used microprocessors, which contain integrated circuits made from silicon substrates. Furthermore, molecular computers could directly interact with their environment, thus making them suitable as intelligent sensors and detectors.[2] At a first glance, such a research goal seems to be very futuristic; however, the fusion of knowledge from several research areas could make it feasible.

Recently, systems chemistry,[3] similar to systems biology,[4] has received great attention for the investigation of complex mixtures of interacting molecules, including the study of systems under thermodynamic control (that is, dynamic combinatorial libraries[5]) or kinetic control (that is, pseudodynamic combinatorial libraries,[6] oscillating reactions, as well as self-replicating[7] and autocatalytic systems). Such molecular reaction systems could be used to trigger supramolecular organization (such as optical switches[8] and chiral switches[9]), thereby resulting in dynamic devices.[10]

Low-molecular-weight gelators based on a chiroptical switch with appended hydrogen-bonding units have been described by van Esch and Feringa.[11] These switches allow for photocontrol of chirality on the molecular level. Of particular interest are molecular systems which fluoresce and can switch between "on" and "off" states in response to chemical stimuli.[12] These designs are based on a photoinduced electron-transfer (PET) mechanism, and open up, for example, the way to the unambiguous detection of biologically active species. Thus, the switching molecule has to possess the following three features: 1) a receptor which reversibly binds the chemical species to be detected, 2) a fluorophore to receive and/or transmit light signals, and 3) a way to report interactions between the chemical target and the receptor to the fluorophore. Even more complex switches can be realized by combining several systems; one example is an "off/on/off" switch which consists of a "fluorophore-spacer 1-receptor 1-spacer 2-receptor 2" system (Figure 1).

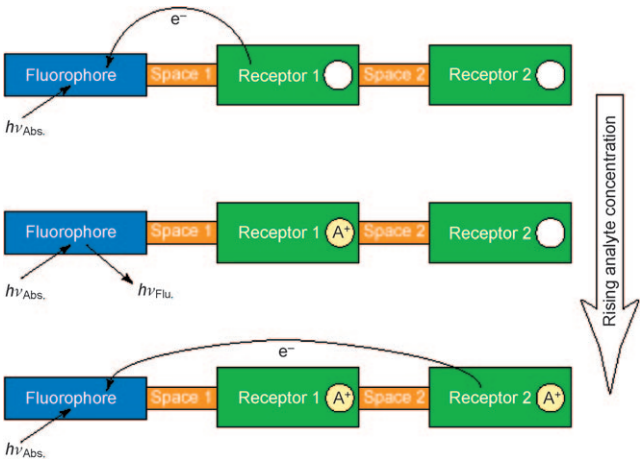

Figure 1. Fluorescent photoinduced "off/on/off" electron-transfer switches. Receptor 1 is a stronger binder of analyte A^+ than is receptor 2. The "receptor 1-spacer 1-fluorophore-spacer 2-receptor 2" format is as valid as the format shown here. Reprinted with permission from reference [12b].

Here, the concept is that both receptors 1 and 2 select the same target compound but at different concentrations, and thus require different binding strengths for the target compound. In the example given, the binding strength of receptor 1 must be greater than that of receptor 2. Furthermore, receptor 1 has to form a PET pair with the fluorophore to give a switch of the "off/on" type, whereas the PET pair of receptor 2 and the fluorophore have to result in an "on/off" state.

The precise switching between "on/off" (or "0/1") states opens up the possibility to perform Boolean operations,[13] and thus logical operations such as AND, OR, and XOR can

[*] Dr. O. Trapp
Max-Planck-Institut für Kohlenforschung
Kaiser-Wilhelm-Platz 1, 45470 Mülheim (Germany)
Fax: (+49) 208-306-2995
E-mail: trapp@mpi-muelheim.mpg.de
Homepage: http://www.mpi-muelheim.mpg.de/kofo/institut/arbeitsbereiche/trapp/trapp_e.html

