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An Au Nanoparticle/Bisbipyridinium Cyclophane-Functionalized Ion-Sensitive Field-Effect Transistor for the Sensing of Adrenaline

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A film consisting of polyethyleneimine (PEI), Au nanoparticles (12 ± 1 nm) and coadsorbed cyclobis(paraquat-*p*-phenylene) (1) was assembled as a sensing interface on the Al_2O_3 insulating layer of an ion-sensitive field-effect transistor (ISFET). Adrenaline (2) was sensed by the functionalized ISFET with a detection limit of 1×10^{-6} M. The sensing ability of the nanostructured device for the analysis of adrenaline originates from the preconcentration of the analyte in the cyclophane by $\pi-\pi$ donor−acceptor interactions. Analysis of adrenaline is accomplished by the measurement of the source-drain current, I_{sd}, or by the gate-source voltage, V_{gs}. The sensing device is reusable (at least 100 cycles) and exhibits high stability.

Nanoparticles attract substantial research efforts due to their unique electronic, optical, and catalytic properties.[1,2] Recent research activities have used functionalized nanoparticles and molecular or polymer components as building blocks for composite microassemblies that yield novel superstructured materials.[3−5] For instance, layered arrays of citrate-capped Au nanoparticles cross-linked by a Zn^{II} porphyrin−bipyridinium diad assembled onto conductive glass have been used for photoelectrochemical applications.[6] Similarly, Au nanoparticle layers have been assembled onto conductive glass and cross-linked by the molecular receptor cyclobis(paraquat-*p*-phenylene) (**1**). The resulting Au nanoparticle/receptor superstructures, exhibiting three-dimensional conductivity, can be used for the electrochemical sensing of hydroquinones by their preconcentration in the bipyridinium receptor sites.[7] Ion-sensitive field-effect transistors (ISFET) provide interesting transducers for sensoric applications. The available technologies for the miniaturization of ISFET devices and the capability for the specific chemical modification of the gate enable the design of new sensitive microscale sensor systems.[8,9] Here we report on the organization of an Au nanoparticle/cyclobis(paraquat-*p*-phenylene) sensing interface for the ISFET detection of adrenaline.

Chart 1 outlines the assembly of the sensing ISFET device. First, the Al_2O_3 insulator of an ISFET (Institute of Microtechnology, University of Neuchatel, Switzerland) was modified with polyethyleneimine[10] (PEI, MW 750.000). The resulting PEI-functionalized surface interacted with citrate-capped Au nanoparticles (12 ± 1 nm) and the Au nanoparticle/PEI array produced then interacted with **1** (30 mM). The modification of the FET device by the various components was qualitatively confirmed by

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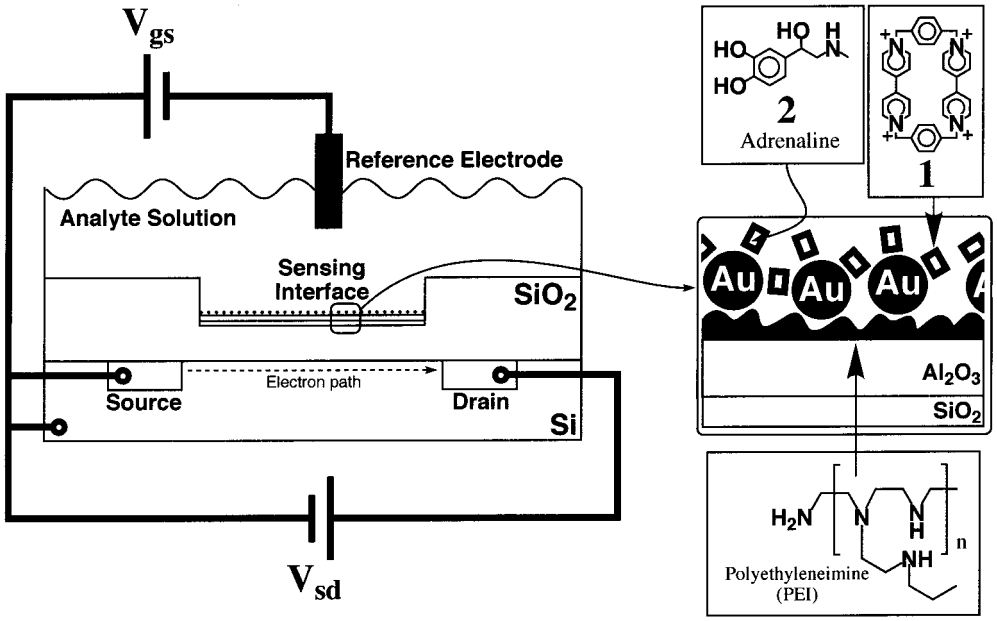
Chart 1. Schematic Representation of the Functionalized ISFET Device and the Configuration of the Sensing Interface Consisting of PEI/Au Nanoparticle/Cyclobis(paraquat-*p*-phenylene) (1)



