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Sensors based on carbon nanotube field-effect transistors and molecular recognition approaches

DOCTORAL THESIS

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ROVIRA I VIRGILI UNIVERSITY

DEPARTMENT OF ANALYTICAL CHEMISTRY AND ORGANIC CHEMISTRY

Sensors based on carbon nanotube field-effect transistors and molecular recognition approaches

DISSERTATION PRESENTED BY

Cristina C. Cid Salavert

TO RECEIVE THE DEGREE OF DOCTOR OF THE ROVIRA I VIRGILI UNIVERSITY

Supervisors:

Dr. Jordi Riu Rusell and Prof. F. Xavier Rius Ferrús

TARRAGONA, 2008

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UNIVERSITAT
ROVIRA I VIRGILI

DEPARTAMENT DE QUÍMICA ANALÍTICA
I QUÍMICA ORGÀNICA

Campus Sescelades
C/ Marcel·lí Domingo, s/n
43007 Tarragona
Tel. 34 977 55 97 69
Fax 34 977 55 84 46
e-mail: secqaqo@quimica.urv.es

Dr. Jordi Riu Rusell and Prof. F. Xavier Rius Ferrús, professors of the Department of Analytical Chemistry and Organic Chemistry at the Rovira i Virgili University,

CERTIFY:

The Doctoral Thesis entitled: "**Sensors based on carbon nanotube field-effect transistors and molecular recognition approaches**", presented by **Cristina C. Cid Salavert** to receive the degree of Doctor of the Rovira i Virgili University, has been carried out under our supervision, in the Department of Analytical Chemistry and Organic Chemistry at the Rovira i Virgili University, and all the results presented in this thesis were obtained in experiments conducted by the above mentioned student.

Tarragona, December 2008

Dr. Jordi Riu Rusell Prof. F. Xavier Rius Ferrús

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During this thesis I was supervised by Dr. Jordi Riu and Prof. F. Xavier Rius, and the work was undertaken in the Chemometrics, Qualimetrics and Nanosensors research group, from the Department of Analytical Chemistry and Organic Chemistry at the Rovira i Virgili University in Tarragona, Spain. I would like to thank my supervisors for their guidance during this period. Also I have to mention Dr. Alicia Maroto and Dr. Santiago Macho for their unconditional support.

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A la meva família.

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Resumen

« Sensores basados en transistores de efecto campo que emplean nanotubos de carbono y principios de reconocimiento molecular »

INTRODUCCIÓN

En los últimos años, los principios de la nanociencia y la nanotecnología se han introducido con fuerza en el campo de la química analítica. Algunas estructuras de tamaño nanométrico (10^{-9} m), presentan propiedades y comportamientos que no se observan cuando el mismo material tiene un tamaño macroscópico. Este hecho se aprovecha para desarrollar sensores con nuevas propiedades. Así, los sensores basados en nanomateriales han ido adquiriendo una gran importancia tanto desde el punto de vista académico como en su aplicación para solventar problemas analíticos de la vida real.

Los nanotubos de carbono (CNTs) presentan unas características físico-químicas muy interesantes. Se ha demostrado que sus propiedades eléctricas se ven considerablemente afectadas por los cambios en el medio ambiente que les rodea. Sin embargo, esta gran sensibilidad, les impide ser selectivos en la detección de un determinado analito. La unión de las propiedades de los CNTs con los principios de reconocimiento molecular se presenta como una base adecuada para el desarrollo de sensores altamente específicos. El objetivo de la presente tesis ha sido desarrollar sensores químicos, del tipo transistores de efecto campo (CNTFETs), basados en interacciones receptor-analito, mediante el empleo de los nanotubos de pared sencilla (SWCNTs), que actúan como transductores de la señal analítica.

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MEMORIA

Las principales etapas de la parte experimental de la tesis han sido:

Crecimiento de SWCNTs por medio de la técnica de deposición química en fase vapor. Optimización de dicho proceso para obtener redes suficientemente densas de nanotubos con carácter semiconductor sobre sustratos de Si/ SiO_2. Utilización de técnicas microscópicas avanzadas para la caracterización visual de las redes de SWCNTs. Entre ellas destacar el microscopio de fuerza atómica y el microscopio de rastreo electrónico.

Integración de los SWCNTs obtenidos en sistemas CNTFET mediante la inserción de electrodos metálicos. En este proceso se han empleado dos técnicas distintas para la inserción de los electrodos. Una consistente en una deposición de una tinta conductora (de plata) mediante una máscara, para obtener los electrodos en el lugar deseado, de una manera sencilla y rápida. Los electrodos metálicos tienen una separación aproximada entre 1 y 5 mm. La otra técnica, mediante litografía óptica, consistente en depositar dos finas capas de metal (Cr/Au) y se ha desarrollado en colaboración con el Centro Nacional de Microelectrónica en Barcelona. Con esta última técnica, la resolución alcanzable es mucho mayor, obteniendo electrodos metálicos separados una distancia de pocos micrómetros (10^{-6} m). Entre los electrodos metálicos debe estar presente una red interconectada de SWCNTs, para dar lugar al canal semiconductor de un sistema CNTFET.

Una vez obtenido el sistema base, el CNTFET, se ha procedido a su empleo como sensor en distintos campos utilizando modelos de reconocimiento molecular. Dependiendo del tipo de funcionalización integrada en los SWCNTs que forman parte de los CNTFETs se pueden obtener sensores para proteínas, iones, etc.

Desarrollo de sensores basados en CNTFETs para la detección de la Inmunoglobulina G Humana (HIgG)

Se ha estudiado la viabilidad de la funcionalización de los SWCNTs mediante los anticuerpos de la HIgG para la detección de la HIgG. Este estudio se ha llevado a cabo mediante dos estrategias de funcionalización independientes. La primera,

mediante la unión directa del anticuerpo sobre el SWCNT de una manera no covalente, y la segunda, mediante el recubrimiento de los nanotubos con un polímero (polietilenimina) y posterior anclaje del receptor mediante un enlace covalente. Este trabajo ha dado lugar a dos publicaciones:

« Carbon nanotube field-effect transistors for the fast and selective detection of human immunoglobulin G », Analyst, 2008, 133, 1005-1008.

« Detection of Human Immunoglobulin G at physiological conditions with chemically functionalizated carbon nanotube field-effect transistors », Current Nanoscience, 2008, 4, 314-317.

Desarrollo de sensores selectivos de iones basados en CNTFETs para la detección de iones potasio

En este estudio se ha combinado el conocimiento de los transistores de efecto campo selectivos de iones (ISFET)[1] con el conocimiento obtenido en el transcurso de este trabajo de los CNTFETs. De esta manera se han recubierto los SWCNTs de un CNTFET mediante una membrana selectiva de iones potasio,[2] para obtener un ISFET basado en SWCNTs. Los resultados se han publicado en: « Ion Sensitive Field-effect Transistors Using Carbon Nanotubes as Transducing Layer » Analyst, 2008, 133, 1001–1004.

Desarrollo de ioxide basados en CNTFETs para la detección de un analito gaseoso, el dióxido de azufre

Debido a su capacidad de interaccionar con distintas moléculas en fase gas, [3] los CNTFETs se han propuesto como sensores de gases a temperatura ambiente. Aún así estos sensores no son selectivos a un gas en particular. En este estudio los SWCNTs se han funcionalizado con un receptor sintético de platino, y bloqueando la superficie de los nanotubos de una manera adecuada para evitar su interacción con posibles interferentes, se ha desarrollado un sensor selectivo para el dióxido de azufre. Los resultados son recogidos en « Selective detection of SO_2 at room temperature based on

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organoplatinum functionalized single-walled carbon nanotube field-effect transistors», enviado para revisión.

RESULTADOS

Obtención de sensores basados en CNTFETs para la detección distintos analitos de interés, como son la HIgG,[4, 5] los iones potasio[6] y el dióxido de azufre.[7]

Todo este trabajo ha dado lugar a tres artículos científicos, ya publicados en revistas internacionales, más otro artículo que se encuentra en proceso de revisión, además de un capítulo de un libro. También se han presentado varias comunicaciones en congresos (1 oral y 3 tipo póster).

CONCLUSIÓN

Este trabajo aporta una aproximación al uso de nuevos materiales nanoestructurados, como son los SWCNTs, como integrantes de sensores químicos. De esta manera, se ha intentado buscar nuevas alternativas para el desarrollo de sensores basados en SWCNTS, que por sus propiedades, confieren al sensor unos parámetros analíticos mejorados. Entre ellos caben destacar: la no necesidad de marcadores en el caso de las inmunoglobulinas, un límite de detección más bajo en el caso de la determinación de potasio por medio de un sistema ISFET, y la detección de un gas de efecto invernadero a temperatura ambiente.

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1 Objective

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The general objective of this thesis is to develop chemical sensors whose sensing capacities are based on the principle of molecular recognition and where the transduction is carried out by single-walled carbon nanotubes (SWCNTs).

The sensing device used throughout this thesis is the carbon nanotube field-effect transistor (CNTFET). According to their molecular structure, individual SWCNTs can display a metallic, semimetallic or semiconductor character, however, a network of SWCNTs always exhibits a semiconducting nature. Because of this electrical property, a network of SWCNTs is used as the semiconductor channel in CNTFETs.

Although SWCNTs are highly robust and inert structures from the chemical point of view, their electrical properties are extremely sensitive to the presence of different molecules. This makes SWCNTs highly sensitive to many kinds of analytes. Unfortunately, this high sensitivity is associated with a very low selectivity. To overcome this problem, the SWCNTs' surface has to be protected using a non-covalent functionalization process. In this way, two main objectives are achieved: i) to avoid non-specific binding of non-desired compounds and ii) to anchor a receptor molecule selective to a target analyte. When the target analyte binds to the receptor molecules there is an induced change in the electrical conduction of the SWCNT, thus providing the mechanism for detecting and transducing the electrical signal.

The host-guest concept forms part of the process since both the target analyte and the receptor (i.e. the element which gives selectivity to the sensor) are molecules that display highly selective interactions. These pairs of molecules establish a selective and reversible interaction that results in a supramolecular complex. In this way we take advantage of the fact that SWCNTs are highly sensitive semiconductors and of the molecular recognition processes provided by the receptors that are attached to them. Our specific objectives are therefore to functionalize SWCNTs with several types of molecular receptors such as antibodies, ion selective membranes, and synthetic receptors, to achieve sensors that display a high selectivity towards the analyte of interest.

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2 Introduction and theoretical aspects

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2.1 INTRODUCTION

The present doctoral thesis aims at contributing to the field of sensors based on carbon nanotubes (CNTs). According to the IUPAC, a chemical sensor "is a self-contained integrated device, which is capable of providing specific quantitative or semi-quantitative chemical information using a recognition element which is retained in direct spatial contact with a transduction element".[1]

A chemical sensor is thus defined as a device that is able to convert some chemical information into an analytically useful signal. Compact and self contained usually means small, not expensive, in direct contact with the investigated sample, with a short response time and continuous operation or, at least, in repeated cycles. Chemical sensors are basically made up of the recognition, transduction and detection systems, which are responsible, respectively, for the recognition step and the transformation into a measurable signal that is subsequently detected, recorded and processed.

Nanoscience and nanotechnology deal with the study and application of structures of matter with at least one dimension of the order of less than 100 nm (1 nm = 10^{-9} m). This is the standard way of classifying what belongs to the 'nano' world. However, properties related to low dimensions are more important than size. Nanotechnology is based on the fact that some structures usually smaller than 100 nm have new properties and behavior that are not exhibited by bulk matter of the same composition. Perhaps two of the most perceptive effects are due to the change in the surface/volume ratio and the quantum effects. When the size of the structure is decreased, this ratio increases considerably and the surface phenomena predominate over the chemistry and physics in the bulk.

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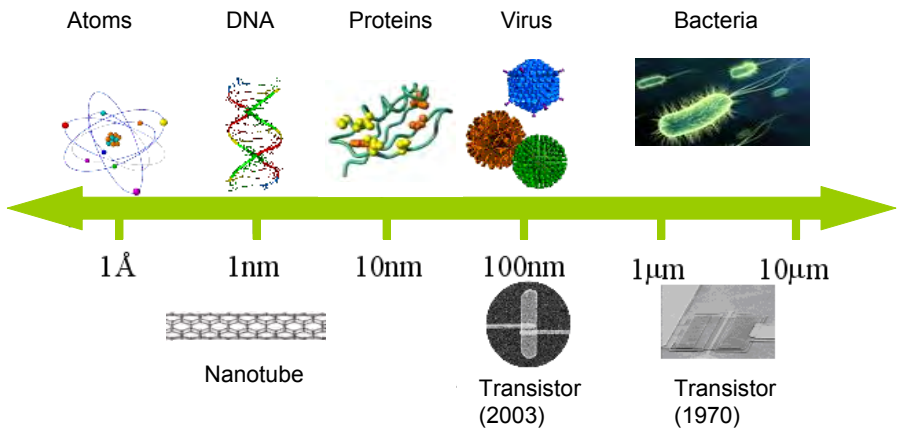

Figure 2-1. Dimensions of the natural and synthetic structures studied within nanoscience and nanotechnology.

In recent years, the principles of nanoscience and nanotechnology have been widely incorporated into the field of analytical chemistry.[2-6] Nanoscience and nanotecnology are enabling the development of analytical sensors with enhanced parameters. Nanostructures are being incorporated either as recognition elements or as transducers in the new generation of sensors. Sound knowledge of the behavior of these new nanostructures will lead to a better understanding of their properties, and thus, to their use as improved components in sensors. The small size of nanostructures is correlated to the practicable miniaturization of devices, thus reducing several factors such as reagent consumption, energy, sample size, etc.

1D nanostructures are the smallest dimension structures that can be used for efficient transport of electrical charges and therefore they are essential for the integration and performance of nanoscale based devices. Due, among other factors, to their high surface-to-volume ratio and tuneable electron transport properties because of the quantum confinement effect, their electrical properties are strongly influenced by small perturbations.[7] Thus nanostructures are very sensitive to the surrounding environmental changes.[8, 9] Additionally, the dimensions of the nanostructures allow them to be in close contact with the recognition layer of sensing devices. Consequently, new sensing devices with improved properties are now appearing. For instance, these devices are more sensitive, being able to detect very low concentrations of target

analytes. Lower limits of detection can be achieved, very small amounts of sample are required for each measurement and they can operate without the need of labels. Moreover, as the analytical processes are miniaturized, reagent consumption is low and "in situ" measurements are made easier. Although nanoscale based devices seem to have interesting properties, more detailed studies dealing with their suggested properties have to be carried out. Nowadays, many potential nanosensors are being described in the literature, but they often lack a detailed description of their analytical performance characteristics.

The following introduction is divided in different Sections. Section 2.2 introduces the CNTs, which are the transducer element of the sensor developed within this thesis. This Chapter provides an insight into some of the properties that makes this nanomaterial, CNTs, so valued as a key element in electronic devices. Section 2.3 briefly describes the molecular recognition mechanisms also used in the present thesis. Synthetic receptors (Section 2.3.1) and immuno-based methods (Section 2.3.2) are the two big blocks of molecular recognition that have been employed with the CNTs to develop practical sensors. Special attention is given to the receptors used as the recognition elements in such sensors. These are on the one hand, valinomycin and a platinum complex, and on the other hand, the human immunoglobulin G antibody. Subsequently, there is an introduction to general concepts and origins regarding field-effect transistors (FETs). A more detailed description is shown of the electrical device used, an FET based on CNTs (Section 2.4). The transducer part together with the molecular recognition elements makes up the CNTFETs sensors that have been developed in the course of the present thesis.

2.2 CARBON NANOTUBES

Since their discovery in 1991 by Sumio Iijima,[10] CNTs have become one of the most intensively studied materials. CNTs have unique structural, mechanical, chemical, thermal, optical, optoelectronic and electronic properties, and these have attracted the interest of many fields of science, who wish to understand the fundamentals of their behavior and the possibility of using them in a huge range of applications.[11-13].

Preparing carbon fibers from catalysts over gaseous species was first reported more than a century ago.[14] Some of the first nanometric carbon filaments were grown by Morinobu Endo as part of his PhD studies at the University of Orleans in France in the 1970s. However, it was not until 1991, when Sumio Iijima of the NEC Laboratory in Tsukuba (Japan) used high-resolution transmission electron microscopy to observe CNTs that the interest of scientific community started to grow. In 1991, Iijima observed multi-walled nanotubes, but less than two years later he observed single-wall carbon nanotubes, just as Donald Bethune and colleagues were doing at IBM Almaden in California.[15]

2.2.1 Structure, synthesis and properties

Structure: CNTs are an allotropic form of pure carbon (Figure 2-2). Materials made of pure carbon display only two types of hybridized covalent bonds: sp2 and sp3. Sp2 is the hybridization present in graphite and sp3 is present in diamond. Sp2 hybridization forms strong bonds within a plane but weak bonds between different planes. The most stable material structure made of pure sp2 carbon bonds is in the form of a honeycomb pattern. Graphite is formed by overlaying successive graphene sheets, therefore, every single layer displays a high stability but it can be peeled off with relative facility from the bulk material. By hypothetically wrapping one of these graphene sheets, like rolling it into a cylinder, we obtain a tube, which is known as a carbon nanotube.

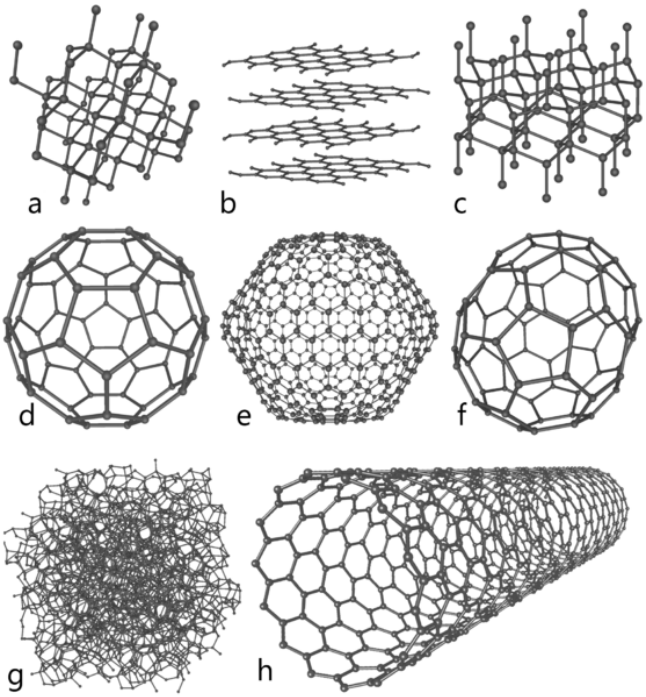

Figure 2-2. Allotropic forms of pure carbon. (a) Diamond (b) Graphite (c) Lonsdaleite (d) C60 (e) C540 (f) C70 (g) Amorphous carbon (h) Carbon nanotube.

CNTs can therefore be described as a monolayer sheet of graphene arranged in a hexagonal grid pattern that has been rolled into a tube (Figure 2-3). They can have a single wall (SWCNT) or they can have several concentrical tubes, as in the case of multi-walled carbon nanotubes (MWCNTs) (Figure 2-4).

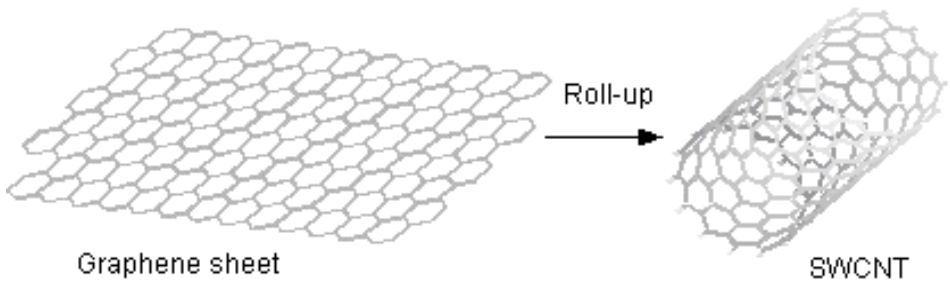

Figure 2-3. The structure of a SWCNT is like a monolayer of graphene rolled up.

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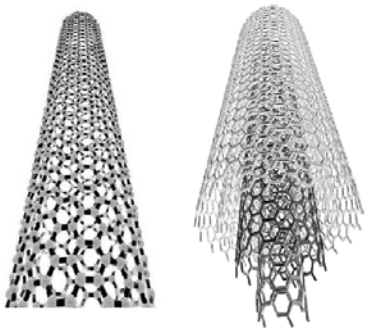

Figure 2-4. SWCNT (left) and MWCNT (right) (Adapted from reference [17).

There are many ways to roll a graphene structure to form a SWCNT, resulting in structural variations. These variations, as well as the tube diameter, determine the electrical properties displayed by the various types of tubes. The most fundamental of these properties is whether the tube will behave as a metal or as a semiconductor.