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be achieved.[14] Molecular logic gates able to process chemical inputs can be loaded with arrays of logic functions.[1a] This can, for example, be realized in enzyme cascades (Figure 2).[15] For example, the enzyme glucose dehydrogenase (GDH) uses glucose as a substrate (input 1) in the presence of the cofactor NAD^+ to produce gluconic acid (output 1). Horseradish peroxidase converts H_2O_2 (input 2) into H_2O with formation of NADH. These two enzymes are coupled by the same cofactor cycle involving two redox states (NAD^+ and NADH). If there is no NAD^+ available and the system has reached a steady state, the NADH concentration will only drop if there is no glucose but H_2O_2 is present. If the system is operated in this way and the change of absorption is detected as output 2, this enzyme system represents an inhibit (INH) logic. This example demonstrates that even single molecular species can be used to execute logic and algebraic operations, for example, addition and subtraction.[16] Recently it has been demonstrated that fluorescein can act as a model molecular calculator with a reset capability.[17]

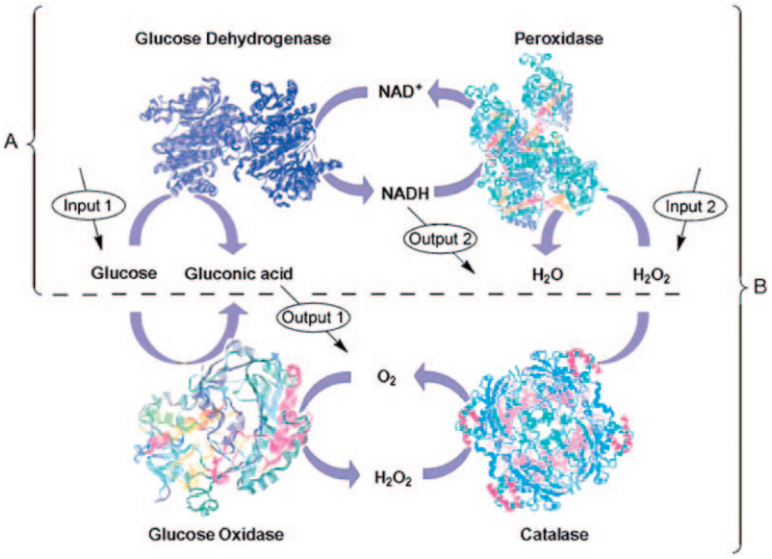


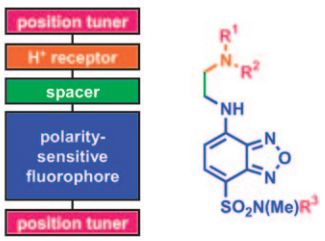
Figure 2. a) Logic gates based on two coupled enzymes. b) Half-adder based on four coupled biocatalysts. Reprinted with permission from reference [15].

The discovery of suitable methods to transport information and to encode signals is as important as the information processing. Multiplexing[18] (that is, multiple analyses on the same bulk sample at the same time) is one of the most efficient methods to encode signals and to deconvolute signals mathematically. There are various multiplexing methods, including modulation of the signals and transport of the information by electromagnetic waves or molecular beams as well as through the use of several signal sources in arrays of sensors which result in overlapping signals. The advantages of this approach are the improvement in the signal-to-noise ratio (Felgett advantage) and the throughput by decreasing the acquisition time.

A highly interesting example of integrating some of the above described concepts is given in a recent publication by Uchiyama et al.[19] This study describes a novel multiplexing fluorescent sensor composed of 18 structurally different fluorescent sensors (Figure 3). These sensor molecules are built according to a modular concept, with 4-sulfamoyl-7-aminobenzofurazan as the fluorophore, and are used to simultaneously monitor local proton concentration and polarity in micellar systems through variation of their emission properties.

The study of proton concentration and polarity distributions near micellar membranes is of great importance for understanding and controlling processes that take place at such interfaces and which are hard to access by other techniques. Furthermore, proton mapping of micelles could give further insights in to the mechanism of acid/base catalysis in such systems. As the polarity $\bar{\varepsilon}$ depends on the position of the sensor in the micellar system, and it can be expected that the polarity $\bar{\varepsilon}$ only depends on the radial distance in spherical micelles, polarity data give exact information about the position of the sensor in the micellar system. However, such probes can also influence the shape, aggregation, and stability of micelles, and thus a proper sensor design is crucial for successful application.