following the source-drain current (I_{sd}) as a function of the gate-source potential (V_{gs}) (see Supporting Information). To evaluate the composition of the array quantitatively, we performed complementary microgravimetric quartz crystal microbalance analyses. Au/quartz crystals were modified with PEI[11] that yielded a frequency change of $\Delta f = -1370$ Hz, corresponding to a mass change of $\Delta m = 7.49 \times 10^{-6}$ g, and a surface coverage of $\sim 5.1 \times 10^{-11}$ mol·cm^{-2}. The resulting PEI-functionalized crystal was interacted with the Au nanoparticles which caused a frequency change of $\Delta f = -82$ Hz, which corresponds to a mass change of $\Delta m = 4.48 \times 10^{-7}$ g, and a surface coverage of the Au nanoparticles of $\sim 1.6 \times 10^{11}$ particles·cm^{-2}. Subsequent treatment of the PEI/Au nanoparticle array with **1** yields a frequency change of ~ -10 Hz that corresponds to a surface coverage of $\sim 2.7 \times 10^{-11}$ mol·cm^{-2}. Since the molecular receptor **1** does not interact with the bare Au electrode or the Au−PEI-functionalized surface, the binding of **1** to the interface is attributed to the electrostatic association of the receptor **1** to the Au nanoparticles. From the respective values of surface coverages of the Au nanoparticles and **1**, we estimate that ~100 molecules of **1** are associated with each nanoparticle. This value is in good agreement with the value derived from electrochemical assay of Au nanoparticle/**1** arrays.[7] It should be noted that the association of **1** with the citrate-capped Au particles originates from electrostatic interactions. Previous studies[7] have indicated that very stable Au nanoparticle/**1** arrays are formed, which can be removed from the surface only by physical polishing. Thus, the Au particles act as a "glue component" to bind **1** to the sensing interface.

The functionalized ISFET device was used to sense adrenaline (**2**) by two different modes: (i) The source-drain current is monitored at different concentrations of adrenaline, while the gate-source potential (V_{gs}) and the source-drain potential (V_{sd}) are maintained constant. (ii) The source-drain current (I_{sd}) and the source-drain voltage (V_{sd}) are varied at different concentrations of the analyte to keep the other parameters constant.

Figure 1A shows the source-drain current (I_{sd}) at different concentrations of adrenaline ($V_{gs} = 1.5$ V; $V_{sd} = 0.5$ V). Figure 1B shows the changes in the gate-source voltage upon keeping the source-drain current and the source-drain voltage constant ($I_{sd} = 100$ mA; $V_{sd} = 0.5$ V). Both signals yield comparable results and allow the sensing of adrenaline with a sensitivity limit of 1×10^{-6} M.[12] Control experiments reveal that the changes in I_{sd} and V_{gs} upon addition of the analyte originate from specific interactions between adrenaline and the receptor **1**. No changes in the I_{sd} and V_{gs} values of the ISFET device are observed upon the addition of adrenaline within this concentration range to the bare FET device, to the PEI-functionalized system, or to the PEI−Au nanoparticle-modified FET. The specific interactions between adrenaline (**2**) and the receptor (**1**) are attributed[13] to the specific binding interactions between the analyte and the host receptor. The observed I_{sd} levels off at a high concentration of **2**. This is attributed to the saturation of the receptor sites associated with the sensing interface by the host−analyte. The changes in the gate potential upon the complexation of adrenaline to the receptor sites originate from changes in the charge of the gate interface. Since adrenaline is positively charged at pH 7.6, its association to the receptor sites enhances the positive charge of the gate interface. Benesi−Hildebrand analysis of the curves shown in Figure 1, assuming that each molecule of the analyte (**2**) associated with

(11) Au/quartz crystals (EG&G, 9 MHz, AT-cut) were used. Measurements were performed in air after each modification step. We are aware that the Au/quartz support is different from the insulating Al_2O_3 layer of the ISFET. The frequency changes of the crystal upon the immobilization of Au nanoparticles and the receptor (**1**) allow us to estimate the relative content of the different components in the composite array.

(12) The sensitivity limit was determined by experimental results where the signal-to-noise ratio was higher than 3. The reproducibility of the V_{gs} value at the lowest detectable concentration corresponds to ±1.0 mV for a series of six experiments.