Although CNTs are not actually synthesized by rolling graphite sheets, it is possible to explain the different structures by considering the way graphite sheets might be rolled into tubes. An SWCNT can be formed by rolling a sheet of graphene into a cylinder along an (*m,n*) lattice vector in the graphene plane, where *n* and *m* are integers of the vector equation $OA = C_h = na_1 + ma_2$, which is known as the Hamada vector.[18] The chiral angle (Θ) is formed between the Hamada vector and the unit lattice vector a_1. The values of *n* and *m* determine the chirality and the diameter of a CNT (Figure 2-5, Table 2-1). The chirality in turn affects the conductance of the nanotube, its density, its lattice structure, and other properties. An SWCNT is considered metallic if the value resulting from $(n - m)/3$ is an integer. Otherwise, the nanotube is semiconducting (for a detailed description of the chirality and radius characteristics in SWCNTs, see Dekker[19]). Consequently, when tubes are formed with random values of *n* and *m*, we would expect two-thirds of nanotubes to be semi-conducting, and one third to be metallic.[14, 20]

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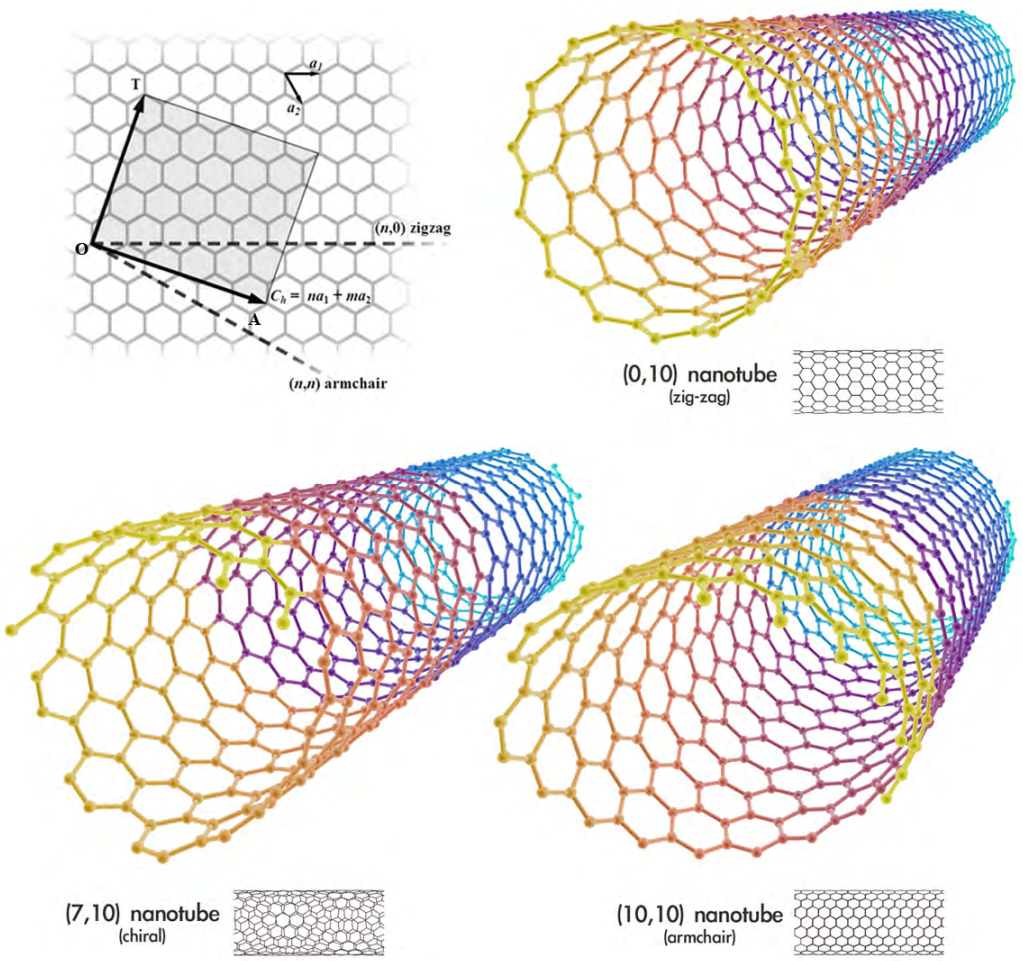

Figure 2-5. Diagram of the different ways of rolling a graphene sheet to make a SWCNT. Three different SWCNT structures resulting in graphene sheets rolled differently, a zig-zag-type nanotube, an armchair type nanotube, a chiral nanotube.

Type	Integer coefficients	Chiral angle	Morphology	Electrical characteristics
Armchair	n=m	30º	No twist with respect to tube axis	100% metallic
Zigzag	$n = 0$ or $m = 0$	0º	Maximum twist angle	25% metallic 75% semiconducting
Chiral	Both n and m vary in value	Angle varies between 0º and 30º	Twist angle between no twist and maximum twist	

Table 2-1. Effect of integer coefficients on tube morphology and electric behavior (Adapted from reference [21]).

Synthesis: Arc-discharge, laser ablation, and chemical vapor deposition are the three main methods used for CNTs synthesis.[20, 22, 23] The first two methods employ solid-state carbon precursors to provide the carbon source needed for nanotube growth, and they are carried out at high temperatures (thousands of degrees Celsius) to vaporize carbon. These methods are well known for producing high-quality carbon nanotube structures, despite the large amounts of secondary products associated with them. Chemical vapor deposition (CVD) uses hydrocarbon gases or volatile compounds as the source for carbon atoms and metal particles as catalyst for nanotube growth. CVD is performed at relatively low temperatures (500 - 1000 ºC). For producing SWCNTs, none of the methods mentioned produces nanotubes with homogeneous diameters and chiralities. However, arc-discharge and laser ablation techniques have produced SWCNTs with notably narrow diameter distributions that average ~1.4 nm. By contrast, and depending on the experimental conditions used, CVD methods also produce carbon fibers, filaments, and MWCNTs. Also, the SWCNTs produced by this method have high degrees of crystallinity and perfection compared to those synthesized by arc and laser materials.

The advantages of using the CVD method to synthesize SWCNTs compared to other methods are, among others, the low power input, the lower temperature range, the

comparatively high purity of nanotubes and the possibility of scaling up the process to produce them in large quantities. In our laboratory we have implemented the chemical vapor deposition method (CVD) to obtain the SWCNTs used in the experimental part of the present thesis.

Properties: The properties of CNTs are very different depending on whether they are, SWCNTs or MWCNTs.[14] SWCNT-type diameters are of the order of few nanometers and can be tenth of micrometers long. SWCNTs are stable up to 750 ºC in air (but in an oxidating atmosphere they start to become damaged earlier) and up to 1.500 ºC in an inert atmosphere. They have half the mass density of aluminum. While SWCNTs can be tenths of microns long, their diameter is ~0.2 nm to 4 nm and thus can be considered having only one molecular dimension. In this way, properties are closely related by the distribution of the atoms along this molecular direction. Their unique structural features give SWCNTs exceptional physical and chemical properties.[11, 20, 23, 24]

2.2.2 Electronic characteristics of carbon nanotubes

The structure of CNTs means a cloud of π-electrons appear at their inner and outer surfaces. Depending on their diameter and chirality, SWCNTs display a metallic or semiconducting character.[25] As described in Section 2.2.1, the tubes that have an atomic structure (*m,n*) where $(n - m)/3 \neq$ integer, are semiconducting, otherwise they will display a metallic character. SWCNTs, arranged in the semiconducting layer of a field-effect transistor, show a p-type electrical behavior in air, which implies that conduction is through the holes instead of electrons. This fact is based on the effect of oxygen absorption on either SWCNT[26] or the metal electrode contacts.[27]

The band gap, E_g, in the π-electrons density of states (DOS) of the semiconducting SWCNT is inversely proportional to the diameter, having a magnitude that ranges from 0.3 to 0.5 eV for diameters between 3 and 1 nm.[28] Figure 2-6 shows the typical diagram of DOS as a function of energy for semiconducting and metallic SWCNTs.[18, 25, 29] In the case of metallic SWCNTs there is no gap in the DOS between the valence band (VB) and the conduction band (CB). On the other hand, semiconducting SWCNTs exhibit a gap between the VB and CB. Two features can be

noticed. First, the DOS are symmetrical around the Fermi energy, defined as the energy corresponding to the top of the collection of the energy levels that are filled with electrons at absolute zero temperature (i.e. the energy at which all bonding orbitals are filled and all antibonding orbitals are empty).[30, 31] However, at higher temperatures there is a probability, given by the Fermi function, that a given available energy state, above the Fermi level, will be occupied by an electron. Second, it can be seen that metallic SWCNTs contain more electrons near the Fermi level, as opposed to semiconducting SWCNTs, which have zero energy DOS around the Fermi energy.

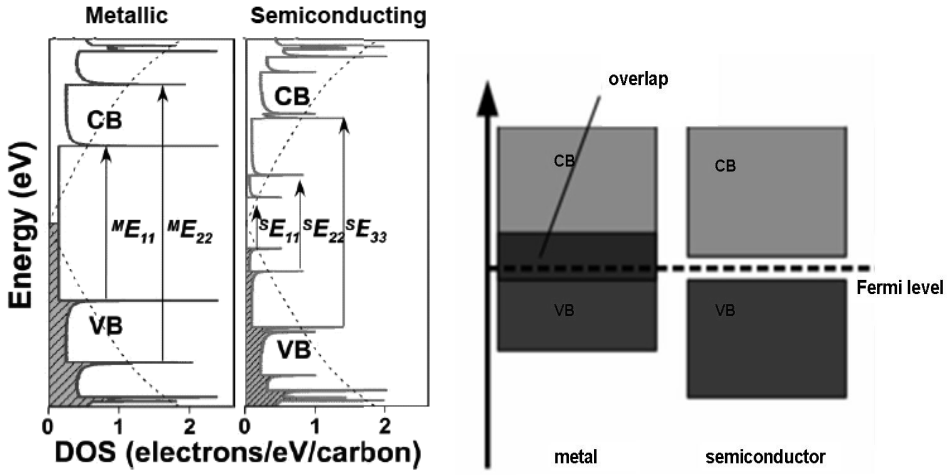

Figure 2-6. Diagram of DOS versus energy for metallic SWCNT and semiconducting SWCNT. The valence band is shaded and the conduction band is white. The vertical arrows show the electronic transition allowed (right). (Adapted from reference [18]). Classical valence and conduction bands in a metallic and a semiconducting material (left).

SWCNTs are highly suitable nanostructures for electrochemical sensing. Due to their cylindrical, quasi-one-dimensional structure, they have particular electronic properties:

- SWCNTs display low charge carrier density[1] that is directly comparable to the surface charge density of proteins,[31] thus facilitating electrostatic interactions.

- Networks of SWCNTs exhibit a mobility of charge carriers,[32] that is 102 to 104 times the mobility in organic semiconductors. This means that devices using SWCNTs and alternate current can operate at higher frequencies. Due to the high mobility of charge carriers, the overall device conductance is often limited by the Schottky barriers (energy differences that should overcome the charge carriers to cross the metal-semiconductor junction), that are formed at the metal-nanotube contacts and at the junctions between nanotubes of different conducting nature.[33]

- The electrical fields near the SWCNTs (which are generated by electrostatic charges, in many instances) display a striking influence on the conductance of the nanotubes. The partial charge-transfer from ions or molecules in the nearest chemical environment of the nanotubes leads to a significant change in the conductance of semiconducting SWCNTs.

The size and the physico-chemical characteristics of their structure also give SWCNTs other sensing advantages:

- The size of the SWCNTs is comparable to the size of single biomolecules, facilitating the interaction between analytes and nanotubes.

- SWCNTs have all their carbon atoms at the surface, facilitating the interaction with the surrounding molecules with an increased sensitivity.[34]

---

[1] The charge carrier density is the number of charge carriers per volume unit. A charge carrier is a free particle carrying an electric charge. E.g. electrons, ions, holes.

- Finally, the reactivity of CNTs is reasonably well known, therefore they can be chemically functionalized with a variety of receptors that provide selectivity to the analytical systems.[8, 35]

2.3 MOLECULAR RECOGNITION

The goal of developing new sensors using molecular recognition mechanisms is to adapt classic instrumental techniques and traditional transduction principles to solve analytical problems. This is done by integrating molecular recognition in devices that have been specially designed to be simple and efficient. Therefore, the main purpose of these recognition systems is to provide the sensor with a high degree of selectivity so the analyte can be measured.

Molecular recognition between molecules is one of the fundamental processes in chemistry and biology. Without molecular recognition, there would be no life on this planet. Enzymes, antibodies, membranes and their receptors, carriers and channels all use the event of molecular recognition.

The term "molecular recognition" has been defined as the energy and the information involved in the selection and binding of substrate by a given receptor molecule. Molecular recognition therefore implies the molecular storage and supramolecular read-out of molecular information.[36] Molecular receptors can be used to convert the chemical information present in binding and recognition processes into information useful for the analyst. Molecular receptors can be integrated into biosensors, which can be defined as analytical devices consisting of an immobilized biological component (the molecular receptor) in intimate contact with a transduction device that converts a signal from the biological element into a quantifiable signal.

The fundamental point of molecular recognition is the complementarity between the receptor and substrate. This is like the complementarity of a lock and key, where the lock is the molecular receptor and the key is the substrate that is recognized in order to provide a receptor-substrate complex. With this knowledge, chemists are being able to design new synthetic systems mimicking the interesting properties observed in nature and can also produce new organic chemistry that is of great interest to both science and technology.

Molecular recognition involves non-covalent bonds between the receptor and the target molecule. There are several mechanisms that stabilize the supramolecular

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complex formed between them, usually non-covalent bonds. All of these non-covalent bonds are essentially electrostatic: ion-ion, ion –dipole, dipole-dipole, cation–pi cloud, hydrogen bonding, hydrophobic, Van der Waals, and pi stacking.[37] The effectiveness of the recognition is strongly influenced by steric factors. If the immobilized receptor is not sufficiently well orientated to be able bind the target analyte correctly, the molecular recognition process will not proceed.

A molecular recognition event is typically a specific interaction that is reversible. As has been said, it is analogous to the interaction between key and lock, though in many cases the binding would more accurately be described as an induced fit, during which the recognition element changes shape upon binding. Association between receptor and ligand is, then, an equilibrium process. There is a specific association constant for each interaction in the molecular recognition event. Each receptor-ligand has its own equilibrium constant in terms of recognition and interaction forces. This constant is larger because many non-covalent interactions are present in the binding. As it is a non-covalent binding between receptor and analyte, external parameters such as temperature, ionic strength, concentration of analytes, etc. could influence the degree of interaction between them. When equilibrium constants are in the range of 10^7 to 10^{11} M^{-1} the association process is favorable, and when they are below 10^7 M^{-1} they are unfavorable. These values allow the prediction of weak or strong binding events. The equilibrium constant is sometimes called the affinity constant and is thus a measure of the strength of the binding between the receptor and the target molecule, because the stronger the bind between receptor and target, the higher the value of the affinity constant.

In general a high degree of selectivity is present in molecular recognition events such as antigen-antibody reactions, however, similar analyte structures that are present in real samples could lead to cross reactivity processes. Among the different performance characteristics, sensitivity, selectivity and stability of the signal are usually the three most important parameters to be considered in order to develop analytical sensors based on molecular recognition.[38, 39]

2.3.1 Synthetic receptors

Starting in the late sixties, J.M. Lehn and others have been developing the principles of the field that years later would become known as supramolecular chemistry.[36, 40] The interaction between receptors and targets takes place through non-covalent bindings and chemists use the concepts of complementarity, receptor preorganization and chelate and macrocyclic effects to try to synthesize receptors that could selectively link to predetermined molecules. The receptors are usually molecules that have cavities and/or different binding sites able to establish simultaneously different interactions with targets. The target analytes to be determined have complementary stereoelectronic functionalities to receptors and can range from small inorganic cations or anions to larger organic molecules such as proteins or even whole cells.

Although the aim is to mimic nature on many occasions, there are some differences between the host-guest interactions useful for developing nanosensors and their parent situation in the supramolecular laboratory or in living organisms. The host-guest interaction in nanosensors usually takes place through a solid-liquid interface where the receptor is bound to the solid surface of the sensor. This is not the case for most living organisms and certainly differs from the synthetic chemistry in solution. The stability constants of the receptor–target complexes may therefore display significant differences between both situations. Moreover, the linked receptor must keep (or must be able to regenerate) its suitable structure in a solid state in order to be able to bind the target analyte. The thousands of millennia of evolution have produced sophisticated molecules with complex structures that cannot be reproduced easily by synthesizing organic scaffolds. Put another way, when using a sensing layer of biological origin we must take into account that reactions in living organisms take place at the relatively fixed physiological conditions of temperature, pH and ionic strength which are not common in chemical analysis. Many receptors are well adapted to their function in biological systems but cannot be easily translated to nanosensors. For instance, the binding force of some natural occurring complexes is so high that it makes them practically useless for sensors destined for multiple determinations. However, they might be useful, for instance, in environmental remediation, where the aim is to eliminate the presence of a certain compounds (in a similar way as the body eliminates

the intruders by linking antibodies to them). Finally, the aim of sensing is to develop devices with the highest degree of selectivity. This is not always the case in living organisms. For instance, the potassium transport through the cell membranes is carried out efficiently by valinomycin (Figure 2-7), but sodium ions are not allowed to cross through cell membrane. However, for sensing purposes, this receptor displays high selectivity with respect to sodium ions but only a moderate selectivity for larger monovalent ions and bivalent cations (Table 2-2).

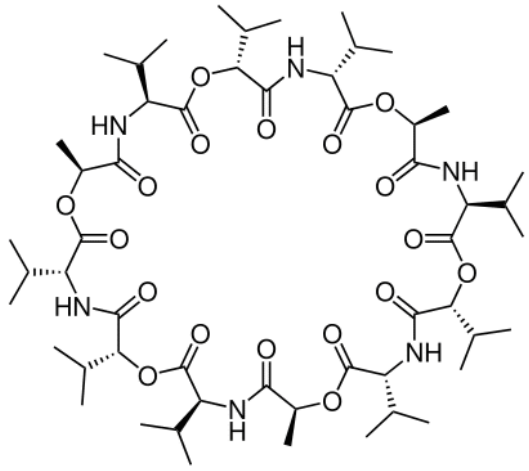

Figure 2-7. The biological receptor valinomycin, which is able to transport cations across cell membranes.

Medium	H^+	Na^+	K^+	Rb^+	Cs^+
1	-	0,7	4,5	4,8	3,9
2	-	2,6	6,7	6,9	6
3	5,3	6,7	10,4	11,7	10,1

Table 2-2. Logarithms of stability constants of some univalent cations with valinomycin in methanol (1), acetonitrile (2) and nitrobenzene saturated with water (3) (Adapted from reference [41]).

A wide range of chemical receptors has been synthesized in recent years. Here we have selected a few of them as representative examples of different interactions with cations, anions and molecules of increasing complexity.[42] The main receptors for cations have been reviewed by Lehn *et al*.[43] Podands, crown and lariat ethers, cryptands, spherands, calixarenens and other receptors designed for organic cations have been used as recognition elements.

For example, recognition of potassium ions has been reported using CdSe/ZnS quantum dots (QDs) modified with 15-crown-5 ether, in aqueous samples.[44] The selectivity of the system has been achieved by correctly designing the functionalized QDs, that is, by including two adjacent 15-crown-5 rings. The complex formed is the 15-crown-5/K^+/15-crown-5 sandwich type. The selectivity is in terms of supramolecular forces. Although upon addition of an excess amount of interfering metal ions will bind to the functionalized QDs, K^+ will not need this overload. The K^+ hydrophobicity may cause straight the QDs precipitation compared with Na^+ and other metal ions. In this way, the system will no produce a response upon the addition of different cations, such as Li^+, Cs^+, Mg^{2+}, and Ca^{2+}.

The current state of anion recognition and sensing has been reviewed by Beer et al.[45] Preparing molecular receptors to recognize anions is not as easy as preparing them to recognize cations. Many factors must be taken into account, such as pH, ion geometry and low charge to radius rate. Jin and coworkers[46] have described modifying luminescent CdSe QDs with 2-mercaptoethane sulfonate to produce a selective receptor for detecting the cyanide anion in water samples. The solution must be fixed at a pH 9 or higher, regarding the toxicity of the analyte. This receptor shows no signal when exposed to different anions such as SO_4^{2-}, SO_3^{2-}, NO_2^-, NO_3^-, SCN^-, Cl^-, Br^-, I^-. It should be said, that some anions in high concentrations get a tight luminescence response from the device.

The recognition of neutral molecules usually takes place due to hydrogen bonding or electrostatic or donor-acceptor interactions. Cyclodextrins have been used as synthetic receptors.[47] These are sugar molecules that possess the structure of a curtailed cone with a hydrophobic cavity. The analyte can be complexed in this

hydrophobic environment. For example, cyclodextrins form stable complexes with nonpolar compounds, such as pyrene. Depending on the cavity and the possible interactions, different cyclodextrins may be selective to different compounds.

2.3.1.1 Valinomycin

The presence of natural products that can recognize particular molecules was already known by the 1950s. Valinomycin, a natural antibiotic, was discovered in *Streptomyces fulvissimus* cultures in 1955. It forms complexes with alkali metal ions, the stability of which depend on the ion radius. The very large difference in the stability of the potassium and the sodium complexes causes the high potassium selectivity in the valinomycin-based ion selective electrodes. Valinomycin is said to be a potassium ionophore.[2]

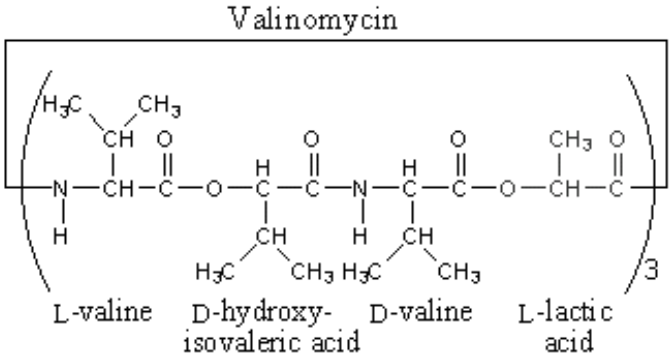

Figure 2-8. Structure of valinomycin.

Its structure shows a polar interior and a non-polar lipophilic exterior (Figure 2-7), defined as a macrocyclic depsipeptide assembled from a 3-fold repetition of the

[2] Ionophores are small hydrophobic molecules that dissolve in polymeric membranes and increase the permeability of specific ions.

alternating amino- and hydroxyacid residues L-Valine, D-α-hydroxyvaleric acid, D-valine, and L-lactic acid (Figure 2-8). When valinomycin is not bound with cations its structure is solvent dependent. By contrast, when bound to potassium ions, it adopts a configuration in which the amino- and hydroxyacid carbonyl oxygens from the hydroxy-acid residues suggest that the centre forms a cavity for ion complexation (Figure 2-9).

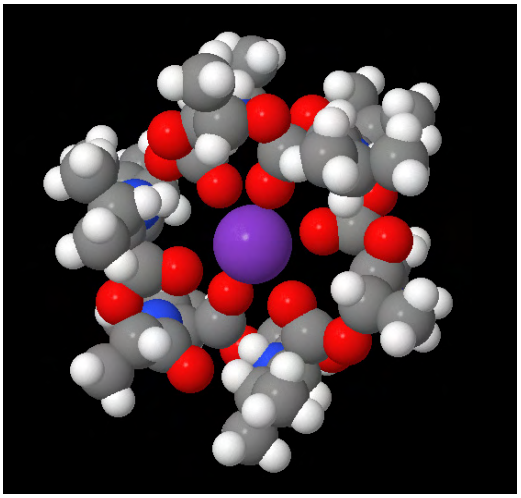

Figure 2-9. 3D picture of valinomycin with a K^+ bound at the centre.

In solution, valinomycin is stabilized by water molecules in its inner and outer hydration sphere. When a K^+ replaces the water molecules the valinomycin ring-structure is stabilized by hydrogen bonds. Moreover, six oxygen atoms of the ionophore can interact with the bound K^+. The smaller Na^+ ion, for instance, cannot simultaneously interact with all six oxygen atoms. Thus it is energetically less favorable for Na^+ to discard its waters of hydration to form a complex with valinomycin. Valinomycin is then highly selective for K^+ compared to Na^+.

Because ionophores interact selectively with specific ions to form stable complexes, they have formed the basis of ion selective membrane development, which have become recognition elements ion selective electrodes (ISE). When sensing potassium ions, most of these sensors use valinomycin as the ionophore in the membrane composition because valinomycin is much more selective to potassium than to similar ions that could be found in the sample. Ion sensing is performed mainly in

aqueous media. In this way the membrane is in direct contact with water, so the membrane has to avoid the possibility of allowing some of its components to be dissolved, and to avoid contaminating the sample whilst maintaining its intrinsic properties. Therefore membrane constituents are usually hydrophobic. Ionophores are dissolved in a suitable solvent and enclosed in a matrix of organic polymer. The ionophore is present in about 1% of the total composition of the matrix. The most popular matrix is high molecular weight poly vinyl chloride (PVC), among other polymers, which typically constitutes about 30% (by weight) of the membrane. The remaining major component is the plasticizer, which ensures the mobility of the ionophore, providing the membrane with suitable mechanical properties, and determines the dielectric constant (Table 2-3).