The modular concept of the structures used as sensors is depicted in Figure 3. As mentioned above, the sensors are built from a polarity-sensitive fluorophore that is linked through a spacer to a substituted amine group that acts as the H^+ receptor. The substituents function as position tuners, and in an ideal case a continuous radial distribution of the probes near the micellar membrane is achieved. It can be expected that the more hydrophobic substituents will reside longer in the hydrophobic areas of the micelle while hydrophilic substituents reside preferentially in the hydrophilic areas. The local proton concentration can be determined from the change in the pK_a value in the micellar solution relative to that in water (ΔpK_a). The difference in the pK_a value is



R^1	R^2	R^3 = Me	R^3 = *n*Oc
CH_2COO^-	CH_2COO^-	**1**	**10**
CH_2COO^-	Et	**2**	**11**
H	H	**3**	**12**
CH_2CH_2OH	CH_2CH_2OH	**4**	**13**
$CH_2CH_2OCH_2CH_2$		**5**	**14**
Me	Me	**6**	**15**
H	Et	**7**	**16**
CH_2COOMe	Et	**8**	**17**
Et	Et	**9**	**18**

Figure 3. Fluorescent multiplexing sensors **1**–**18**. The orders of **1**→**9** and **10**→**18** are determined by the log *P* value of the corresponding amine R^1R^2NH (*P* = *n*-octanol/water partition coefficient). Reprinted with permission from reference [19].

independent of the intrinsic acidity/basicity of the sensor and is only changed by the electrostatic potential and dielectric constant at the sensor location. Another important feature of the sensor is the "off/on" switching capability arising from the "fluorophore-spacer-receptor" arrangement, which controls the PET process. Therefore, the ΔpK_a value can be determined from the fluorescence intensity, and the local polarity, which gives the exact position, is obtained from the emission wavelength of the polarity-sensitive fluorophore. Uchiyama et al. studied proton gradients in micelles of Triton X-100 (micelle radius $r = 4.8$ nm), octyl-β-D-glucopyranoside ($r \approx 2.3$ nm), sodium dodecylsulfate ($r < 3.6$ nm), and cetyltrimethylammonium chloride (CTAC, $r < 3.5$ nm) with these sensors.

The ΔpK_a value is directly obtained from the fluorescence intensity. The determination of the local dielectric constants from the emission wavelengths is more complicated because of the difference in the polarity-sensing properties of the sensor in acidic and basic conditions. Two relationships between the emission wavelength and the ε value of the solvent are needed—one under acidic and one under basic conditions—to estimate the local polarity near the sensors. A median ε value ($\bar{\varepsilon}$) is used as the parameter for the polarity near a sensor. As expected for the position-sensitive proton receptors **1**–**18**, the position of the sensor changes near the micellar membrane when the conditions are switched from acidic to basic. This change is caused by the increased hydrophilicity through the protonation of the receptor and causes the sensor to relocate to a more hydrophilic region of the micelle. Figure 4 shows the results, in the form of a

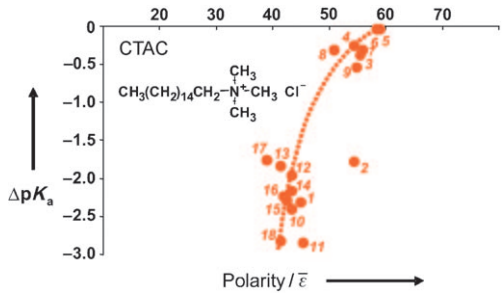


Figure 4. $\Delta pK_a/\bar{\varepsilon}$ diagram obtained with sensors **1**–**18** (10 μM) for CTAC (5.0 mM). The numbers indicate the sensor according to the nomenclature in Figure 3. Reprinted with permission from reference [19].

$\Delta pK_a - \bar{\varepsilon}$ diagram, for micelles formed from CTAC. The diagram demonstrates that the fluorescent multiplexing sensors are distributed at different positions—starting from bulk water to the interior of the micelle. This diagram shows that the gradual decrease in the effective proton concentration near a micelle can be mapped on the nanoscale by using multiplexing fluorescence sensors.

Such molecular sensors deliver a remarkably high space resolution and are not limited to the measurement of proton concentrations; other compounds can also be detected. Such systems can also be used as models to understand information flow and processing in biological systems as well as to realize intelligent and self-organizing molecular systems.

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