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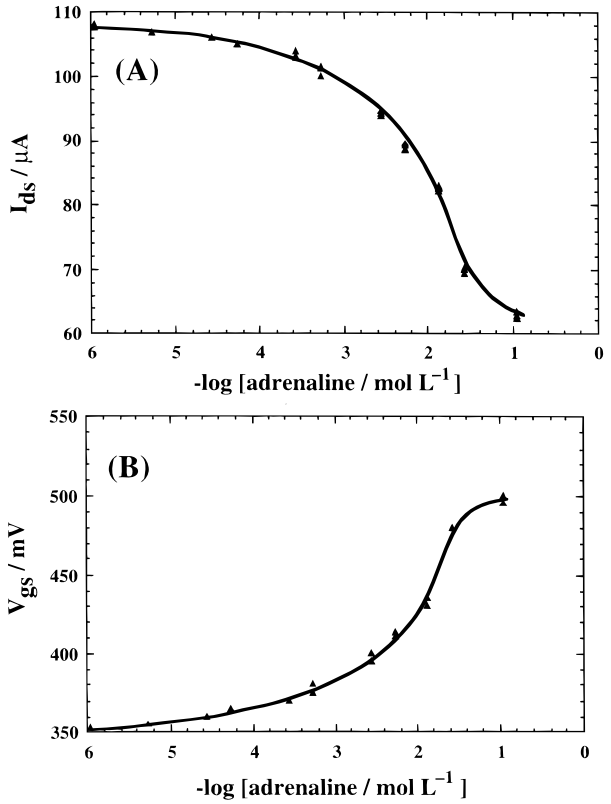

Figure 1. (A) Source-drain current at different concentrations of adrenaline (**2**). In all experiments, $V_{gs} = 1.5$ V and $V_{sd} = 0.5$ V. (B) Gate-source potential at different concentrations of **2**. In all experiments, $I_{sd} = 100$ mA and $V_{sd} = 0.5$ V. All experiments were recorded in 0.1 M phosphate buffer solution (pH 7.6) using an Ag/AgCl as the reference electrode.

the receptor units has a similar effect on the gate interface and the transduced signal, gives an association constant of 200 ± 30 M^{-1} for the binding of adrenaline to the receptor **1**. It should be noted that only π-donor compounds capable of binding to the receptor sites associated with the sensing interface have an effect on the transduced I_{sd} values. Furthermore, other neurotransmitters, such as serotonin or dopamine, could be discriminated by the functionalized ISFET device. While the sensitivity of the sensor for adrenaline corresponds to ~70 mV·decade^{-1}, the sensitivity of the devices for the analysis of serotonin and dopamine is 7.5 and 15 mV·decade^{-1}, respectively. Thus, the low sensitivity of the device for the analysis of the latter neurotransmitters enables the selective analysis of adrenaline (**2**) within the concentration range 10^{-6}–10^{-1} M. The lower sensitivity of the ISFET device to serotonin or dopamine is attributed to the lower association constants of these neurotransmitters to the receptor sites **1** of the sensing interface.

Whenever host–guest interactions operate as a driving force, the time constant (t_{eq}) required to obtain a fixed saturated transduced signal from the ISFET device is an important parameter. Figure 2 shows the source-drain current as a function of time upon interaction with an adrenaline solution (1.0×10^{-6} M). The

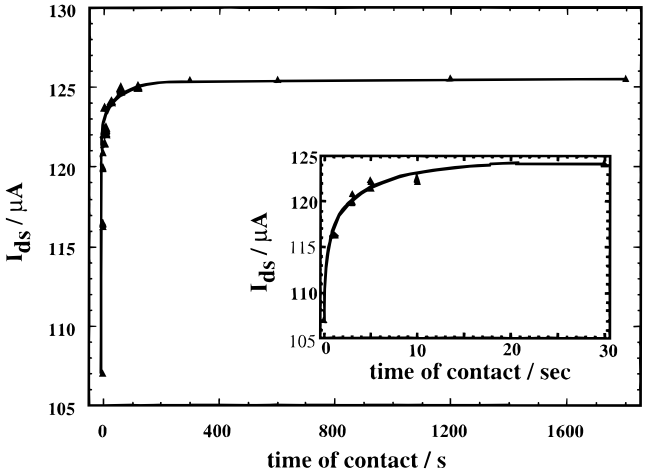

Figure 2. Dynamics of the transduced source-drain current by the ISFET device as a function of time in the presence of adrenaline (**2**), 1.0×10^{-6} M. Inset: Expanded profile of the time-dependent equilibration of the ISFET device.

current response rises within a few minutes and then reaches a constant equilibrated value. We find that, within the entire concentration range of the analysis of adrenaline, 90% of the current response is observed after 5 min of interaction with the analyte solution ($t_{90\%} = 5$ min). The Au nanoparticle/cyclophane-modified ISFET is reusable and reveals excellent reproducibility. Simple rinsing of the sensing interface with phosphate buffer solution (pH 7.6) removes the noncovalently bound adrenaline and regenerates the sensing interface. Using this method, a single sensing interface was regenerated for 100 analyses.

In conclusion, we have demonstrated that, by the appropriate functionalization of the gate of ISFET device with an Au nanoparticle/receptor interface, a sensitive sensor for adrenaline has been developed. The sensing ability of the device and its sensitivity originate from the concentration of the analyte at the receptor sites as a consequence of specific binding interactions.

SUPPORTING INFORMATION AVAILABLE

The source-drain current (I_{sd}) as a function of the gate-source potential (V_{gs}) (at constant $V_{sd} = 0.5$ V) is displayed upon the buildup of the PEI–Au nanoparticle/**1** sensing interface on the ISFET. This material is available free of charge via the Internet at http://pubs.acs.org.

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