Composition	Characteristics	Example	Function
Polymer	High molecular weight Lipophilic	PVC	Support Rigid structure
Ionophore	Ionic carrier Lipophilic	Valinomycin	Forms complexes with the target ions
Plasticizer	Liquid Lipophilic	dioctyl sebacate (DOS)	Improves the diffusion of other components
Ionic additive	Enhance the ionic transference Lipophilic	potassium tetrakis (4-chlorophenyl) borate (KTClPB)	Enhances the analyte extraction process
Solvent	Organic	Tetrahydrofuran (THF)	Dissolves all the matrix components

Table 2-3. Typical constituents of PVC ion selective membranes.

2.3.1.2 Platinum pincer complexes

A pincer type complex comprises a metallic atom in the centre of the structure and a pincer type ligand containing donor atoms that are able to coordinate in a

tridentate manner (Figure 2-10). The ligand consists of an anionic aryl ring which is ortho, ortho-disubstituted with a heteroatom substituent (e.g. CH_2NR_2, CH_2PR_2 or CH_2SR), which is able to coordinate to the metal centre, giving an stable M-C σ bond.[48] The general formula of a pincer type ligand is $[2,6\text{-}(ECH_2)_2C_6H_3]^-$, abbreviated as "(ECE)". E,C,E is a terdentate coordinating monoanionionic array, where C represents the anionic aryl carbon atom of the 2,6-disubstituted phenyl ring and the E is a neutral two-electron donor, such as O, S, N or P (Figure 2-10).[48] Pincer ligand complexation with metals leads to the formation of complexes of the general formula $[MX_n(ECE)L_m]$, (X= Cl^-, Br^-, I^-; L= substituent group) which have shown several functions, however our interest is in their role in molecular recognition.

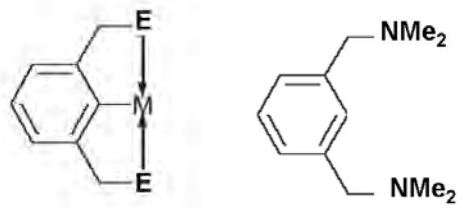

Figure 2-10. Typical representation of a pincer type complex. E is a donor atom (O, S, N, P) and M is the metal centre (left). Example of a pincer type ligand (NCN) (right).

All pincer metal complexes display Lewis base properties due to a high electron density on the metal centre. NCN ligands containing hard electron-donating amine nitrogen atoms are specially related to this nucleophilic character.[49] An example of an interaction between a Lewis acid and a Lewis base was found between SO_2 and platinum (II) and nickel (II) complexes containing these NCN ligands. When a square-planar platinum or nickel complex containing a NCN pincer ligand is in contact with an SO_2 atmosphere the result is an immediate and reversible formation of a five-coordinated adduct (see Figure 2-11). These reactions take place either in the solid state or in solution, and are totally reversible for the platinum complexes. The corresponding nickel complexes gradually decompose since the five-coordinate nickel adduct shows a low stability.[50]

The molecular recognition process of the platinum complex towards SO_2 is highly selective and not influenced by the presence of humidity (H_2O) or other

atmospheric gases (including CO and HCl).[49] The reversibility of the interaction between the platinum complex and SO_2 is a very fast process at room temperature.[51]

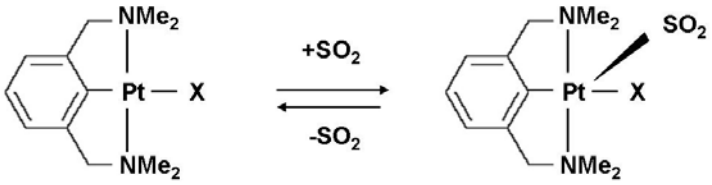

Figure 2-11. Reversible binding of SO_2 on NCN platinum complexes with formation of five-coordinate adducts.

2.3.2 Immuno-based methods

Immunochemical techniques are based on the interaction of antibodies (Ab) with antigens (Ag). An antibody is an immunoglobulin molecule that has an array of definite amino acid sequences by virtue of which it interacts only with the antigen that induced its synthesis, or with an antigen that is closely related to it. In their structure, antibodies contain binding sites that recognize specific molecular structures of the antigen. Antibodies can be described as Y-shaped molecules (Figure 2-12), consisting of two identical heavy and light chains, held together by disulfide bonds. According to the 'key-lock' analogy, an antibody is going to interact in a highly specific way with its particular antigen. This interaction is reversible, and is established through electrostatic forces, hydrogen bonding and hydrophobic or Van der Waals interactions.[52, 53]

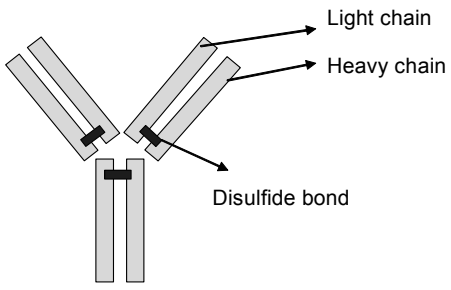

Figure 2-12. Y- shape of antibody.

Applications of antibody immobilization techniques in sensing devices are numerous and well developed.[54, 55] Usually the receptor molecule (antigen or antibody) is attached to a solid support, in intimate contact with a transducer mechanism. Once immobilized, either the antigens or antibodies have to preserve their biological properties so they can establish the interaction leading to the formation of an immunocomplex. The main immobilization approaches include physical adsorption, covalent binding, use of crosslinking agents, entrapment, and exploitation of biological interactions.[56] Classically, the binding Ab-Ag is usually registered by means of labels. Labels are mainly organic dyes or nanoparticles attached to the antigen or to the antibody. Different detection methods can be used such as optical fluorescence, chemiluminiscence, immunofluorescence microscopy or electrochemical methods, depending on the nature of the label used.

Immunosensors display remarkable sensitivities and selectivities derived from the ability of the antibodies to recognize and bind specific sites of the complementary antigen. The immunoreaction is governed by the affinity constant when the thermodynamic equilibrium is reached. Thus, some factors need to be controlled such as temperature or the ionic strength of the medium, which affect the stability of the immunocomplex formed. A remarkable attribute of immunoreactions is its reversibility, which allows the development of reusable immunochemical sensors.[52]

Immunoanalytical techniques, such as enzyme-linked immunosorbent assay (ELISA), immunoelectrophoresis or fluoroimmunoassays, have been used for many years due to their proven usefulness. However, the need to use labels and to add specific reagents makes them frequently costly and time consuming. These techniques are not direct in the sense that they need a secondary mechanism to be able to detect the recognition event. Therefore, developing new improved methods for rapidly detecting antigens or antibodies is important and applicable to several fields such as medical diagnosis, environmental analysis or forensic medicine.[57, 58]

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2.3.2.1 Human Immunoglobulin G

Immunoglobulin G (IgG) is usually employed as a model antigen when performing immunoassays.[59] IgG belongs to the family of five classes of humoral antibodies (immunoglobulin G, immunoglobulin A, immunoglobulin M, immunoglobulin D, and immunoglobulin E), each of which mediates a characteristic biological response following antigen binding. IgG is the most abundant protein class in humans (~75%).[60] IgG is the smallest of the immunoglobulins, with an approximate molecular weight of 150.000 Da. It is composed of two different kinds of polypeptide chains, two heavy and two light chains held together by interchain disulfide bonds. Heavy and light chains of immunoglobulins are identical, giving up two identical antigen binding sites, able to bind two antigen molecules.[61] An intra-chain disulfide bond is responsible for the domain-like structure and loop formation of the immunoglobulin molecule.

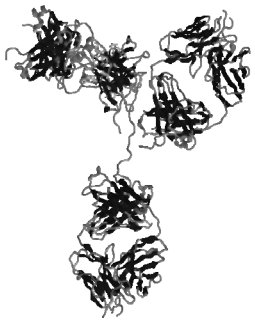

Figure 2-13. Human immunoglobulin G structure.

Human immunoglobulin G (HIgG) is one of the most frequent proteins found in human body fluids (Figure 2-13). Its synthesis is controlled as a response towards antigenic stimuli. Its main function is related to defense mechanisms to protect the human body from foreign malicious agents. It can pass through the placenta, giving immunity to the fetus.

HIgG can be divided into four different subclasses: IgG1, IgG2, IgG3, and IgG4. These subclasses were designated according to their relative abundance in human sera (Table 2-4).[62] A deviation in the normal concentration ranges of each subclass could be related to the presence of one or several diseases. A change in the distribution

of the human IgG subclasses as a consequence of an antibody response can increase or diminish one or more subclass levels, depending on the antigen nature, frequency and duration of the antigenic stimulation.

Subclass	g / L
IgG 1	4.9-11.4
IgG 2	1.50-6.4
IgG 3	0.20-1.10
IgG 4	0.080-1.40
Total IgG	7.0-16.0

Table 2-4. Reference ranges in g / L of IgG subclasses in human adults.

Classic techniques for determining HIgG involve ELISA or enzyme immunosorbent assay (EIA).[63] These are reliable and selective techniques, however, they are time and reagent consuming, and have other disadvantages such as the need for labeling. The development of sensitive, rapid, straightforward and reagent-free methods of biomolecule detection is of great interest due to their potential application in the diagnosis of diseases. Determining HIgG is extremely important in diagnosing illness, because several diseases are accompanied by changes in the concentration of this protein.

2.4 FIELD-EFFECT TRANSISTORS

Despite having important structural differences from their predecessors, field-effect transistors (FETs), carbon nanotube field-effect transistors (CNTFETs) display some similarities with respect to the basic operation mechanisms. Therefore, it is useful to briefly summarize the operational characteristics of FETs.

2.4.1 The origins: from MOSFETs to CHEMFETS

MOSFETs: Field-effect transistors used in analysis have their origins in electronics. The metal-oxide-semiconductor field-effect transistors (MOSFET) are widely employed in the integrated circuits used in microprocessors and other electronic applications. Their basic structure and functionality have greatly influenced the development of analytical FETs. The two basic components of a MOSFET are a capacitor combined with a transistor. Although nowadays the materials used have evolved, traditionally the capacitor is formed by a dielectric layer of SiO_2 placed between a semiconducting layer of p- or n- type doped silicon, and a metallic electrode known as 'gate' electrode. The transistor consists of the doped silicon layer in contact with two spatially distinct regions of doped silicon having opposite conductivity. These regions are contacted by the 'source' and 'drain' electrodes and a voltage is established between them. Figure 2-14 shows the disposition of the different components in the device. The capacitor is situated vertically while the transistor is placed horizontally, perpendicular to the former. It should be noted that the whole system can be built using Complementary Metal Oxide Semiconductor (CMOS) technology and, consequently, nowadays can be miniaturized to a size in the order of units of micrometers.

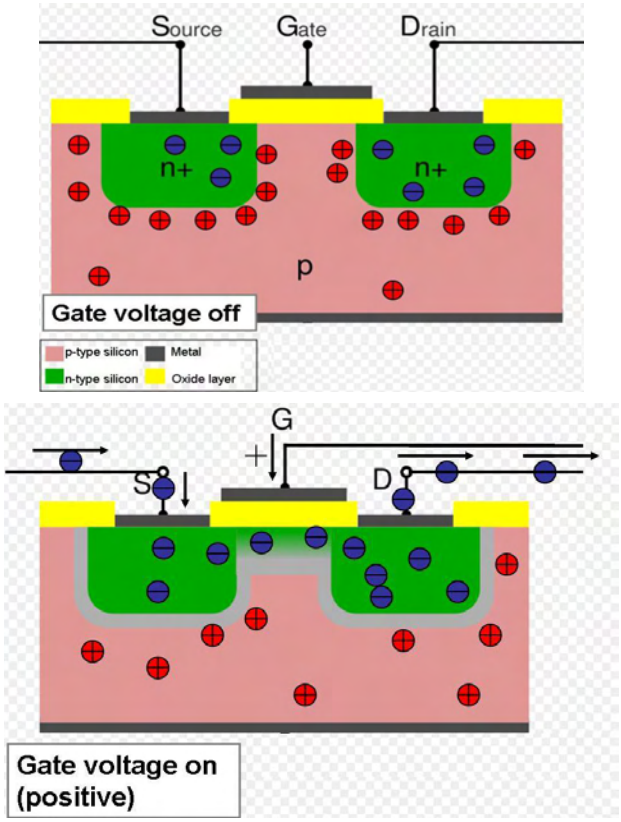

Figure 2-14. The physical disposition of the different components of a MOSFET (top), and their working principle (down).

The working principle is simple: if a variable voltage is applied to the gate electrode, it will modulate the field strength across the insulating SiO_2 layer and enhance or deplete the density of the mobile charge carriers in the doped silicon (holes in case of p-type or electrons in case of n-type) depending on the polarity of the field. Therefore, the change in the capacitor field strength is translated to a change in the channel resistance of the transistor, and consequently, variations can be detected in the measured conductivity between source and drain electrodes.

CHEMFETs. The field strength across the SiO_2 can be modulated in different ways. If the gate electrode of a MOSFET (Figure 2-15a) is replaced by an electrolyte solution and an external reference electrode is used to close the circuit, a chemical sensitive field-effect transistor (CHEMFET) is obtained. CHEMFETs differ according to the nature of the interaction that gave rise to their response.[64] In ion sensitive field-

effect transistors (ISFETs) (Figure 2-15b) an electrochemical field depends on the concentration of the target ion present in the solution (e.g. sodium or potassium ion). This modulates the change of mobile charges in the semiconducting inversion layer and a current flows through the source and drain electrodes.[65] Bergveld showed that the recorded electrical current depends not only on the ions in solution but also on the hydronium concentration giving rise to a pH sensor.[66] Soon after the development of the pH sensor, Moss *et al*. deposited the ion selective membranes used in ion selective electrodes (ISE) onto the dielectric layer of an ISFET.[67] Thus selective ISFETs appeared, where the electrochemical membrane potential generated at the interface between the ion selective membrane and the solution[68] is the origin of the electrical field that influences the current through the semiconducting channel.

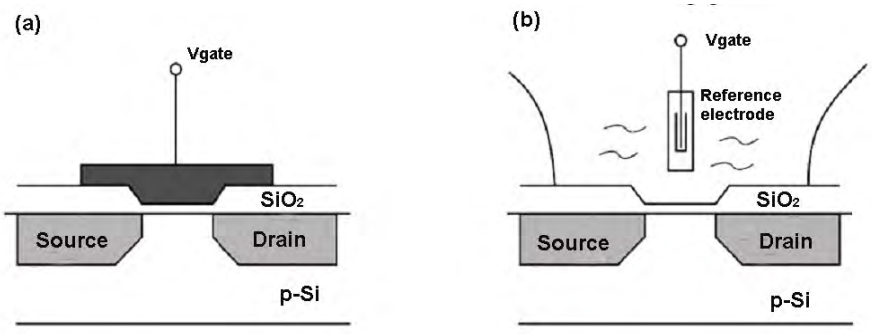

Figure 2-15. Schematic representation of: (a) MOSFET (b) ISFET.

Following the same operating principle used in MOSFETs, when the potential applied to the gate is fixed, the changes at the solution-electroactive material interface are reflected in changes of the source-drain current. However, if the source-drain current is kept at a constant value by a supplementary electronic circuit, then the output is the potential difference between two electrodes. The later is the usual mode of operating in ISFETs, therefore, in these devices, similarly to ISEs, the recorded signal is a voltage. This voltage varies with the activity of the tested ion in relation to the Nernst equation. Figure 2-16 shows a schematic representation of an ISFET sensor which is ready to take measurements in aqueous solution and which has a spatial disposition similar to that of an ISE.

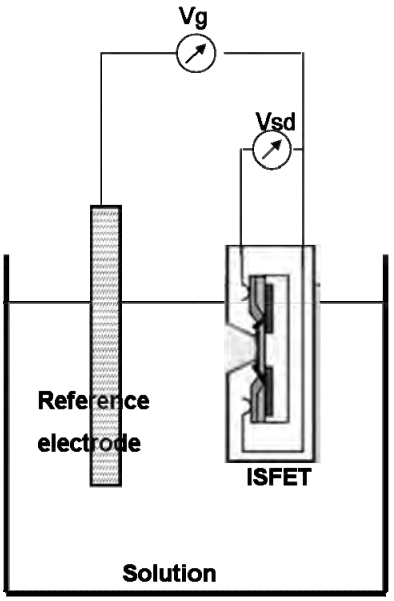

Figure 2-16. Schematic representation of an ISFET measuring the potential difference similar in way similar to that of an ISE. The electric contacts of the ISFET are encapsulated in order to prevent contact with the solution.

The need to use an external reference electrode both in ISFETs or CHEMFETs represents a drawback for miniaturizing the system. This is due to the serious technological problems when trying to create reference electrodes in the micrometer range.[64] Other technical problems are the well known instability associated with the lack of a thermodynamically reversible interface between the polymeric membrane and the transducer electronics.

2.4.2 Field-effect transistors based on carbon nanotubes

Tans *et al.*[71] and Martel *et al.*[72] demonstrated simultaneously that FETs can be built by using a semiconducting SWCNT. Semiconducting SWCNT can be integrated as the semiconductor channel in FETs because of their particular band gap in the DOS.[18] Two years later, Kong *et al.*[73] demonstrated that these FETs could be used for analysis in developing the first chemical sensor based on a CNTFET.

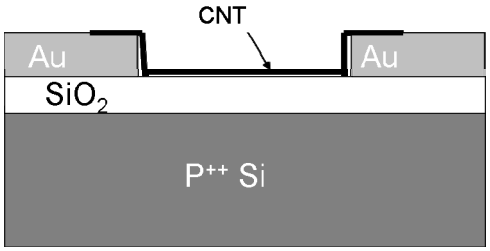

Figure 2-17. Representation of the first CNTFET, with the CNT deposited over the metal electrodes.

2.4.2.1 Structure and working principle

In an FET configuration, SWCNTs are connected to two metal electrodes (source (S) and drain (D)) and by applying a source-to-drain voltage, an electronic current flows through the SWCNT. This current is further modulated by a third electrode, the gate electrode. The gate electrode is usually a doped substrate placed in indirect contact with the channel through an insulating material of few hundreds of nanometers thick (see Figure 2-17). When applying positive gate voltages, the conductance (or current) of the SWCNT can be reduced by several orders of magnitude up to practically an insulating state because of the above mentioned p-type electrical behavior (Section 2.2.2) of SWCNTs. If a constant bias voltage between source and drain electrodes is applied while sweeping the gate voltage, the resulting curve of conductance (or current) versus gate voltage (Figure 2-18) is the so-called transistor transfer characteristics.[74] From this curve, one can determine typical parameters of the transistor, such as the maximum conductance value, the modulation (the signal compared to the noise level), the transconductance (slope at zero gate voltage, indicating the kind of carrier mobility, electrons or holes), and the threshold voltage.

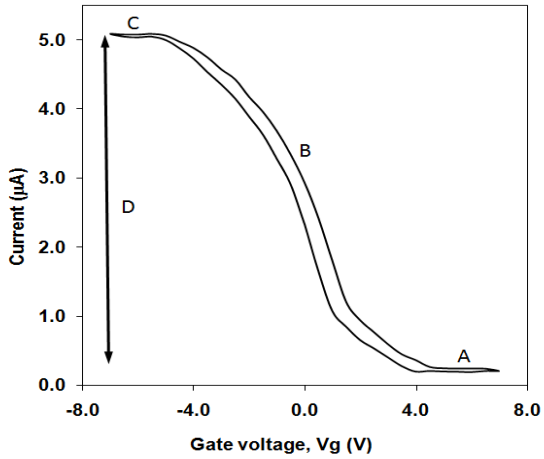

Figure 2-18. Transistor transfer characteristics for an ideal CNTFET. (A: Threshold voltage B: Transconductance; C: Maximum conductance; D: Modulation)

A Schottky barrier (an energy barrier for carrier transport in semiconductor-metal interfaces) is found in devices with a contact between a metal and a semiconductor (e.g. SWCNTs contacting the source or drain electrodes). Usually this limits such devices, but in the case of CNTFETs it is a less severe drawback due to the quasi one dimensional structure of the CNTs.[75] Prior to setting up the CNTFET, it has to be remembered that the semiconducting SWCNTs and the source and drain metallic contacts have different Fermi energy (E_F) levels (Figure 2-19a).[30] Subsequent contact of source and drain electrodes with SWCNTs will equilibrate these levels as result of a donation of electronic density from the metals into the VB of the SWCNT. This effect causes band bending both in the VB and CB of the SWCNTs, creating a potential barrier, the so called Schottky barrier in the interface between SWCNTs and metal contacts (Figure 2-19b).[18, 74] This phenomenon restrains the transmission of holes from the metal electrode into the SWCNTs. When a positive gate voltage is applied both VB and CB bend more strongly, and the source and drain metals suppress the hole transport into the VB of the SWCNT. In this case, the source-to-drain current is reduced and the device is considered to be in the "off-state". Negative gate voltage will have the opposite effect. The VB and CB bend less than for a zero gate voltage, reducing the SB. In this latter case, the electrical current of the transistor will increase, leading to the "on-state" when the current achieves saturation.

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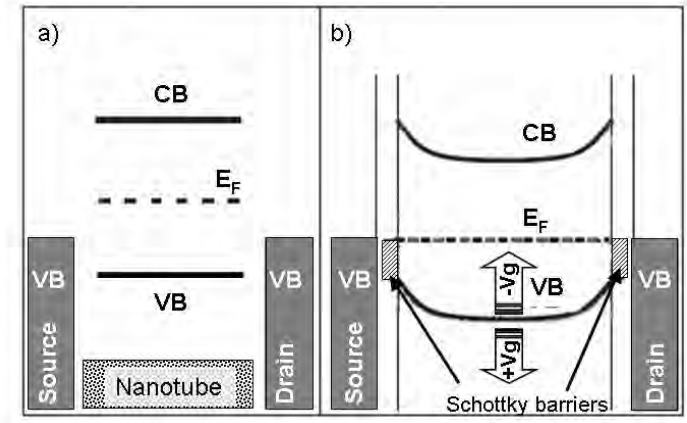

Figure 2-19. Basic band diagrams for (a) SWCNTs and metal electrodes independently and (b) CNTFET with contacted source and drain electrodes with a SWCNT. By applying positive or negative gate voltages (Vg) an increase or decrease respectively of the band bending can be seen.

The transistor performance occurs due to the generation of an electric field when the gate voltage modulates the Schottky barrier at the metal nanotube interface. For nanotubes with a length smaller than 1μm, the effect of the gate voltage on channel resistance is minimal. The source and drain electrodes need to be sufficient separated one of each other to prevent electrons tunnelling between them. By contrast, a channel length over 100 μm reduces the effect of the Schottky barriers, where the resistance of the bulk of nanotubes is the most responsible for the device performance.[33, 70] Moreover, the geometry used to contact CNTs with metal electrodes is crucial for the turn-on performance at low bias voltage.[76] Different studies have discussed about improving the configuration of the CNTFETs at the metal nanotube interface[77, 78] or doping the contacts.[79, 80]

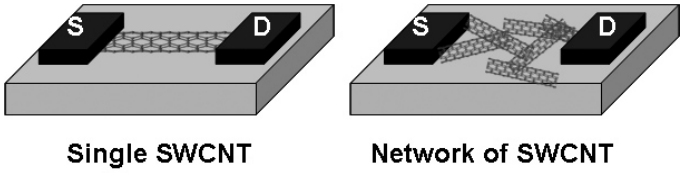

Figure 2-20. Two types of FETs using SWCNT to connect source and drain electrodes: single semiconducting SWCNT or network of SWCNT.

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FETs can be built either using a single semiconducting SWCNT or a network of SWCNTs (see Figure 2-20). In a network there will be both metallic and semiconductor SWCNTs. In a CNTFET configuration many metallic SWCNTs will lead to screen the gate potential, reducing the on/off ratio of the transistor (Figure 2-21).[33, 81] Therefore the network density has to avoid the possibility of finding several conduction paths through metallic SWCNTs.[33] In a random network of nanotubes, the ratio of semiconducting to metallic tubes is found to be 2 to 1, if the density is not very high[14] (see Section 2.2.1). Thus, the possibility to form a continuous pathway of metallic tubes is not likely to occur.[18, 78, 82] Hu *et al.*[33] calculated a theoretical limit of 1.43 conducting sticks (to account for the possibility of bundles of CNTs) per μm^2. If the density of SWCNTs is much higher than this limit there would be too many conduction paths through the metallic SWCNTs and hence the on/off ratio of the CNTFET would be reduced. Nowadays several techniques can be found in the literature either to separate both kinds of nanotubes[83-85] or to eliminate specifically the metallic ones.[86-88]

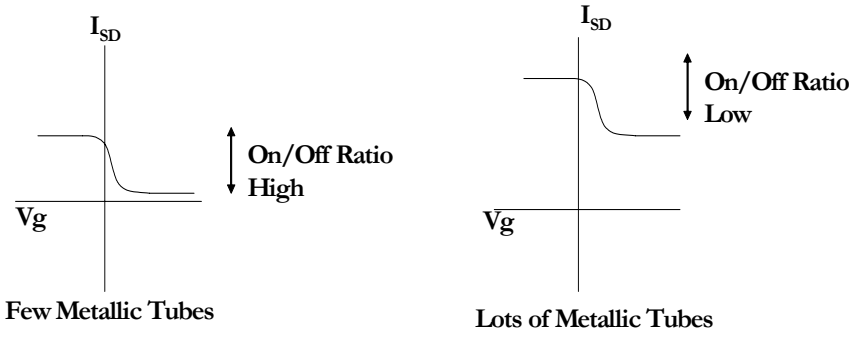

Figure 2-21. Schematic effect of the presence of few or many metallic nanotubes.

2.4.2.2 Gate configurations

Once described the basic structure of a CNTFET, the different gate configurations available are briefly discussed below.

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a. Back-gated CNTFETs.

Figure 2-22a shows a schematic representation of a back-gate CNTFET. There are several basic differences between their structure and that of their predecessors. In back-gate CNTFETs, the capacitor is made of a dielectric layer of SiO_2 that is placed between two semiconductor layers. The lower layer is made of p- or n-doped silicon and the upper layer is made either of a single semiconducting SWCNT or a network of SWCNTs. The nanotubes in contact with the metallic source and drain electrodes that are deposited on top of the silica layer behave as a transistor.[71, 72] Therefore, unlike the FETs in Section 2.4.1, the inversion layer is not made of silicon buried under the dielectric layer of silica, rather it is made of SWCNT(s) in direct contact with the sample to be analyzed. If a voltage is applied through the gate electrode, (now called the back-gate electrode since it is placed at the bottom of the device in contact with the doped silicon layer, see Figure 2-22a) that is connected to the source electrode, the modulation of the field strength across the insulating SiO_2 layer is obtained, and the density of mobile charges in the semiconducting SWCNTs will be modified. Consequently, the conductivity through the nanotubes will change.

It is important to realize that this structure allows two important functions. First, the electrochemically generated field, usually related to the presence of analytes of interest, can influence the semiconducting nature of the nanotubes because the sample is in proximity to the nanotubes. Second, the gate electrode is now integrated into the device and it is not necessary to have an external electrode, unlike in the ISFET or CHEMFET devices. The presence of an electrochemical field also affects the conductivity of the nanotubes, therefore it is measured as a change in the resistance in the source-to-drain current. Unlike in ISFETs and CHEMFETs, the change in the electrical current between the transistor is now the output signal.

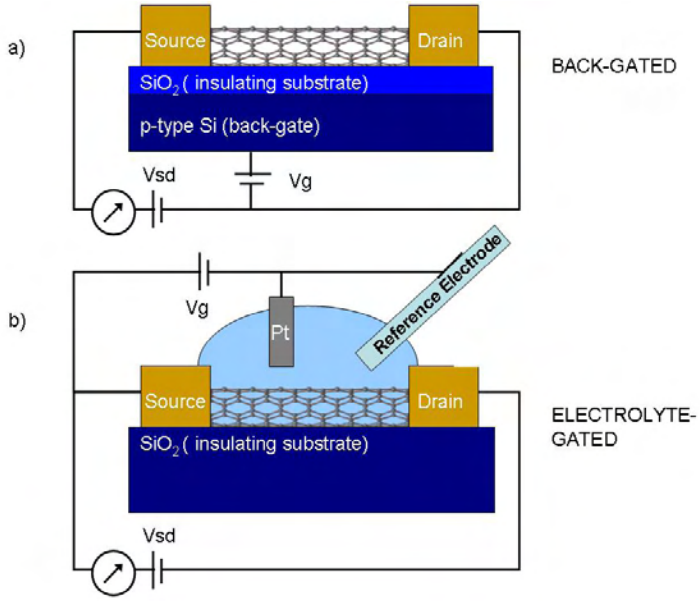

Figure 2-22. Schematic representation of the different gate configurations for FETs based on CNTs: (a) back-gated CNTFET (b) electrolyte-gated CNTFET.

b. Electrolyte-gated CNTFETs.

CNTFETs with a solution used as an electrolyte gate have also been developed.[89-92] (Figure 2-22b) The reference electrode is responsible for fixing the potential of the solution.[93] The characteristics of the two devices, back-gated and electrolyte-gated CNTFETs, are different because the capacitor established in each system is different.[94] In electrolyte-gated CNTFETs, the role of the reference electrode is very crucial, as was reported by Minot *et al*.[93] In this kind of device, the reference electrode, usually a Pt electrode is in contact with the solution containing the target analyte which, at the same time, is in contact with the functionalized SWCNTs. The electrostatic potential difference between the electrolyte and the nanotubes is controlled by the gate voltage applied and the potential at the metal-liquid interface. This latter potential is extremely sensitive on the diverse redox reactions that can occur at the metal-liquid interface.[92] Minot *et al.* claim that large molecules in solution can reach the metal surface of the Pt electrode and hence alter the redox conditions at this liquid interface. Biosensors usually operated in buffer solutions where redox species are present, giving an unpredictable and unstable potential that could affect the applied gate

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potential. This problem can be overcome using a reference electrode (e.g. an Ag/AgCl reference electrode) that ensures that the redox conditions at the metal-liquid interface are well controlled. The use of electrolyte gated CNTFETs is found to increase the sensitivity of the devices, but this effect has to be balanced against the difficulties either of miniaturizing the reference electrode and/or conditions of the electrolyte when using Pt electrodes (electrochemical reactions at the metal liquid interface have to be well defined).

c. ISFETs based on CNTs.

As in the case of CHEMFETs, when adding an ion selective membrane to an ISFET we obtain a different device. In this case, the semiconductor channel made from an SWCNT network has been covered by a polymeric ion selective membrane[95] (see Figure 2-22). In this case, when placing an ion selective membrane, the nanotubes are isolated from the electrolyte containing the analyte due to the membrane layer.

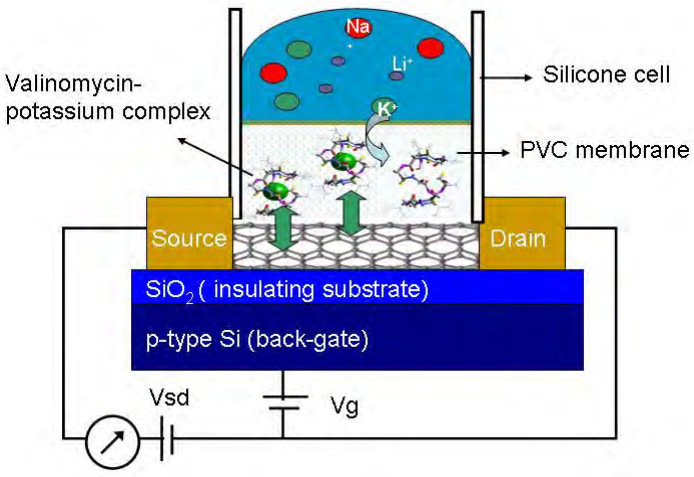

Figure 2-23. Schematic representation of an ISFET based on CNTs (not scaled).

With this configuration we include an extra modulation to the electrical back-gate potential since we add a new source of electric field provided by the membrane/electrolyte potential. This potential (as with ISEs) depends, according to the Nernst equation, on the logarithm of the activity of the ion present in the solution.

Therefore, by maintaining the back-gate potential constant (at the optimum value), the current between source and drain electrodes will depend on the activity of the ions in the solution. In this way, specific ions present in the solution can be determined using the suitable membranes.

d. Other configurations

Other configurations of CNTFETs have appeared recently, such as polymer-gated CNTFET,[96, 97] or top-gated CNTFET.[70] All are based on the same principles described in this Section above, but display different structural characteristics to enhance the performance of such devices (see Figure 2-24).

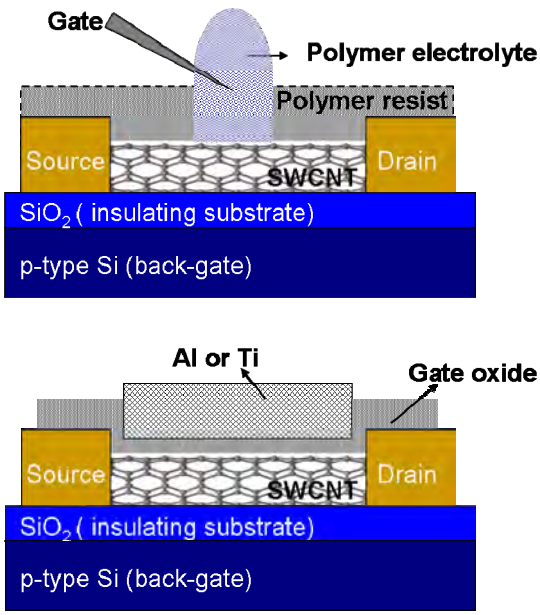

Figure 2-24. Schematic cross-Section of a polymer-gated (up) and top-gated (down) CNTFETs.

2.4.3 Applications of CNTFETs classified according to the receptors used

All field-effect devices are basically surface-charge measuring devices and therefore, they can principally measure the charge of adsorbed macromolecules or the charge change due to a hybridization event.[98] In a CNTFET, a source-to-drain voltage is applied, and then an electrical current flows through CNTs. This electrical current is further modulated by applying an extra potential, the source-to-gate potential. This second voltage modifies the electrical current of the nanotubes, this electrical current being the output signal in an analytical device.

As a nanotube has no inherent selectivity, that is, it needs to be functionalized to achieve selectivity. Functionalizing the nanotube surface with the desired receptor allows the detection of the target analyte when it interacts with the receptor. A modification of the electrical field can be detected and related with the base signal (keeping in mind that SWCNTs are highly affected by the surrounding chemical environment). This process enhances sensitivity significantly and enables the detection of very low concentrations of analyte, up to the picomolar range.[78] Functionalised CNTFETs are capable of being prominent molecular sensors because of their high sensitivity, fast electrical response time, and compatibility with array fabrication.[99]

Examples reported in the literature have demonstrated the effectiveness of these sensors using receptors, mainly for recognizing bioanalytes.[18, 35, 100] The recognition event has mainly been focused on DNA hybridization[101-104] and antigen-antibody interactions.[105-107] In this way, the receptor is usually attached to the SWCNT surface, with a subsequent detection of the molecular recognition event. Different strategies have also appeared to attach specific molecular recognition abilities withthe use of synthetic receptors (e.g. functionalizing nanotubes with aptamers) to improve their receptor characteristics.[106, 108] Recently, studies using CNTFETs able to detect bacteria have appeared.[109, 110] Other chemical sensors have been developed using CNTFETs with receptors selective towards the target analyte. For example Zhao et al.[111] decorated SWCNTs with pyrene-modified beta-cyclodextrin in order to sense several small organic molecules. Another interesting example is the combination of a CNTFET covered with single-stranded DNA (as recognition layer), to

sense different vapors that bare CNTs cannot detect.[112] These sensors display a very short time response and recover rapidly (in seconds) and the sensor surface is self-regenerating.

Enzyme based nanosensors have also been discussed and applied to CNTFETs.[35, 113] Enzymatic reactions produce an electron transfer between molecules so that even enzymes could temporarily have different conformational states and some groups change their charge state. This means, that charge changes are being simply detected by electrical nanodevices. The most commonly used enzyme in this field is Glucose Oxidase (GOx) in glucose nanosensors. GOx has been immobilized on CNTs.[114] Compared to the conventional electrochemical detection method, these nanosensors represent a simple and low-cost platform with real time and re-usability biosensing capability.

In all the examples described above the goal is to achieve low limits of detection and high sensitivity, among other performance parameters, by employing nanotube-based sensors. But to do this, as has been previously commented, the nanotubes have to be functionalized because of their lack of selectivity. However, many of the literature reports report the proof-of-concept establishing the basis for the detection capability of host-guest interactions. That is to say, they apply this strategy to obtain qualitative results which suggest that if one type of interaction works as a sensing system, so will all similar structures using the same type of receptor-analyte. An example is the functionalization of nanotubes with carbohydrates as biosensor materials for detecting pathogenic cells, e.g. *E. Coli*, via specific adhesin-receptors, etc.[103, 115] The field needs quantitative results to demonstrate the feasibility of the sensors developed.

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3 CNTFET sensor: Experimental development

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Table of contents

3.1 INTRODUCTION

The carbon nanotube field-effect transistor (CNTFET) is the common device used in all the chapters of this thesis, specifically, a field-effect transistor built with a network of SWCNTs. Although the fundamentals of the device have been described in the previous Section, in this chapter we specify the reagents, materials and procedures followed to assemble the CNTFET and the subsequent functionalization steps to develop selective sensors for the target analytes. This chapter aims to provide a detailed protocol so that the results found in this thesis can be reproduced. Results and theory have been intentionally left out.

The laboratory development of these CNTFET-based sensors can be divided into three main steps: 1) the synthesis of nanotubes, 2) the construction of the CNTFET and 3) the functionalization of SWCNTs. In a subsequent step we describe the process of recording the instrumental responses. We also describe the characterization of the CNTFET device either by electrical techniques or by microscopy.

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3.2 MATERIALS

3.2.1 Synthesis of single walled carbon nanotubes

3.2.1.1 Laboratory Equipment

- Horizontal split tube furnace HST 12/600 (Carbolite , Hope Valley, UK)
- Quartz tubular reactor (4 cm x 120 cm) (Afora, Barcelona, Spain)
- Ultrasonic bath 100 W (Selecta, Barcelona, Spain)
- Spin coater WS-400B-6NPP/LITE (Laurell Technologies Corporation, North Wales, PA, USA)
- Mass controllers for methane and hydrogen including PC software (Bronkhorst, Ruurlo, The Netherlands)

3.2.1.2 Gas Supplies

- Methane C-45 (Carburos metálicos, Barcelona, Spain)
- Hydrogen C-50 (Carburos metálicos, Barcelona, Spain)
- Argon C-50 (Carburos metálicos, Barcelona, Spain)
- Nitrogen C-50 (Carburos metálicos, Barcelona, Spain)

3.2.1.3 Reagents and other materials

- Acetone 99.5 % (Sigma, Tres Cantos, Spain)
- Iron nitrate (III) nonahydrated 99.99 % (Sigma, Tres Cantos, Spain)
- Isopropanol 99.5 % (Sigma, Tres Cantos, Spain)
- Deionized and charcoal-treated water (18.2 MΩ·cm specific resistance) obtained with Milli-Q PLUS reagent-grade water system (Millipore, Billerica, MA, USA)
- Substrates of Si/SiO_2. 500 nm of SiO_2 grown thermally over type n low resistivity Si. Dimensions: 1 x 1 cm and 0.5 x 0.5 cm (D+T Microelectrónica, National Microelectronics Centre, Bellaterra, Spain)

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3.2.2 CNTFET construction

3.2.2.1 Reagents and other materials

- Electrodag® 1415 M (Acheson Industries, Scheemdam, Netherlands)
- Photolitography of Cr/Au metal contacts (*D+T Microelectrónica,* National Microelectronics Centre, Bellaterra, Spain)

3.2.3 Functionalization procedures

3.2.3.1 Human immunoglobulin G antibody

- Polyethyleneimine (PEI), high molecular weight, water-free (Sigma, Tres Cantos, Spain)
- Human immunoglobulin G (heavy & light chain) antibody (HIgG) affinity purified produced in goat. (Bethyl Laboratories. Inc., Montgomery, USA). Antibody concentration: 1 mg/mL. Physical state: liquid. Buffer: phosphate buffered saline, pH 7.2. Preservative: 0.1% sodium azide[3]
- Dulbecco phosphate buffered saline solution (PBS), 150 mM, pH: 7.1 - 7.5 (Sigma, Tres Cantos, Spain)
- Glutaraldehyde grade I, 25 % in water (Sigma, Tres Cantos, Spain)[4]
- Glycine powder (Sigma, Tres Cantos, Spain)
- Tween 20 (Sigma, Tres Cantos, Spain)
- Deionized and charcoal-treated water (18.2 MΩ·cm specific resistance) obtained with Milli-Q PLUS reagent-grade water system (Millipore, Billerica, MA, USA)

[3] Storage temperature: 2 – 8 ºC.

[4] Storage temperature: 0 °C.

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3.2.3.2 Potassium ion selective membrane

- Valinomycin (potassium ionophore) (Sigma, Tres Cantos, Spain)
- Potassium tetrakis (4-chlorophenyl) borate (Sigma, Tres Cantos, Spain)
- Dioctyl sebacate (bis(2-ethylhexyl) sebacate) (Sigma, Tres Cantos, Spain)
- Poly(vinyl chloride) high molecular weight (Sigma, Tres Cantos, Spain)
- Tetrahydrofuran anhydrous (Sigma, Tres Cantos, Spain)

3.2.3.3 Synthetic receptor for SO_2

- Polyethyleneimine, high molecular weight, water-free. (Sigma, Tres Cantos, Spain)
- Platinum (II) complex: $[PtI(4\text{-}C_4O_2NOCO)\text{-}2,6\text{-}\{CH_2NMe_2\}2\text{-}C_6H_2]$ synthesized at the Department of Organic Chemistry and Catalysis, Utrecht University (Utrecht, The Netherlands)
- N-acryloxysuccinimide 90 % (Sigma, Tres Cantos, Spain)
- Dichloroethane anhydrous 99.8 % (Sigma, Tres Cantos, Spain)
- Deionized and charcoal-treated water (18.2 MΩ·cm specific resistance) obtained with Milli-Q PLUS reagent-grade water system (Millipore, Billerica, MA, USA)

3.2.4 Characterization of the CNTFET

3.2.4.1 Laboratory equipment

- Precision semiconductor parameter analyser Agilent 4157A (Agilent Technologies, Las Rozas, Spain)
- MP 1008 Manual probe station (Wentworth Laboratories, Sandy, UK) placed within a Faraday box (SIRM, Badalona, Spain) over an anti-vibration table (SIRM, Badalona, Spain)

3.2.4.2 Microscope equipment

- Scanning electron microscope (SEM), JSM 6400 (Jeol, Tokyo, Japan)
- Environmental scanning electron microscope (ESEM), Quanta 600, (FEI, Hillsboro, OR, USA)

- Atomic force microscope (AFM), PicoPlus (Molecular Imaging, Tempe, AZ, USA)

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3.3 METHODS

3.3.1 Synthesis of single walled carbon nanotubes [1-3]

1. Prepare the catalyst solution. 100 mg/L of iron nitrate in isopropanol sonicated (ultrasonic bath, 100W) about 10 min.[5]
2. Clean the Si/SiO_2 substrate by one cycle of consecutive immersions in the following solvents: acetone, isopropanol, and finally deionized water in the ultrasonic bath. Time of bath: approximately 5 minutes for each solvent. Dry under a gentle flow of nitrogen.
3. Spin-coat three times 20 µl of the catalyst solution over the surface of the substrate of Si/SiO_2 when it spins at 3000 r.p.m., and leave it spinning until the solvent completely evaporates (about 30 seconds).
4. Introduce the substrate into the quartz reactor (Figure 3-1 and Figure 3-2).[6] Set the furnace temperature at 900 ºC. An argon current of 1000 sccm, acting as purging gas, flows through the reactor from room temperature up to 900ºC. Once 900 ºC is reached, the argon flow is turned off and at the same time the flows of methane and hydrogen are opened. The methane and hydrogen flows are then kept constant (600 and 200 sccm, respectively) for about 20 minutes. After this time, the methane and

[5] The catalyst solution must be translucent and homogeneous without any kind of aggregate or precipitate. The solution can be kept in use for 1 month at room temperature if it maintains the mentioned properties.

[6] The substrates had to be placed in the last third of the tubular oven. The gases should arrive at the substrate placement at maximum temperature.

hydrogen flows are turned off and the argon flow is turned on again while the system cools to room temperature.[7, 8]

5. At this point, a network of SWCNT is grown over the silica substrates.

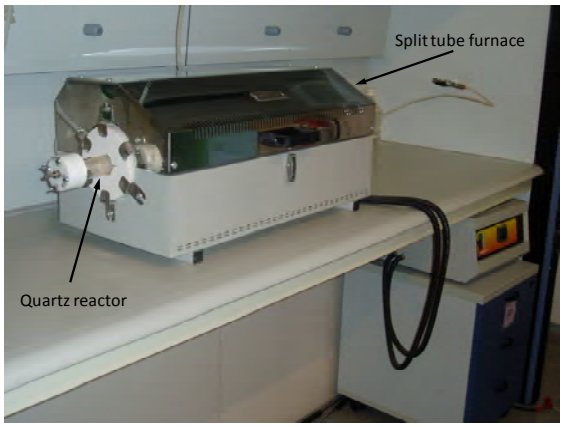

Figure 3-1. Image of the split tube furnace with the quartz reactor at 900 ºC used for the synthesis of SWCNT using the chemical vapor deposition method

[7] Methane and hydrogen flow must be carefully controlled; this is why we used mass controllers. Since argon is the carrier gas, its flow can be controlled with a manometer.

[8] Catalyst concentration and synthesis time (when methane and hydrogen gases flow through the reactor) influence the overall density of the network of SWCNT's. 100 mg/L of iron nitrate in isopropanol is the concentration normally used to obtain a medium-high density of SWCNT's. Lower concentrations, i.e. 50 mg/L and 25 mg/L, were used whenever a low density of SWCNT's was required. Additionally, the time of synthesis is directly related to the density of the nanotubes. If the density of the network is too high at 20 min of synthesis, it could be reduced down to 10 or 5 min.

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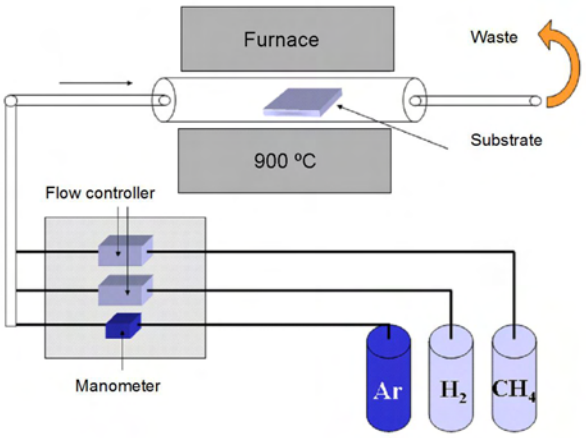

Figure 3-2. Schematic of the experimental setup for the chemical vapor deposition method.

3.3.2 CNTFET building

To measure the electric current flowing through the SWCNT network, the instrumental signal that we will relate to the concentration of the target analyte, electrical contacts are placed at both ends of the selected network. These two metal contacts, the source and drain electrodes, have been patterned using two different procedures. One involves a lithographic process and the other was done using homemade screen printing.

Photolithography. (Figure 3-3) The source and drain electrodes are double-layered chromium/gold with a thickness ratio of 2/30 nm. The gold layer (upper layer) is used as the electrode metal since it remains unoxidized when it comes in contact with air due to its noble metal characteristics. The chromium layer (lower layer, placed directly over the Si/SiO_2 substrate) is needed so the gold layer adheres properly to the Si/SiO_2 substrate. The distance between pairs of Cr/Au electrodes is 2-3 μm.

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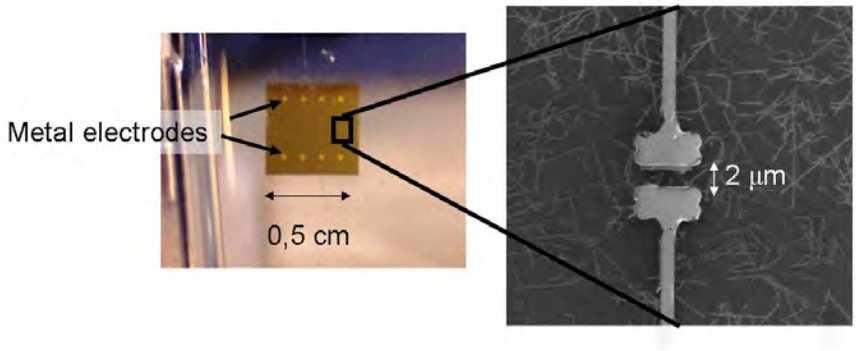

Figure 3-3. Electrodes deposited lithographically. Picture of the whole substrate containing four pairs of metal electrodes (left), and a zoom with an environmental electron scanning microscope (right).

Screen printing. (Figure 3-4) A conductive solution (commercially called Electrodag® 1415 M, made of silver and 4-methylpentan-2-one) is placed manually over the Si/SiO_2 substrate containing SWCNT using a silicone mask. The mask allows the metallic electrodes to be printed at the desired sites. Subsequently this substrate (Si/SiO_2 with SWCNT and metallic electrodes) is cured at 150 ºC for 10 min. With this process, the correct distance between source and drain electrodes can be achieved with lower precision than with optical lithography. The distance between the metallic electrodes ranged from 1 mm to 5 mm, according to what the device was to be used for. This is a fast and inexpensive method to roughly place electrodes in our laboratory.

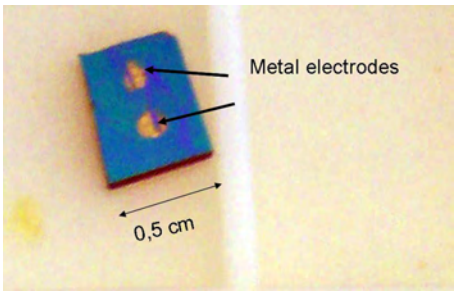

Figure 3-4. Home screen-printed electrodes.

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3.3.3 Functionalization procedures

3.3.3.1 HIgG antibody for HIgG detection

We used two different immobilization strategies to functionalize SWCNT with HIgG antibodies in order to build HIgG sensors.

a. Direct immobilization of the antibody on the surface of SWCNT.[4-7]

In this method, there are two functionalization steps. The first step is the adsorption of antibody molecules, which act as the receptor part of the sensor, over the SWCNT.[8] The second step is preventing the non-selective binding of undesired substances, such other proteins found in the sample (e.g. bovine serum albumin). This latter step is performed by immobilizing a small molecule, Tween 20 (Figure 3-5),[8] over the remaining free surface of SWCNT.

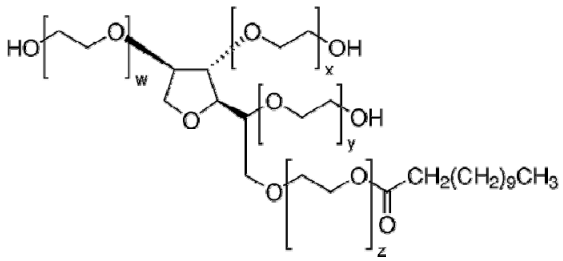

Figure 3-5. Tween 20 structure.

1. Prepare a diluted solution (10 mg/L) from the commercial antibody (1000 mg/L) in phosphate buffered saline solution (PBS) (15 mM, pH=7.4).
2. Immerse the CNTFET in the prepared antibody solution overnight to have the antibodies adsorbed over the SWCNTs. Subsequently, rinse with deionized water twice and dry with nitrogen.

3. Prepare a solution of 0.5 % of Tween 20 in PBS. Immerse the CNTFET containing the HIgG antibodies adsorbed over the SWCNTs in the Tween 20 solution for 2 hours. Subsequently, rinse with deionized water twice.
4. The devices are ready to use to detect the HIgG.[9]

b. Polymer coating of SWCNT and further covalent linkage of the antibody to the polymer[3, 4, 9-12]

In this procedure four functionalization steps were performed. First, SWCNT were coated with a polymer, PEI (Figure 3-6). This isolates the entire surface of SWCNT from the surrounding environment via the adsorbed PEI. Consequently, the functional amine groups provided by PEI are incorporated, promoting posterior covalent attachment of the receptor. In the second step, a typical linker molecule used in biosensors, glutaraldehyde (GA) (Figure 3-7) is used as a bridge molecule between the PEI surface and the antibody molecule. After the antibody binds to the GA, some GA molecules may remain unreacted, leaving reactive aldehyde groups, with which interferences could react. Glycine (Figure 3-8) is used to block these unreacted aldehyde groups in order to prevent non-specific binding of other proteins on the sensor surface.

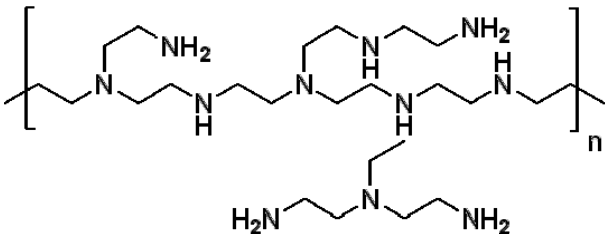

Figure 3-6. Polyethyleneimine structure.

[9] If the sensors are not used, they must be kept dry and refrigerated (2 - 8 ºC).

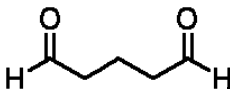

Figure 3-7. Glutaraldehyde structure.

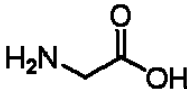

Figure 3-8. Glycine structure.

1. Prepare a PEI aqueous solution at 10 %. Immerse the CNTFET for 4 hours and subsequently rinse thoroughly with deionized water twice and dry with nitrogen.[10]
2. Prepare a 2.5 % GA aqueous solution (obtained from a 25 % solution of GA and adjusted to pH= 7.4 with NaOH 0.1 M). Immerse the PEI-functionalised CNTFET in this prepared GA solution for 2 hours and afterwards rinse thoroughly twice with deionized water.
3. Prepare a diluted solution (10 mg/L) of anti-HIgG from the commercial antibody (1000 mg/L) in phosphate buffered saline solution (PBS) (15 mM, pH=7.4). Immerse the PEI-GA-functionalized CNTFET in this solution overnight. Rinse with deionized water twice.
4. Prepare a solution 0.1 M of glycine with deionized water adjusted at pH=7 with NaOH 0.1 M. Immerse the PEI-GA-anti-HIgG-functionalized CNTFET for 1 hour and then rinse thoroughly with deionized water.

[10]The effective coating of the SWCNT's by PEI is observed electrically by checking the change from a p-type to an n-type conduction of the SWCNT's. If this change is not observed, the CNTFET is immersed overnight in the same PEI solution.

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3.3.3.2 Potassium ion selective membrane

1. Prepare the ion selective membrane.[13] The composition of the potassium ion-selective membrane is listed in Table 3-1. All the components except tetrahydrofuran are weighed and mixed together, and then tetrahydrofuran is added. Leave the solution to agitate for about 30 min until all the components became perfectly mixed and dissolved.[11]

Membrane Component	Amount
Valinomycin	0.05 mg
Potassium tetrakis (4-chlorophenyl) borate	0.015 mg
Dioctyl sebacate	0.75 mg
Poly vinyl chloride	1.6 mg
Tetrahydrofurane	2 mL

Table 3-1. Composition of the potassium ion-selective membrane

2. Cast the membrane solution over the CNTFET surface using a spin coater. Coat the desired surface with a suitable volume of tetrahydrofurane membrane solution (in our case, a single drop of 30 μL is needed to cover a surface of 0.5 cm x 0.5 cm). Spin at a speed of 3000 r.p.m. for 1 minute.[12]
3. The resulting membrane thickness is about 17 mm, with the described conditions and surface.[14]

[11] The solution must be kept sealed and refrigerated (2 - 8 ºC).

[12] If any kind of air bubble appears after the membrane deposition, remove the coating carefully and deposit it again.

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3.3.3.3 Synthetic receptor for SO_2 detection

As mentioned above, a PEI coating isolates SWCNT from possible interference and makes it possible for amine groups to establish further covalent links. In this method, these PEI amine groups are bound to a platinum complex (Figure 3-9), which is the specific receptor for SO_2. In a further stage, once the platinum complex is immobilized on the sensor surface, any interference due to a possible interaction with non-reacted amine groups is eliminated through treatment with an N-acryloxysuccinimide solution (Figure 3-10).

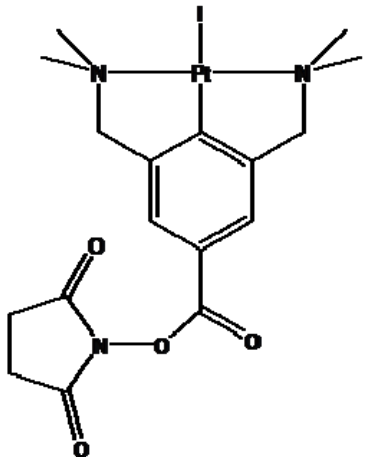

Figure 3-9. Platinum complex structure.

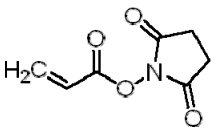

Figure 3-10. N-acryloxysuccinimide structure.

1. Prepare a PEI aqueous solution at 20 %. Immerse the CNTFET overnight and afterwards rinse thoroughly with deionized water twice and dry with nitrogen.[13]
2. Prepare 3 mg/mL solution of the platinum complex in dichloroethane. Immerse the PEI-coated CNTFET for 3 hours and after rinse thoroughly with dichloroethane.
3. Prepare a 3 mg/mL N-acryloxysuccinimide aqueous solution. Immerse the PEI-platinum complex-CNTFET for 2 hours at room temperature. Afterwards, rinse with deionized water and dry with nitrogen.

3.3.4 Characterization of the CNTFET

3.3.4.1 Electrical characterization

The characterization of the electrical properties of SWCNT networks is an essential step in assessing their behavior as the transducer part in FET-based sensors. It has been established that synthesis with CVD can produce both metallic and semiconducting SWCNT. This creates nanotubes of both types in random spaghetti-like network. This network is grown on the SiO_2 layer of the Si/SiO_2 substrate. With this configuration we use the silicon substrate as a back gate, i.e. the third electrode of the FET. The SiO_2 acts as a dielectric layer, isolating nanotubes electrically from the silicon. The electrical properties of the CNTFET were measured using a semiconductor parameter analyzer at room temperature. Source and drain electrodes are contacted with thin tungsten tips of the probe station, the tips are then connected to the semiconductor parameter analyzer. Using electrical characterization we can check every step of CNTFET construction, from the synthesis of SWCNTs to the individual steps of the functionalization process.

[13] See note 10

1. Check the existence of an electrical channel that connects source and drain electrodes. Apply a source-to-drain sweep voltage (Vsd) (e.g. + 0.25 V to - 0.25 V)[14] while keeping constant at 0 V the gate voltage (Vg). With this test we obtain: a) the resistance of the channel (R = V / I), b) the optimum value of Vsd,[15] c) the source-to-gate current ("gate leakage") at Vg = 0 V. If the values of the gate leakage are above 1 nA, then the device cannot be used.[16]
2. Register the electrical current at a fixed Vsd while sweeping the Vg (e.g. +5 to -5 V). This curve determines whether the nanotube network exhibits a semi-conducting or metallic behavior response, and is referred to as the "device characteristics".[17]
3. Perform the on-line measurements with the solution[18] containing the analyte, employing the best values of Vsd and Vg, and record the electrical current (ordinate axis) versus time (abscissa axis). Vsd and Vg values may vary slightly depending on the specific CNTFET used. However, the

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[14] High Vsd sweeping values have to be avoided in order to prevent burning the SWCNT's.

[15] In our devices, we considered the optimum Vsd value to be that which produces electrical current values of few microampers. This Vsd value is usually found between 0.1 V and 0.25 V.

[16] Sometimes a large gate leakage current is due to a high density of SWCNT's over the SiO_2 layer. It can be reduced by isolating the network under study: a thin surface cut is made around the network of the SWCNT's containing the source and drain electrodes.

[17] By observing the magnitude and polarity of the gate dependence we can assess if the network grown by CVD behaves as a *p*-type semiconducting field effect transistor in air.[3],[15]

[18] Or gas mixture.

different CNTFET obtained using the same procedure should provide the response signal within the same logarithmic unit. The best value of Vg is usually selected according to the value that produces the highest source-to-drain current, and at the same time maintains the capacity of modulate (i.e. with small variations of the gate voltage a high change in the source-drain conductivity is observed).

3.3.4.2 Microscopy characterization

Several powerful microscopic techniques are used to view one-dimensional nanometric structures such as SWCNT. We used scanning electron microscopy (SEM), environmental scanning electron microscopy (ESEM) and atomic force microscopy (AFM) to characterize several parameters of as-grown nanotube networks such as density, diameter, length, etc.

SEM	ESEM[19]	AFM
Normal and high density networks of SWCNT	Normal and high density networks of SWCNT	Low density networks of SWCNT
Medium speed imaging	High speed imaging	Long time for image acquisition
High vacuum mode	Atmospheric pressures at the specimen chamber	Atmospheric pressure
High range of visualization	High range of visualization	Small range of visualization. Maximum 100 μm x 100 μm
Composition information	Composition information	Topographic information. Possibility to measure the height of individual SWCNT
Able to image large size compounds (e.g. receptor, analyte)	Able to image large size compounds (e.g. receptor, analyte)	High-resolution images of nanometric structures
Electrically conductive samples (sample pre-treatment)	Electrically or non-electrically conductive samples	All kind of samples
Dehydrated samples	Hydrated sample in its liquid phase	All kind of samples

Table 3-2. Main attributes of SEM, ESEM and AFM when imaging SWCNT.

[19] ESEM has the same properties as SEM but with some improved parameters. These extra uses of ESEM are listed in the table.

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4 Sensors based on CNTFET and antigen-antibody recognition

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4.1 INTRODUCTION

The recognition of an antigen by means of its corresponding antibody is a very well defined interaction which has led to the development of many practical sensors. Classical techniques that use the antigen-antibody interaction are numerous and well developed (see Section 4.3.2). In fact these are reliable techniques but also they display some drawbacks such as long analysis time and large reagent consumption. Many of them usually employ an optical method of detection that records the analytical signal previously transduced from the recognition event. Therefore, new devices are needed which can detect antigens or antibodies with improved performance properties and operational parameters.

For this reason, CNTFETs have been described as new devices useful for developing innovative biosensors.[1, 2] Star *et al.*[1] showed that a CNTFET sensor is able to detect a protein, streptavidin, in the presence of biotin by means of change in the device's electrical characteristics. Bradley *et al.*[2] demonstrated that streptavidin mediates a charge transfer in SWCNT that is related to a change in the electrical behavior of the CNTFET. Although the interaction of an antibody with its specific antigen has now been described for a CNTFET in the literature,[3-6] it had not been described when the present work was proposed.

As was commented previously, SWCNTs cannot be used directly to determine a specific analyte because they do not display selectivity by themselves (their electrical conductivity is affected by many species in the surrounding environment). Although functionalization of SWCNTs can be performed either through covalent or non-covalent bonding of molecules,[7] all the covalent chemical approaches affect the electronic structure of SWCNTs and their mechanical properties.[8, 9] In this sense, a non covalent functionalization is the best way to minimally disturb the sp^2 graphitic sidewall structure of the nanotube and hence maintain its intrinsic electronic properties. We can find several examples in the literature where different types of antibodies are immobilized onto SWCNTs in a non-covalent way.[9-11]

When dealing with biological samples many kinds of proteins and other molecules are found in the sample composition. When the target analyte is an antigen or an antibody the prevention of the non-specific binding of other undesired biomolecules found in the sample is of major importance. All the sensors, including CNT-based sensors, have to take this fact into account in their design.[7]

This chapter shows the principles for antigen detection using CNTFET based sensors. Random networks of SWCNTs synthesized by a CVD process make up the transducer part of the sensor. SWCNTs act as the semiconductor channel of FET type devices. The principles of molecular recognition have been applied to solve the lack of selectivity shown by raw SWCNTs. SWCNTs are functionalized with HIgG antibody molecules acting as the receptor. The HIgG molecules acting as the target analyte will be detected through their interaction with the previously immobilized HIgG antibody, thus forming an immunocomplex.

Two different functionalization strategies have been proposed to effectively link the specific antibody while preserving the electrical properties of SWCNTs. In the first strategy the antibody is immobilized directly over the SWCNT by means of non specific adsorption. The second strategy involves a covalent coupling of the antibody to a previous non-covalent functionalized SWCNT surface. Through both procedures we avoid the non-specific adsorption of interfering molecules by properly blocking the free possible reacting groups. Also, measurements have been taken under two different sets of conditions. In the first approach the HIgG was detected in a liquid environment, at an adjusted pH and ionic force. In the other methodology, measures were carried out in dry conditions, after rinsing and evaporating the remaining antigen solution. In this latter case, the influence either of the pH or the ionic force in the sensor signal is avoided, although we maintain the physiological conditions when the sample is in contact with our device.

Therefore, we present two CNTFET-based sensors that can be used as effective biosensors to detect a target antigen through its interaction with the corresponding antibody. Many other existing antigens could be further detected by correctly immobilizing the antibody in the CNTFET. Moreover, these CNTFET sensors will

offer a suitable substrate able to detected antigens or antibodies with a reduced amount of reagent and sample volumes required to perform the analysis.

This chapter is complemented by additional experimental results not included in the published papers by the sake of brevity. The conclusions corresponding to the whole chapter and the references are also included.

4.2 ARTICLE: "CARBON NANOTUBE FIELD-EFFECT TRANSISTORS FOR THE FAST AND SELECTIVE DETECTION OF HUMAN IMMUNOGLOBULIN G", THE ANALYST, 2008

Analyst, 2008, 133, 1005–1008

Carbon Nanotube Field-effect Transistors for the Fast and Selective Detection of Human Immunoglobulin G

Cristina C. Cid, Jordi Riu*, Alicia Maroto, F. Xavier Rius

e-mail: jordi.riu@urv.cat

Department of Analytical Chemistry and Organic Chemistry

Rovira i Virgili University

C/ Marcel·lí Domingo s/n. 43007 - Tarragona. Spain

Tel: +34 977 55 84 91

Fax: +34 977 55 84 46

Keywords: Carbon nanotubes, sensors, field-effect transistor, antibody, antigen

We report a field-effect transistor (FET) based on a network of single-walled carbon nanotubes (SWCNTs) which can selectively detect human immunoglobulin G (HIgG). HIgG antibodies, which are strongly adsorbed onto the walls of the SWCNTs, are the basic elements of the recognition layer. The non-specific binding of proteins and the effects of other interferences are avoided by covering the non-adsorbed areas of the SWCNTs with Tween 20. The selectivity of the sensor has been tested against serum albumin (BSA), the most abundant protein in plasma. HIgG in aqueous solution with concentrations from 1.25 mg/L (8 nM) can be readily detected with response times of about 10 minutes. The SWCNT networks that form the basis of the sensor are easily grown by chemical vapour deposition. Silver screen-printed electrodes make the sensor quick to build. The sensitivity obtained with this sensor is similar to other FET devices based on SWCNTs built using much more complicated lithography processes. Moreover, the sensor is a reagent-less device that does not need labels to detect HIgG.

The study of the interaction between an antibody and its antigen is very important in clinical diagnosis, environmental monitoring and biochemical analysis, and immunoassays are the most popular techniques for these studies. Nowadays, many techniques have been developed to carry out immunoassays. Classical determination of HIgG involves techniques such enzyme-linked immunosorbent assay (ELISA) or enzyme immunosorbent assay (EIA). These are reliable and selective techniques, however, they are time and reagent consuming, and have other disadvantages such as the need for labelling. The development of sensitive, rapid, straightforward and reagent-less methods of biomolecule detection is of great interest due to their potential application in the diagnosis of diseases. The determination of HIgG is extremely important in diagnosing illness, as several diseases are accompanied by changes in the concentration of this protein. This antibody is responsible for the primary defence mechanism in humans when external antigenic compounds enter the body.

SWCNTs have outstanding electrical and mechanical properties. Tans *et al.*[1] reported the first field-effect transistor (FET) based on a single semiconducting

SWCNT. Kong *et al*.[2] found that the electrical conductivity of these carbon nanotube field-effect transistors (CNTFETs) was sensitive to various gases, such as ammonia, and thus can operate as sensitive chemical sensors. The functionalization of SWCNTs gives rise to the development of selective CNTFET biosensors based on the principles of molecular recognition.[3] These biosensors are based on CNTFETs in which the conductor channel can be either a single semiconducting SWCNT or a network of SWCNTs.[3] The biosensing mechanism of CNTFETs is mediated by chemical or electrostatic gating (i.e. by transferring charge to, or withdrawing charge from, SWCNTs)[2] or by the Schottky barrier (SB) modulation effect produced by molecules that are adsorbed very near to the metal-nanotube contacts.[4, 5] In these cases, the charge transfer between the target analyte and the SWCNTs shifts the source-drain current towards more positive (electron donation from the target analyte to the SWCNTs) or towards more negative (electron withdrawing from the target analyte to the SWCNTs) gate voltages. According to Heller *et al*, .[6] a combination of these two mechanisms explains the majority of their experiments about measurements in solution involving protein adsorption over SWCNTs, although other mechanisms are also possible. Grüner[3] pointed out that molecules on the surface of the SWCNTs may also act as scattering centres since these molecules, without a charge transfer, can decrease the mobility of electrons in SWCNTs, thus decreasing the current without shifting the characteristics of the device. Another mechanism was described by Besteman *et al.*[7], who pointed out that the immobilization of enzymes over SWCNTs can also decrease the conductance, which can be explained by a change in the total capacitance of the SWCNTs. In all cases, changes in the current intensity vs. gate potential curves can be used to experimentally identify between these sensing mechanisms.

CNTFETs have been used in the detection of gases such as NH_3 and NO_2.[8-10] They have also recently been used as biosensors for liquid samples, whereby several kinds of biomolecules have been immobilized on SWCNTs: proteins,[4, 11, 12] aptamers,[13, 14] antibodies,[4, 14] DNA[15] and bacteria.[16, 17] Maehashi *et al.*[14] used both aptamers and antibodies as the sensing part of a FET based on a single semiconducting SWCNT. This latter biosensor detected in real-time a 0.25 nM solution of immunoglobulin E (IgE) by using aptamers as the recognition element, but when using anti-IgE (antibodies) only slight changes in electrical current were observed for nM concentrations of IgE. All

these CNTFETs are built using costly and time-consuming lithography processes. So there is a need to obtain rapid-to-built and less-costly CNTFETs with no significant decrease on quality parameters like sensitivity or limit of detection.

In this communication, we explore the suitability of SWCNT networks integrated in CNTFETs for detecting the presence/absence of low concentrations of HIgG in short analysis times, through a change in the electrical current of a CNTFET. While the SWCNTs are the transducer part of our CNTFET device, the sensing part is the human immunoglobulin G antibody, the anti-HIgG, which selectively binds to HIgG. In this way, we take advantage of the molecular recognition mechanism between an antibody and its antigen to selectively detect our target analyte. The networks of SWCNTs that form the channel of the CNTFETs were grown by chemical vapour deposition (CVD) on top of a layer of silicon dioxide (500 nm of thickness) thermally grown on heavily n-type doped silicon substrates. 100 mg/L of iron nitrate in isopropanol (deposited by spin-coating over the SiO_2 layer) was used as the catalyst for the CVD performed at 900 ºC for 20 minutes with 600 sccm of methane and 200 sccm of hydrogen. The source and drain electrodes, separated by about 5 mm, were screen-printed with silver ink (Electrodag 1415M from Acheson industries (Europe) Ltd., Scheemdam, The Netherlands), avoiding hence any type of lithography processes, and the gate electrode was a layer of aluminium on the back side of Si. Liquid measurements were performed with a 2 μL home-made silicone cell. In all the experiments, neither the solution nor the silicone cell were in contact with the source and drain electrodes (see Figure 1A), so the solution only came into contact with the network of functionalized SWCNTs.

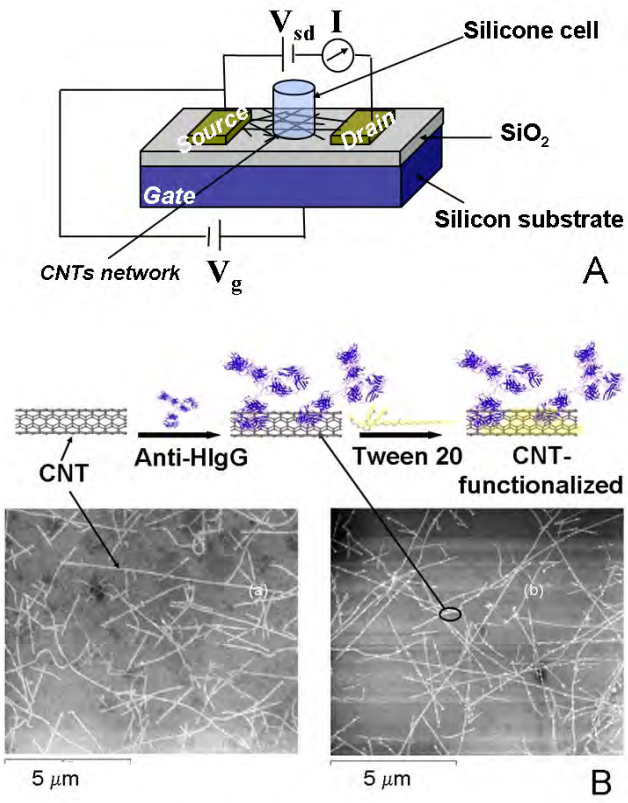

Figure 1. Schematic experimental setup for the detection of HIgG.

CNTFET device with the home-made silicone cell containing the target analyte. V_{sd} is the potential applied between the source and drain electrodes, and V_g is the potential applied to the gate electrode. I corresponds to the measured electrical current between the source and drain electrodes.

Functionalization process of the SWCNTs. 1) Adsorption of anti-HIgG over the SWCNT network. 2) The gaps left after the adsorption of the anti-HIgG onto the SWCNTs are covered by Tween 20. The pictures at the bottom are typical SEM images of the SWCNT network before (a) and after (b) the adsorption of anti-HIgG. The bright dots are the antibodies adsorbed onto the SWCNTs.

Considering a single nanotube from the network of SWCNTs in the CNTFET, Figure 1B shows the functionalization scheme followed. First, anti-HIgG antibodies (1000 mg/L from Bethyl Laboratories, Montgomery, TN, USA) are immobilized on the

SWCNTs by immersing the devices overnight in a 10 mg/L solution of anti-HIgG in PBS (phosphate buffered saline, 15 mM, pH=7.4). Several papers in the literature claim that proteins are strongly and non-specifically adsorbed onto carbon nanotubes.[11, 18] After this, the devices were immersed for 2 hours in a solution of 0.5% of Tween 20 (Sigma-Aldrich, Tres Cantos, Spain), in PBS. Tween 20 is a surfactant that irreversibly binds to the side walls of the SWCNTs by means of hydrophobic interactions.[11] Tween 20 will fill the gaps left between adsorbed molecules of anti-HIgG to prevent the non-specific binding of other proteins.[4, 11, 13] Apart from the coating provided by Tween 20 that protects the sensor from non-selective binding, the selectivity of our sensor is given by the antibody linked to the carbon nanotubes, the anti-HIgG. This antibody interacts selectively with HIgG. The CNTFET device was thoroughly rinsed with water and ready to be used to detect HIgG. A dense network of SWCNTs is obtained with the CVD technique. The scanning electron microscope (SEM) images of Figure 1B show a typical network of SWCNTs before and after the immobilization of anti-HIgG antibodies. Notice that the immobilization of the antibodies can be observed as bright dots on the SWCNTs. As a control experiment, CNTFET devices functionalized with antibodies were immersed in PBS (pH=7.4) during 24 hours, and they were then rinsed with deionised water and dried with nitrogen. After this process the density of antibodies immobilized over the SWCNTs did not change, as observed from the SEM images (not shown) and from the recorded electrical signal.

The CNTFETs were electrically characterized by measuring the dependence of the source-drain current, I, on the back gate voltage, V_g, in the range +4 to -4 V. The source-drain voltage, V_{sd}, was fixed at 0.25 V. Figure 2 shows how each step affects the electrical current of a typical CNTFET measured in dry conditions (i.e. without using any solution in contact to the network of SWCNTs). These dry measurements allow us to check every functionalization step. To obtain the instrumental variability, we carried out all the electrical measurements three times and we plotted the mean value and the range of the measurements. The as-grown SWCNTs exhibited a p-type behaviour due to the electron withdrawal of adsorbed oxygen molecules from the air.[18, 19] The electrical current decreased after the adsorption of anti-HIgG. This decrease was always observed to be independent of the net charge of the adsorbed protein[11] and could be due to the charge donation of base-containing residues located in the external envelope of

the protein.[11, 20] The electrical current of the CNTFET decreased slightly after the adsorption of Tween 20, as previously observed by So *et al.*[13] Tween 20 is a surfactant that strongly adsorbs on the walls of SWCNTs through hydrophobic interactions and protects them from the non-specific binding of proteins.[4, 11, 13] The functionalized devices were then ready to detect HIgG. First we checked the selectivity of the devices with BSA. In this way, we immersed the functionalized CNTFET for two hours in a solution of 1.25 mg/L of BSA at room temperature (Sigma-Aldrich, Tres Cantos, Spain). The error bars of the inset (Figure 2) shows that the slight change of the electrical current between the Tween 20 and the BSA results is due to the variability of the electrical current. The electrical current did not also change significantly with 10 mg/L of BSA (not shown). This proves that Tween 20 avoids the non-specific binding of other proteins such as BSA. The functionalized device was then exposed to a 1.25 mg/L solution of HIgG (1000 mg/L from Bethyl Laboratories, Montgomery, TN, USA) in PBS (15 mM, pH=7.4) at room temperature. The inset in figure 2 shows that the electrical current significantly decreases after HIgG interacts with the anti-HIgG antibodies (i.e. about 16%). The electrical current decreases after the addition of HIgG along the V_g axis without shifting the electrical characteristics. This suggests that HIgG acts as scattering center.[3] As a control experiment, we submerged CNTFET devices in Tween 20 without having adsorbed the anti-HIgG antibodies on the SWCNTs. These devices were subsequently exposed up to 10 mg/L of HIgG. No significant change of the electrical current was obtained after exposing the devices to HIgG. In this way, we proved that Tween 20 was effectively protecting the SWCNTs against non-specific binding and that the decrease of the electrical current was only due to the antigen-antibody interaction.

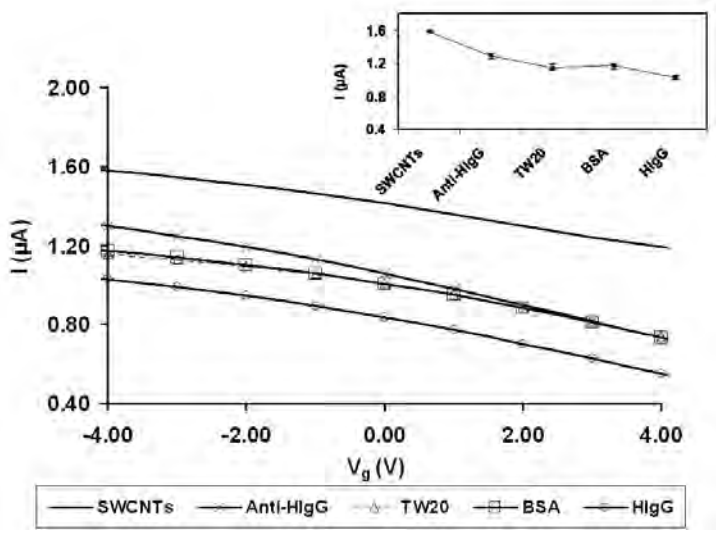

Figure 2. Source-drain current (I) vs. gate voltage (V_g) of a typical CNTFET after each functionalization step: as-grown nanotubes (——), anti-HIgG (–x–), Tween 20 (–Δ–), 1.25 mg/L BSA (–□–) and 1.25 mg/L HIgG (–○–).The immersion time in each solution was 2 hours. All these curves were recorded in a dry environment (i.e. without using the home-made silicone cell). Each electrical curve corresponds to the mean value of three replicates. The inset shows the source-drain current at V_g = -4 V. The error bars correspond to the range of the electrical current obtained for the three replicates.

The functionalized devices were applied to detect HIgG in solution. The test solutions were placed in a home-made silicone cell (see Figure 1A). The silicone cell is a commercial silicone tube (inner diameter: 3 mm, outer diameter: 5mm, with a height < 5 mm) placed between the source and drain electrodes. When no SWCNTs were in contact with the source and drain electrodes, no current was recorded when the solution was placed in the cell. The leakage current was less than 1 nA. The devices were stabilized with the PBS solution for about 10 minutes. Increasing amounts of HIgG were then spiked into the cell. Although the change in the electrical current takes place within few minutes, between each addition the system was left undisturbed for about 5 minutes so that the signal could stabilize. Figure 3 shows the electrical current value versus time at a specific gate and source-drain voltages (V_g = -4 V, V_{sd} = 0.25 V) when adding the above mentioned increasing amounts of HIgG. The results in Figure 3 show

that the electrical current starts to decrease within 60 seconds after each addition of HIgG (total concentration values from 1.25 mg/L up to 8.75 mg/L, i.e. from 8 nM up to 56 nM) and shows a stabilization of the signal about 10 minutes after each addition. Before each new addition of HIgG we always checked that the electrical current was stabilized for at least 4 minutes. The inset in Figure 3 shows that the interaction of HIgG with anti-HIgG significantly decreases the electrical current up to 8.75 mg/L HIgG (i.e. from 15% for 1.25 mg/L to 55% for 8.75 mg/L HIgG). The slight changes of the electrical current at 11.25 mg/L HIgG were only due to the variability of the electrical current. Therefore, we concluded that almost all the anti-HIgG antibodies were already bound with HIgG at 8.75 mg/L HIgG. This device showed a sensitivity of -1.5 nA/(mg/L). This sensitivity corresponds to the slope of the straight line fitted for the linear range of the in Figure 3 (i.e. from 0 to 4 mg/L). The minimum concentration of HIgG that we have been able to detect with a CNTFET device is 0.5 mg/L. The density of the SWCNT networks is known to affect the CNTFET characteristics.[21, 22] Since we applied always the same CVD parameters to grow the SWCNTs, we observed only slight changes of the density of the SWCNTs networks from device to device. Therefore, we were able to detect concentrations of HIgG of the same order of magnitude with our devices. We tried to regenerate the sensor by using several regeneration solutions that are known to dissociate the antigen-antibody complex without affecting the antibody activity.[23] However, we were not able to reuse the CNTFET devices. This may be due to a possible distortion of the SWCNTs that takes place when the HIgG interacts with the anti-HIgG.[3]

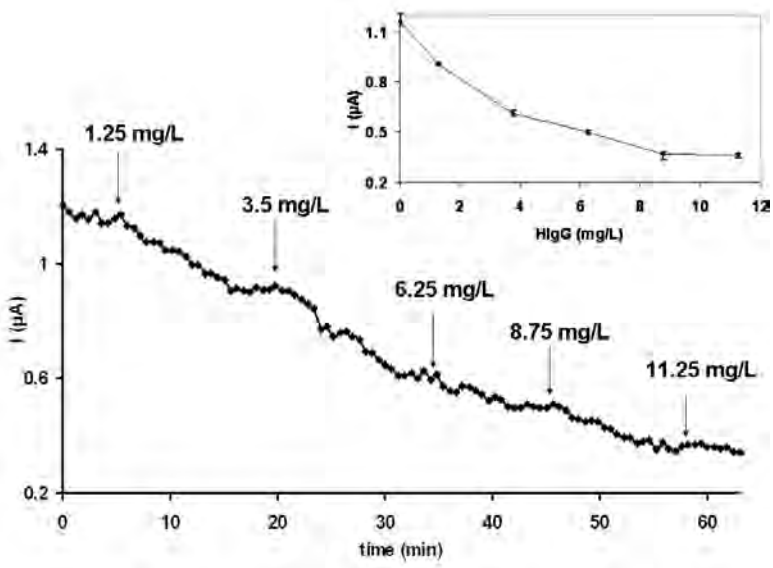

Figure 3. Time dependence of the source-drain current, I (at V_g = -4 V and V_{sd} = 0.25 V), for increasing concentrations of HIgG. Arrows indicate the addition points of HIgG and the total concentration in the cell. The inset shows for each concentration level the mean value of the source-drain current once it is stabilized. The error bars correspond to the range of the stabilized source-drain current.

In this communication we describe a CNTFET device for the fast and selective detection of HIgG in the nM range. This sensor is based on an antigen-antibody interaction and the concentrations detected are similar to the concentrations reported in the literature[14] using CNTFET devices built with lithography processes. Since our device was fabricated using a network of CNTs (grown by CVD) and screen-printed electrodes, we show that low-cost, rapid-to-build CNTFETs can also be used as sensors. The strategy used to selectively detect HIgG can be applied to detect other antigens by functionalizing the CNTFETs with a suitable antibody. The change in the electrical current is due only to the HIgG – anti-HIgG interaction and attributed to a scattering potential. The sensor is selective as the electrical current does not change in the presence of BSA. Since we immobilize directly the anti-HIgG over the surface of the SWCNTs, no linkers are needed. This is an additional advantage of our CNTFET sensing device, since it avoids extra steps in the functionalization process. Moreover, our devices are reagent-less and label free, and the detecting system is direct and does

not require further reagents to be added in different steps. This is a clear advantage over ELISA and other methods which require the addition of labels or enzyme markers for analyte detection.

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4.3 ARTICLE: "DETECTION OF HUMAN IMMUNOGLOBULIN G AT PHYSIOLOGICAL CONDITIONS WITH CHEMICALLY FUNCTIONALIZATED CARBON NANOTUBE FIELD-EFFECT TRANSISTORS", CURRENT NANOSCIENCE, 2008

Detection of Human Immunoglobulin G at physiological conditions with chemically functionalizated carbon nanotube field-effect transistors.

Cristina C. Cid, Jordi Riu*, Alicia Maroto and F. Xavier Rius

Department of Analytical Chemistry and Organic Chemistry
Rovira i Virgili University
C/ Marcel·lí Domingo s/n. 43007-Tarragona. Spain

*Please address correspondence to:
Jordi Riu
Department of Analytical and Organic Chemistry
Universitat Rovira i Virgili
Campus Sescelades
C/ Marcel·lí Domingo s/n
43007 – Tarragona
Catalonia – Spain
Tel.: +34 977 558 491
Fax.: +34 977 558 446
e-mail: jordi.riu@urv.cat

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Keywords: carbon nanotube field-effect transistor, human immunoglobulin G, CNT functionalization, immunosensor, antigen–antibody interaction, physiological conditions.

Abstract

In this paper we report a label-free biosensor able to detect 10 mg/L of human immunoglobulin G (HIgG) at physiological conditions. It is based on a field-effect transistor in which a network of carbon nanotubes (CNTs) acts as the conductor channel. HIgG antibodies are linked to the CNTs in three steps. First, the polymer polyethyleneimine (PEI) covers the CNTs' surface preventing the non-specific binding of proteins. Second, the HIgG antibodies are linked to the CNTs using glutaraldehyde as a cross-linker. . Finally, glycine is used to block the unreacted aldehyde groups and minimize unspecific adsorption effects. The selectivity of the sensor has been tested against 10 mg/L of serum albumin, the most abundant protein in plasma.

Introduction

Immunoanalytical techniques, such as enzyme-linked immunosorbent assay (ELISA), immunoelectrophoresis or fluoroimmunoassays, based on the interaction between an antigen and the corresponding antibody, have been used for many years due to their proven usefulness. However, the need to use labels and to add specific reagents makes them frequently costly and time consuming. These techniques are not direct in the sense that they need a secondary mechanism to be able to detect the recognition event. Therefore, the development of new improved methods for the rapid detection of antigens or antibodies is important and applicable to several fields such as medical diagnosis, environmental analysis or forensic medicine. Immunoglobulin G is usually used as a model antigen when doing immunoassays [1]. Human Immunoglobulin G (HIgG) is one of the most important proteins found in human body fluids. Its primary function is related to defence mechanisms, when foreign agents have entered the human body. HIgG concentration changes are related to several diseases and, therefore, the protein is a relevant diagnosis indicator.

CNTs were first seen by S. Iijima in 1991 [2]. Among other interesting characteristics, semiconducting CNTs modify their electrical conductivity when their

nearest chemical environment changes[3]. In an attempt to take advantage of this property, CNTs have been integrated into field-effect transistors (FETs) [4] as the semiconducting channel of carbon nanotube field-effect transistors (CNTFETs). CNTFETs have recently been used as biosensors and, nowadays, several kinds of biomolecules have been immobilized on CNTs: proteins [5-7], aptamers [8, 9], antibodies [5, 9], and DNA [10]. CNTFET based biosensors show several potential advantages such as needing a low volume of the sample, responding quickly, being sensitive, being label free and allowing miniaturization. Among the numerous studies on CNTs applied to biosensing, there are few reports which use a CNTFET and an antigen-antibody interaction to obtain an immunosensor. Takeda *et al.* [11] used an antigen-antibody mechanism (immobilizing the antibody on the reverse side of the CNT sensor) as a chemical gating effect in order to measure the modification of the electrical current of the nanotubes. We also investigated the viability of CNTFETs as immunosensors [12]. We immobilized the immunoglobulin antibody (anti-HIgG) molecule by physical adsorption onto the walls of the nanotubes and protected the remaining binding nanotube surface with a surfactant. Thus we recorded a reliable response when the HIgG was present in the sample. The measurements were made in a liquid environment, although the ionic strength was lower than in physiological conditions.

Of primary importance in biosensors development is the ability to couple the recognition layer to the transducer part to obtain a fast and measurable signal when the interaction receptor-analyte occurs. Two strategies, among several others, have been followed to link properly the biological receptors to CNTs while retaining their biological properties [13]: i) physical adsorption of the receptors to the walls of the nanotubes [5, 10, 12, 14], and ii) stronger linkage of the receptor to the nanotube by means of chemical bonds [8, 15, 16].

In this paper, we report a procedure to selectively detect HIgG under physiological conditions using a chemically functionalized CNTFET and the selective union between an antigen and its antibody. For this reason, we have covered the CNTs with polyethyleneimine (PEI) [17], a polymer that prevents the non-specific binding onto the CNTs and used the crosslinker glutaraldehyde [18, 19] to covalently bind the HIgG antibody to PEI. After the interaction between the immobilized antibody and the

antigen contained in the liquid test sample, the CNTFETs are thoroughly rinsed and dried before recording the measurement signal. In this way, unlike the measurements in liquid phase [12], we avoid the side effects of the ionic strength or pH of the medium.

This sensor takes the advantage of the properties of the CNTs in two ways. On one hand, CNTs offer a suitable material to immobilize the receptor and, on the other hand, CNTs act as the transducer element of this sensor, with the inherent advantages of changing the electrical current of the CNTFET in the presence of the target analyte. We show that the functionalized CNTs containing the receptor are sensitive enough to detect the presence of the HIgG.

Instrumentation and reagents

All reagents, including bovine serum albumin (BSA), phosphate buffered saline (PBS), polyethylene imine (PEI), glutaraldehyde (GA) and glycine, are from Sigma-Aldrich (Tres Cantos, Spain). HIgG and anti-HIgG (1000 mg/L each) are from Bethyl Laboratories (Montgomery, TE, USA). Electrodag 1415M from Acheson industries (Europe) Ltd. (Scheemdam, The Netherlands) was used as silver ink. The sample images were obtained with an AFM (atomic force microscope) Molecular Imaging PicoPlus. The nanotubes were grown by the chemical vapour deposition (CVD) technique on a quartz tubular reactor placed in a tube furnace (Carbolite). Electrical measurements were carried out using a 4157A Agilent semiconductor parameter analyzer and a MP1008 Wentworth Laboratories probe station.

Experimental part

CNTFETs were built using single-walled CNTs synthesized by chemical vapour deposition (CVD) on top of a 500 nm layer of silicon dioxide thermally grown on highly n-type doped silicon chips. We used 100 mg/L of iron nitrate in isopropanol as the catalyst for the CVD which was done at 900ºC for 20 minutes with 600 sccm of methane and 200 sccm of hydrogen. Fig. (**1**) shows a scheme of the FET device. The source and drain electrodes (1 mm x 1 mm), with a gap distance of 0.5 mm, were screen-printed with silver ink. Since we applied always the same CVD parameters to grow the SWCNTs, we observed only slight changes of the density of the SWCNTs networks from device to device.

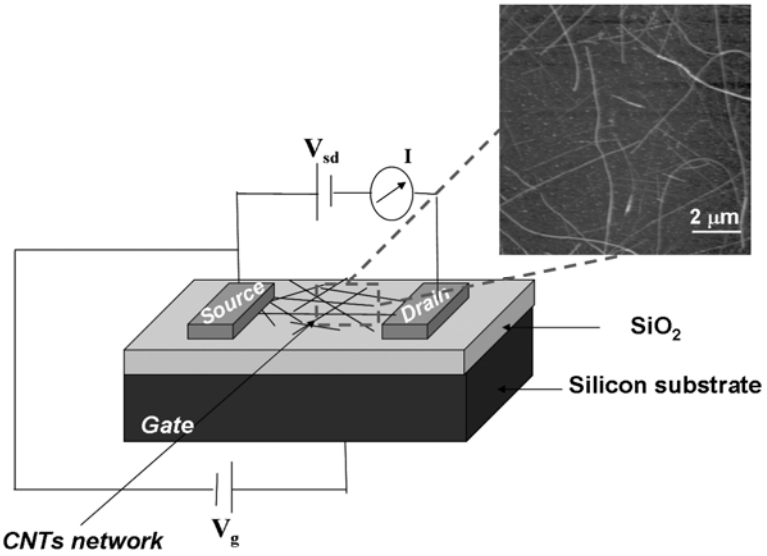

Fig (1). Schematic view of the CNTFET device. V_{sd} is the potential applied between the source and drain electrodes, and V_g is the potential applied in the gate electrode. I corresponds to the measured electrical current between the source and drain electrodes. The picture on the right-upper side is an AFM image of the typical density of the nanotubes network used for the devices.

Fig. (**2**) shows the strategy followed to covalently attach the anti-HIgG to the PEI covering the CNTs. First, the Si/SiO_2 devices with the synthesized CNTs on top were submerged in a 10% solution of PEI (high molecular weight, water-free) in water for four hours and rinsed thoroughly with water. GA was then used as a crosslinker to covalently bind the anti-HIgG to the PEI. The devices were immersed during 2 hours at room temperature in a 2.5% solution of GA in water (obtained from a 25% solution of GA and adjusted to pH= 7.4 with NaOH 0.1 M). In this way, one of the aldehyde groups of GA reacts with the amine groups of the PEI to form imine groups. The devices were subsequently submerged overnight in a 10 mg/L solution of anti-HIgG in PBS (15 mM, pH 7.4) to link the antibodies to the CNTs (i.e. through the reaction of the amine groups placed at the external positions of the protein chain of the antibodies and the free aldehyde group of the GA). After this reaction, the device was finally immersed for 1 hour in glycine 0.1 M at pH=7 to block the remaining free aldehyde groups of the GA that did not react with the anti-HIgG. Since aldehyde groups are very reactive, reaction of these groups with glycine leaves a carboxylic group (which are much less reactive) instead of an aldehyde group, and hence the CNTFETs are less prone to react

with interferences in the surrounding environment. In this way we ensure that we detect the HIgG through the selective binding of anti-HIgG with HIgG. All the electrical measurements were made after having rinsed the devices with water and dried with nitrogen.

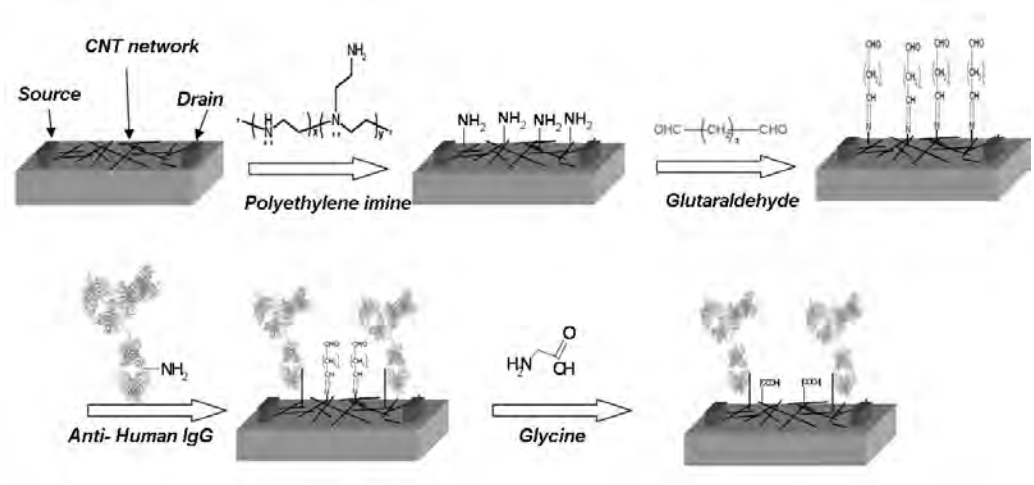

Fig (2). Strategy followed to link the anti-HIgG antibodies to the CNT network.

Results and discussion

A dense network of CNTs is obtained using the CVD technique. Fig. (**1**) also shows a typical AFM image of the CNT network of the FET. The CNTFETs were electrically characterized by measuring the dependence of the source-drain current, I, versus the gate voltages, V_g, ranging from +5 V to -5 V, for a constant source-drain voltage (V_{sd}) of 250 mV. Fig. (**3**) shows the change of the gate dependence for a typical CNTFET after each functionalization step. Each measurement is the average of three replicates. With these kinds of devices we obtained slight semiconductor behavior with resistances ranging from 100 kΩ to 5 MΩ. The leakage current was of nanoampers. The adsorption of PEI on the CNTs means the device characteristics change from p-type to n-type and that the resistance increases roughly tenfold. This is due to the electron donating property of amine groups of the polymer. The p-type behavior is slightly recovered after the functionalization with GA and anti-HIgG. This is because the primary amine groups of PEI have reacted with the aldehyde groups and, as a result, there is a reduction in the overall electron charge (secondary and tertiary amines from

PEI remain unreacted) to the tubes, which leads to an increase in the current for negative gate voltages, which in turn is consistent with the removal of electrons [15]. Fig. (4) shows an AFM image of the CNTs functionalized with the antibodies (anti-HIgG). The antibodies correspond to the clusters of about 5 nm height attached to the nanotubes. The images confirm that the antibodies were effectively attached to the CNTs, and this had already been detected by the change in the electrical characteristics of the CNTFET.

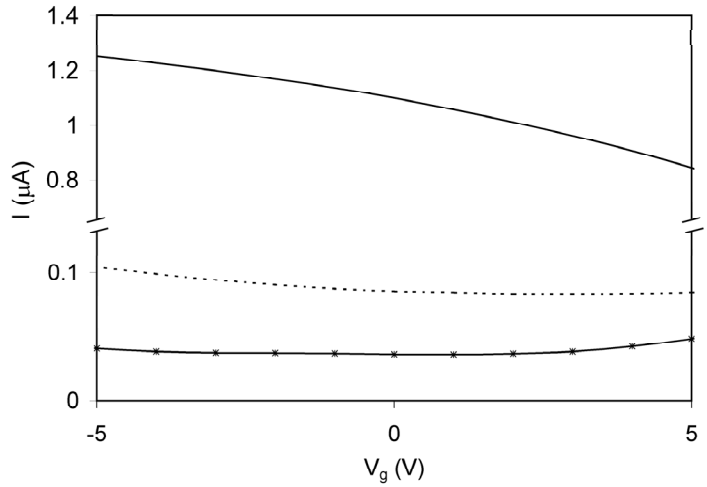

Fig (3). Gate dependence of the source-drain current during the functionalization steps. 1) (—) raw CNTs, 2) (–●–) after adsorbing PEI onto CNTs, and 3) (– –) after reacting with glutaraldehyde, anti-HIgG and glycine.

Afterwards, we submerged the functionalized CNTFET device in a 10 mg/L HIgG solution in PBS for one hour at 25 ºC and we measured the gate dependence. Fig. (**5**) shows that the current decreases (by about 14 %) due to the binding of the HIgG to the anti-HIgG. This decrease in the current value has been found by other authors [9, 15, 20]. This suggests that the complex HIgG - anti-HIgG formed acts as scattering center [3]. We re-immersed the same device in the HIgG solution overnight and we observed that the current decreased even more for negative voltages (by about 40%). Since the kinetics of the reaction is slow [21], more time of incubation means an increase in the registered change of the electrical signal. Similar results were obtained with other functionalized CNTFETS.

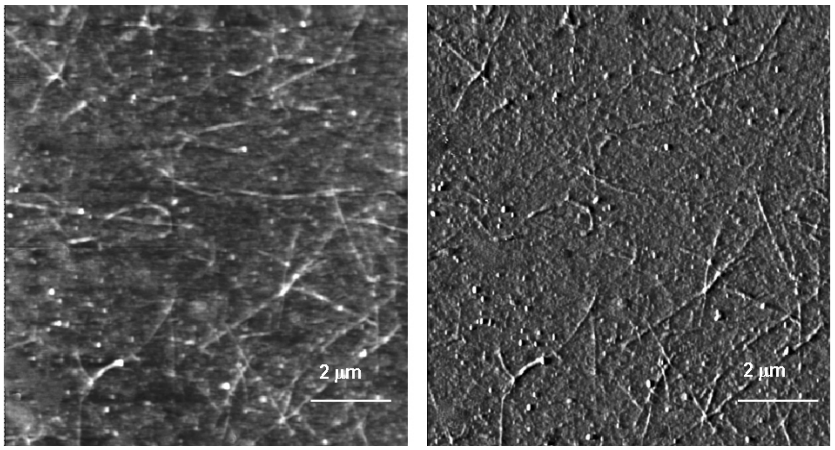

Fig (4). AFM image of nanotubes after being functionalized with anti-HIgG. The clusters attached to the tubes were about 5 nm height.

It is well known, that proteins tend to adsorb onto CNTs sidewalls in a non-specific way [12, 23]. It is therefore necessary to verify that the proposed architecture of the device properly isolates CNTs from proteins. To make sure that the change in the electrical current is only due to the interaction between the anti-HIgG and the HIgG, we tested the behavior of the CNTFET device without containing anti-HIgG (i.e. we functionalized the CNTs only with PEI, GA and glycine). The electrical current did not change after immersing these devices overnight in a 10 mg/L HIgG solution. This proves that change in the sensor's conductivity is only due to the interaction between anti-HIgG and HIgG.

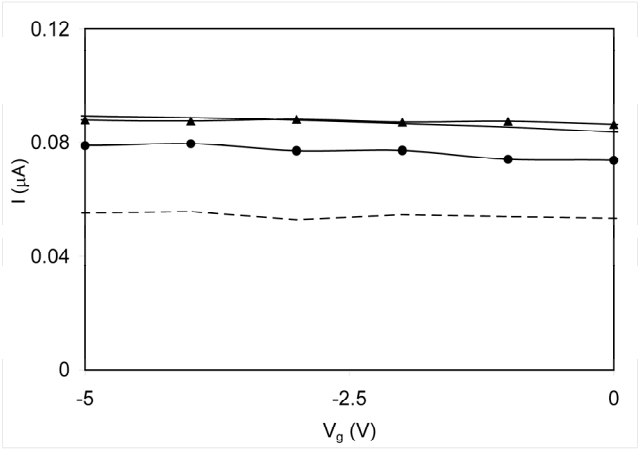

Fig (5). Gate dependence of the source-drain current of a typical CNTFET device functionalized with anti-HIgG: before (–) and after being exposed to 10 mg/L BSA for 1 hour (—▲—) and to 10 mg/L HIgG (for 1 hour (—●—) and (– –) overnight).

To check the selectivity of our devices, the functionalized CNTFETs were first immersed in a 10 mg/L solution of BSA in PBS for 1 hour. Then, they were immersed in a solution of HIgG 10 mg/L in PBS for 1 hour. After being exposed to each solution, the devices were thoroughly rinsed with water, dried with nitrogen and electrically characterized. Fig. (**5**) shows that there is no decrease in the electrical current after the incubation with BSA. However a decrease in the signal is recorded after the incubation of the device with HIgG. BSA was chosen to check selectivity because it is the most common protein in blood serum. The presence of the receptor in this architecture (anti-HIgG), gives the desired selectivity to the target molecule (HIgG). Furthermore, this proves again that the functionalization process protects the CNTs effectively against the non specific binding of other proteins such as BSA.

Conclusions

In this paper we describe a CNTFET device for detecting HIgG based on the selective interaction antigen-antibody that takes place at physiological conditions. The measurements are performed in dry conditions, thus, eliminating possible interferences from the composition of the buffer solution or its ionic strength. We demonstrate that CNTs are sensitive enough to detect HIgG after a functionalization process. The sensor is selective against BSA since the electrical current does not change in the presence of

the major protein in blood. The concentration of HIgG detected is 10 mg/L, similar to the concentrations reported in the literature [5], and, in any case, much lower than the levels of HIgG in blood, which shows that these devices are very sensitive to these kinds of samples. Unlike many sensors based on the interaction antigen-antibody, the biosensor developed here does not need to use labels to detect HIgG. They can be classified as reagent-less in the sense that they do not need the addition of further reagents in different steps, which is a clear advantage over other classical methods for detecting antigens. The strategy followed here can be applied to the detection of other antigens through the functionalization of the CNTFETs with the suitable antibody.

Acknowledgements

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4.4 COMPLEMENTARY EXPERIMENTAL SECTION

4.4.1 Si/SiO_2 substrate

Si/SiO_2 substrates were electrically characterized. The resistance of the layer of SiO_2 and the resistance between the SiO_2 and the Si (through the back gate contact) were recorded. The following graphs show the electrical current values obtained from an Si/SiO_2 substrate when: a) a source-to-drain sweep voltage is applied (e.g. -0.2 to +0.2 V) through the SiO_2 layer (Figure 4-1) and b) a source-to-gate sweep voltage is applied (e.g. -5 to +5 V) measuring the electrical current flowing across both sides of the Si/SiO_2 substrate (Figure 4-2). In both cases the result is a random value of picoampers (pA). This means that the SiO_2 layer is correctly insulating the back gate contact and the source contact, and that within source and drain contacts there is only one electrical channel which results from the presence of the SWCNT network that will be deposited later on.

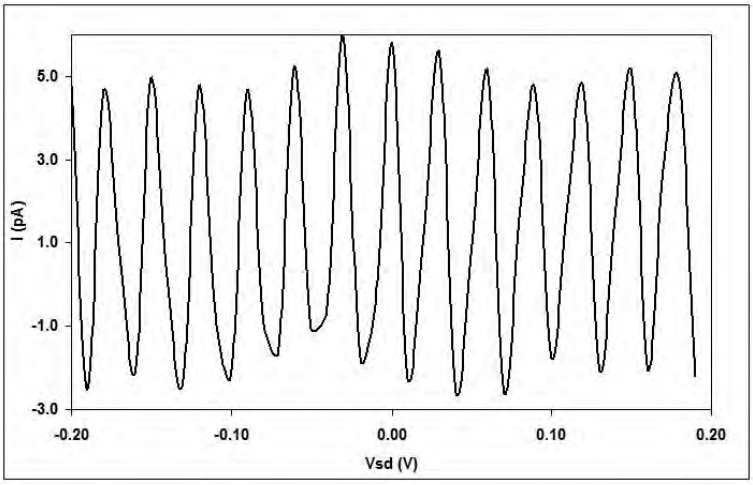

Figure 4-1. Electrical tests applied to the Si/SiO_2 substrate. Source-to-drain current for a sweep of source voltage.

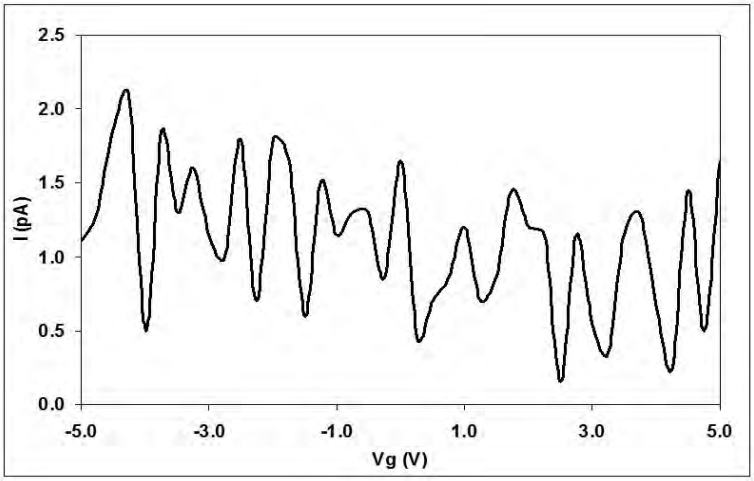

Figure 4-2. Electrical tests applied to the Si/SiO_2 substrate. Source-to-gate current for a sweep of gate voltage.

4.4.2 Synthesis of SWCNT by CVD

During the course of this thesis several variables of the CVD method had been optimized and the current CVD parameters to obtain the network of SWCNT have been detailed in the Section 3.3.1. A brief description of how several key parameters influence the outcome of the CVD is shown in Figure 4-3 to Figure 4-9.

An Fe/Mo catalyst supported on alumina nanoparticles was used in the first attempts to synthesize a network of SWCNTs. The recipe used to prepare the catalyst was taken from Kong et al.[12] From our own experience, this catalyst tended to form aggregates giving unsuccessful results in many cases. For example, Figure 4-3 and Figure 4-4 show the SEM images taken from these aggregates. In these images, a low density of nanotubes and a high amount of catalyst particles in aggregated form can be seen on the overall surface of the substrates. The overall time of the synthesis (when methane and hydrogen flow through the furnace reactor, see experimental Section 5.3.1) affects the density of the network of nanotubes and is thus important in order to obtain a high or a low (or null) density network growth of SWCNTs (see Figure 4-5 and 6 respectively)

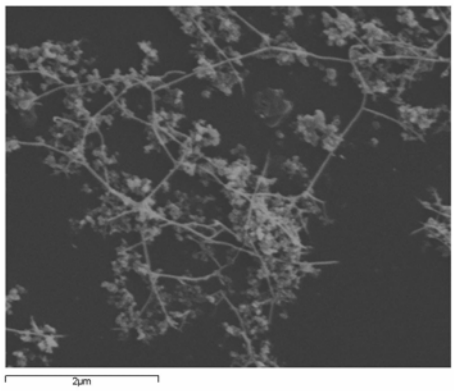

Figure 4-3. SEM image resulting from a CVD process using a catalyst composed of Mo and Fe salts supported on alumina nanoparticles. The scale bare shown is 2 µm. Several catalyst aggregates and a low SWCNT density are observed.

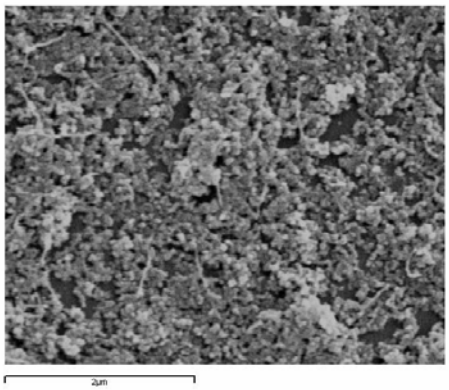

Figure 4-4. SEM image resulting from a CVD process using a catalyst composed of Mo and Fe salts supported on alumina nanoparticles. The scale bare shown is 2 µm. A huge number of catalyst aggregates are on the substrate, and only a few SWCNT are observed.

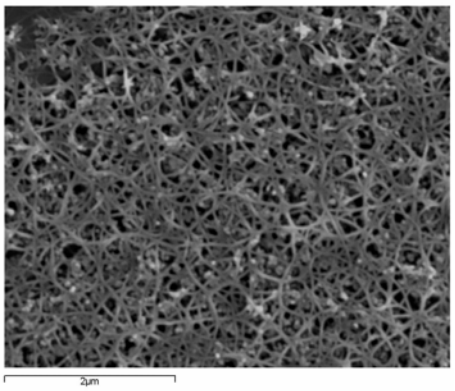

Figure 4-5. SEM image with a high density of nanotubes. Time of synthesis about 20 min. The scale bar is 2 µm.

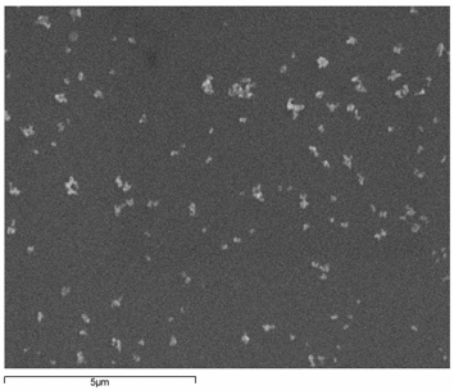

Figure 4-6. SEM image of a substrate with catalyst particles without nanotubes after a CVD process. Time of synthesis about 3 min. The scale bar is 5 µm.

While the thesis was being carried out, new publications have appeared using different catalyst compositions, thus further advancing research into the synthesis of nanotubes. Nowadays, among other possibilities, a simple Fe based catalyst is used in order to promote the growth of carbon nanotubes. Therefore, we changed the catalyst composition that we had been using for some time to one composed only of $Fe(NO_3)_3 \cdot 9H_2O$, with isopropanol the solvent. In this case, the metal particles show a lower tendency to form aggregates. Low (Figure 4-7) and high (Figure 4-8) density networks

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of SWCNTs have been obtained with this catalyst. From time to time, we can find strange shapes, such as bundles, (Figure 4-9) in the growth process of the nanotube network.

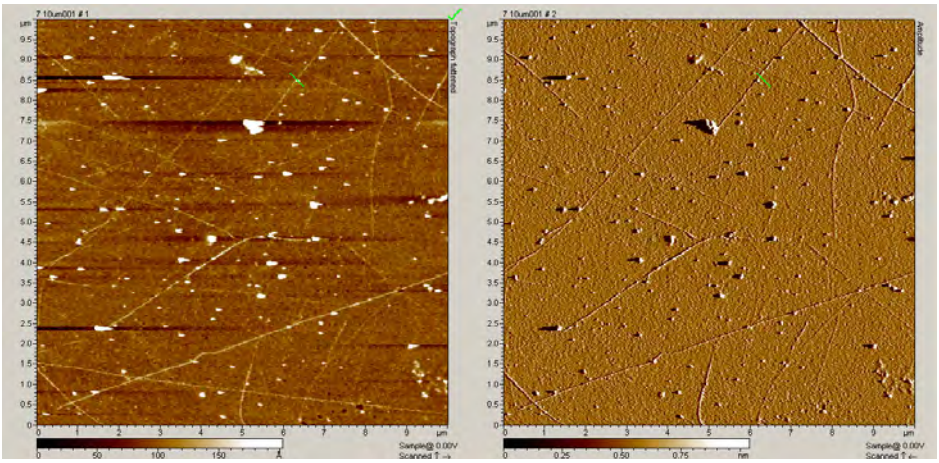

Figure 4-7. AFM images of a low density network of SWCNTs grown using an Fe based catalyst according to the CVD method.

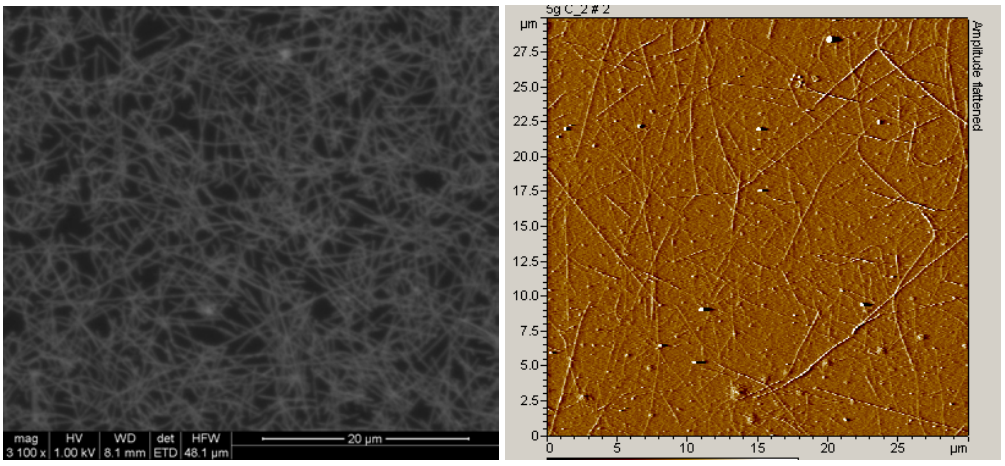

Figure 4-8. ESEM (left) and AFM (right) images of high density SWCNTs grown using an Fe based catalyst according to the CVD method.

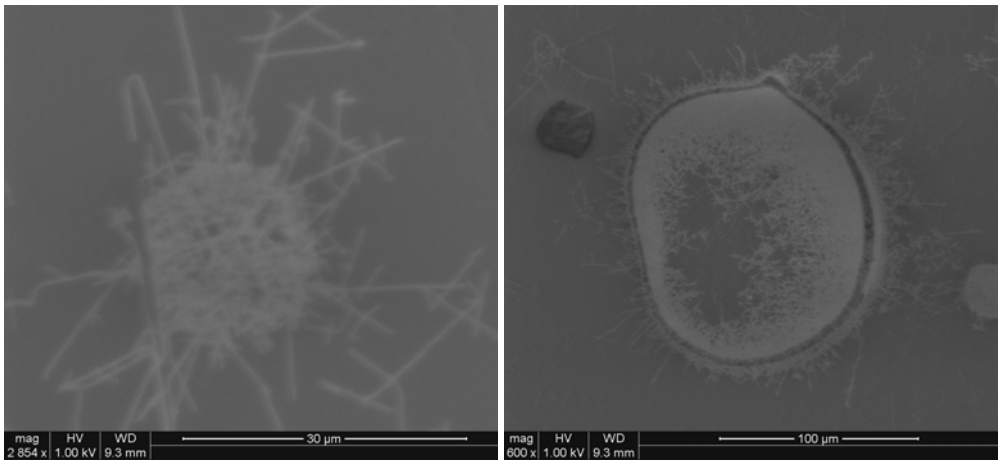

Figure 4-9. ESEM images of two kinds of bundles of nanotubes.

4.4.3 CNTFET electrical characterization

Our main interest is in recording the SWCNT network's conductance dependence versus the gate voltage, which provides an idea of how SWCNTs can be modulated by external agents. The fact that SWCNTs can be electrically altered externally makes our system sensitive to variations in its surrounding environment. In this way, further changes in the CNTFET's electrical current could be related to the presence of target analyte molecules.

There were several CNTFETs in which SWCNTs did not connect all the gaps between the drain and source metal electrodes. In these cases, we could monitor only noisy signals in the data from electrical measurements similar to those observed in Figure 4-1. In other cases, a network of SWCNTs was present between the metal contacts, but either it did not show proper semiconductor characteristics or the metal contacts were electrically connected through a metallic contact. In this latter case, a high electrical current combined with a non-existent modulation through the gate voltage were recorded (Figure 4-10). Finally, there were samples with a semiconductor channel formed by a network of SWCNTs between the electrodes, making up a CNTFET (Figure 4-11). It is these samples that we are interested in for building CNTFET-based chemical sensors.

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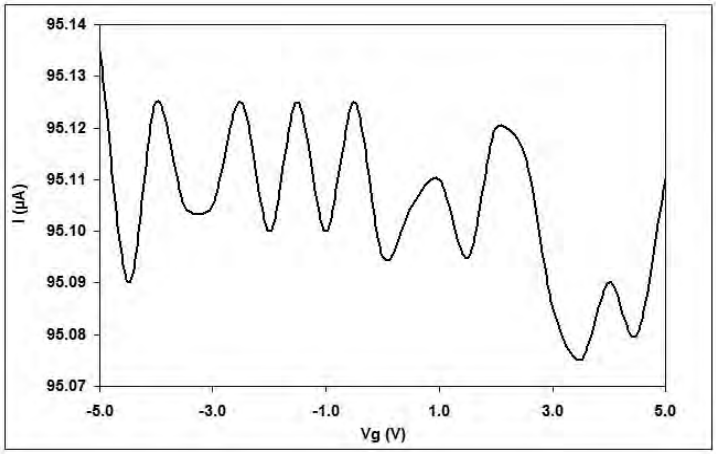

Figure 4-10. Typical CNTFET response when the metal electrodes are contacted. Source-to-drain current versus a gate voltage sweep.

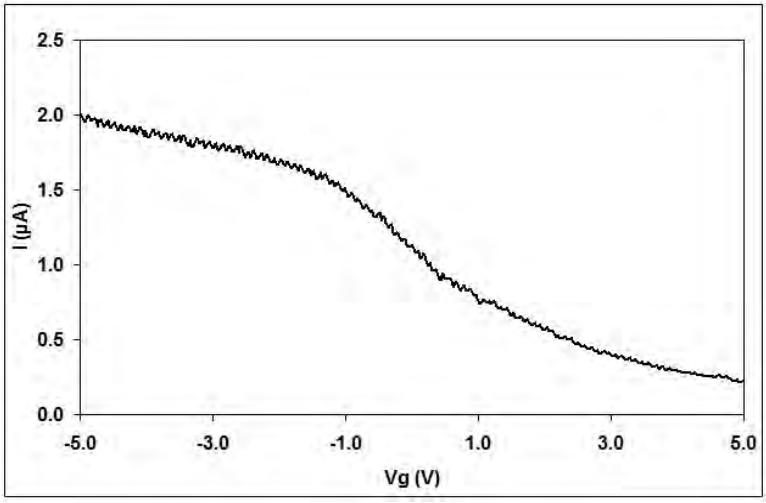

Figure 4-11. Characteristic curve of a p-type semiconductor obtained from our own CNTFET. Source-to-drain current versus gate voltage.

Another important parameter in the characterization of a CNTFET is the source-to-gate current or "gate leakage". Since source and gate electrodes are separated by a layer of SiO_2, the current between these two electrodes has to be almost negligible. If the gate leakage is high or directly related to the applied gate voltage, the principles of a FET are not preserved. Figure 4-12 shows the random character of the leakage current recorded for a successful CNTFET.

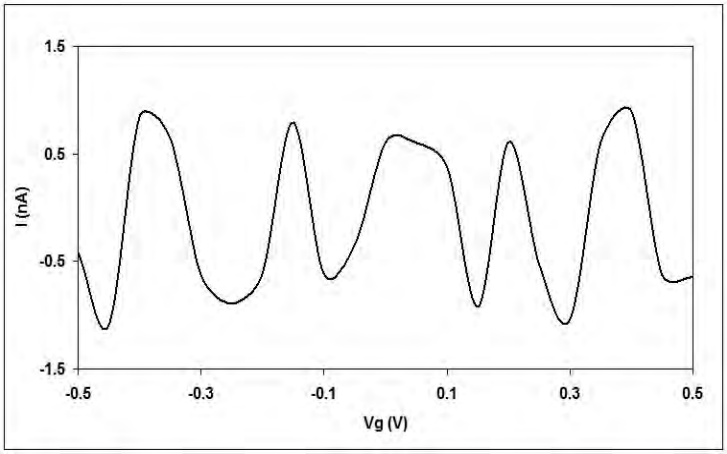

Figure 4-12. Source-to-gate (gate leakage) current versus gate voltage in a working CNTFET.

4.4.4 Polyethyleneimine functionalization

The complementary results of polyethylenimine (PEI) functionalization in this Section contrast with other functionalization stages (e.g. Tween 20, glutaraldehyde, etc.) because they have led to several problems. A correct PEI functionalization can be checked using either an atomic force microscope or by electrical characterization. The PEI coating of the SWCNT network produces a clear change in the semiconducting behavior of the SWCNTs, from p- to n-type.

PEI (see Figure 3.6) is a polymer that adsorbs onto the nanotube sidewalls. The objective of this functionalization stage, is to coat the SWCNTs with a monolayer (or a few layers) of the polymer. However, if the concentration of the PEI solution in which SWCNTs are immersed is too high (more than 20 %) or if the substrate is not rinsed vigorously with water at least a couple of times after the immersion time, an excess of polymer over the substrate is found (see Figure 4-13). Figure 4-14 shows a typical image of a substrate covered with an appropriate layer of PEI.

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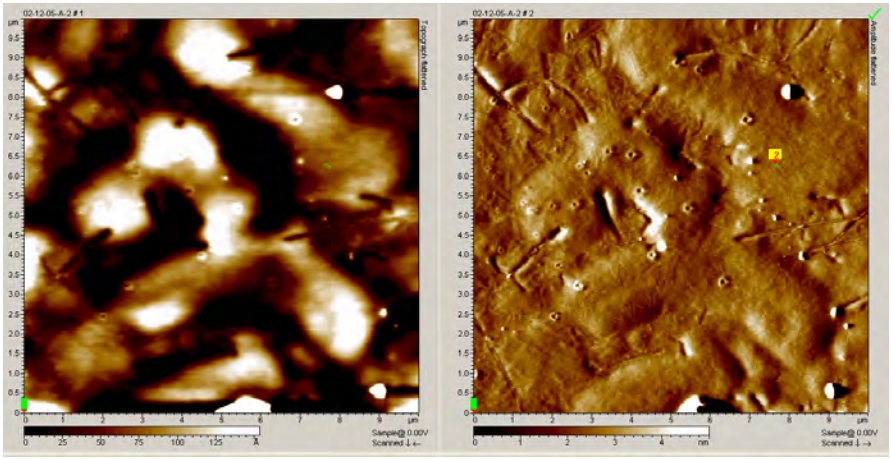

Figure 4-13. AFM image of substrate completely covered of polymer.

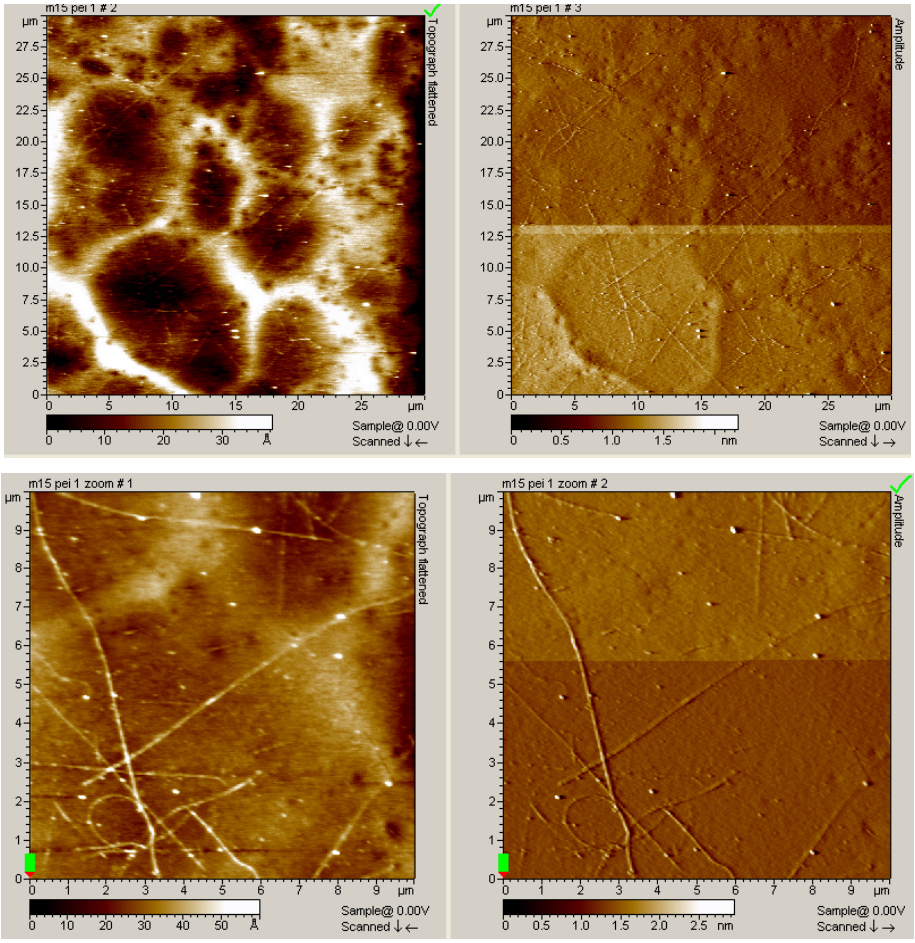

Figure 4-14. AFM image of a polymer coated SWCNT (up). Zoom (down).

4.4.5 Antibody functionalization

Using SEM we can see that after attaching antibodies to the network of SWCNTs there is a clear difference for both functionalization procedures applied in this chapter (i.e. using PEI + GA or directly attaching antibodies over the SWCNTs). This can be seen if we compare typical SEM images of the as-grown SWCNT network (see for example the image shown in Figure 1 of the paper "*Carbon Nanotube Field Effect Transistors for the Fast and Selective Detection of Human Immunoglobulin G*") with those where the antibodies have been immobilized. The molecules of antibodies appear as spots over the nanotubes (see Figure 4-15 and Figure 4-16). The presence of dark spaces where the network density is lower indicates that antibodies are rather immobilized on the SWCNT surface. In SEM imaging, the beam of primary electrons interacts with the sample, producing secondary electrons, which are responsible for the topographic image visualized, and the remaining energy is conduced to mass. Since antibody molecules are not conducting, they start to accumulate an electric charge, producing the brighter spots observed in the image (see Figure 4-16). The network of SWCNTs is mostly semiconducting, therefore when increasing the time the sample is exposed to the beam of primary electrons, a brighter image is visualized (this is more intense where the antibodies are attached on the SWCNTs).

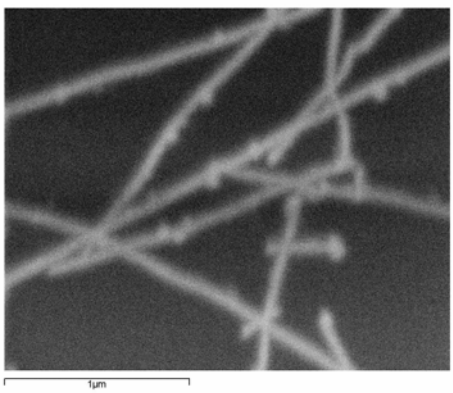

Figure 4-15. SEM image of SWCNTs functionalized with anti-HIgG. The antibodies are observed as irregular dots over SWCNTs. The scale bar is 1 µm.

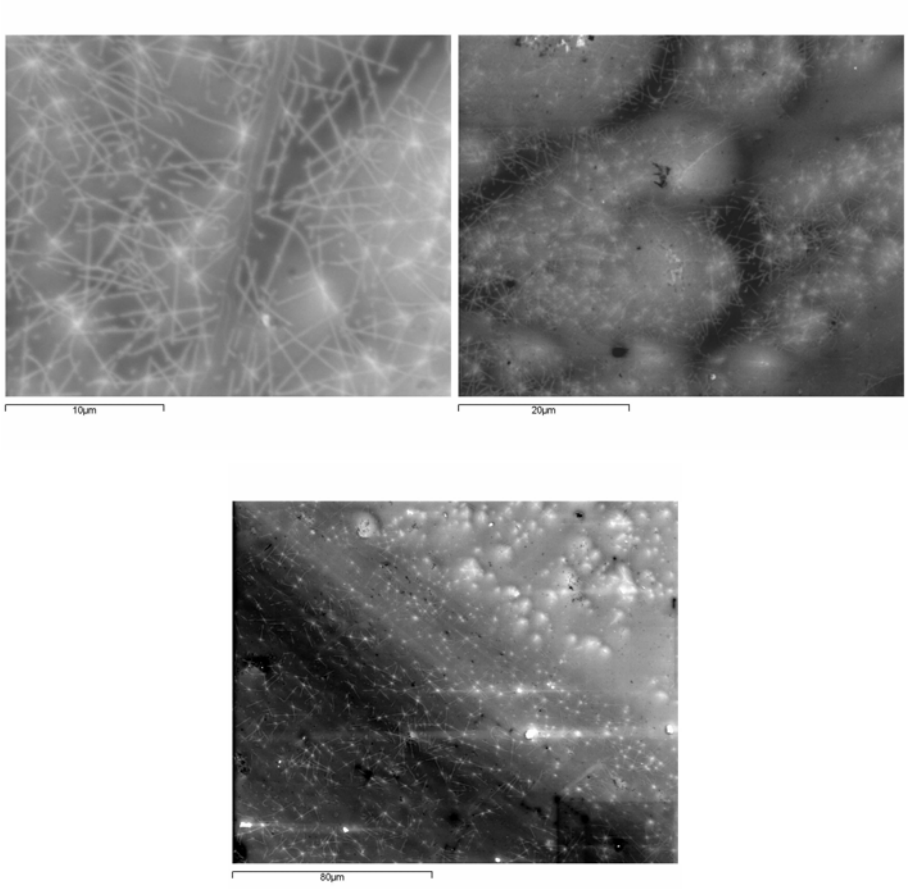

Figure 4-16. Several SEM images of a network of nanotubes functionalized with PEI-GA and anti-HIgG, with different magnification (the scale bar is 10 - 20 - 80 µm, respectively). The antibodies appear as luminous spots over the nanotubes. The dark spaces appear where the network density is lower, indicating that antibodies are rather immobilized on the SWCNTs surface.

4.4.6 Electrical results

Additionally to the results shown in the previous articles, different tests were performed to ensure that the sensors were working properly. Some of these tests are graphically shown below.

We used a device which had not been functionalized with the receptor to check whether the change which occurs when the target analyte is added (i.e. HIgG) is due to the interaction between the analyte and the receptor rather than between the analyte and the SWCNTs. This setup consisted in blocking the SWCNTs with the Tween 20, but without previously immobilizing the anti-HIgG. Tween 20 will prevent the non selective binding of the proteins on SWCNTs, including the HIgG. These results are shown in Figure 4-17, which shows the current versus the gate voltage for the raw SWCNTs and the SWCNTs functionalized with Tween 20, as well as the signal when the system is exposed to 10 mg/L of HIgG. At negative voltages we can see a slight increase in the electrical current when HIgG is in contact with the system, but this is the contrary effect that occurs when the receptor is present, so this change is probably due to a random variation in the electrical current. The same experiment was performed with functionalized SWCNTS with antibody molecules through PEI and GA steps, giving a similar result.

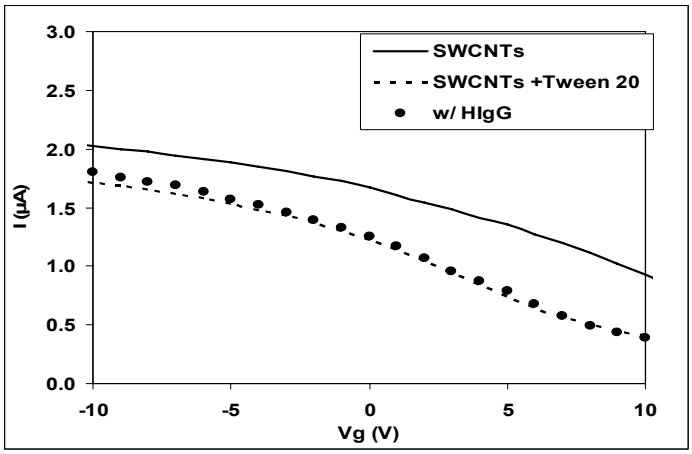

Figure 4-17. Tween 20 effectively shields SWCNTs from the interaction with proteins such as HIgG.

The following results refer to on time measurements using a home-made silicone cell (from the procedure involving the direct functionalization of SWCNTs with antibody molecules). The left ordinate axis in Figure 4-19 shows three replicates of the current recorded for the sensor in contact with a PBS solution while sweeping the gate voltage (abscise axis). The right ordinate axis in Figure 4-19 shows the random values of the leakage current. It can be seen that the values do not exceed 1 nA.

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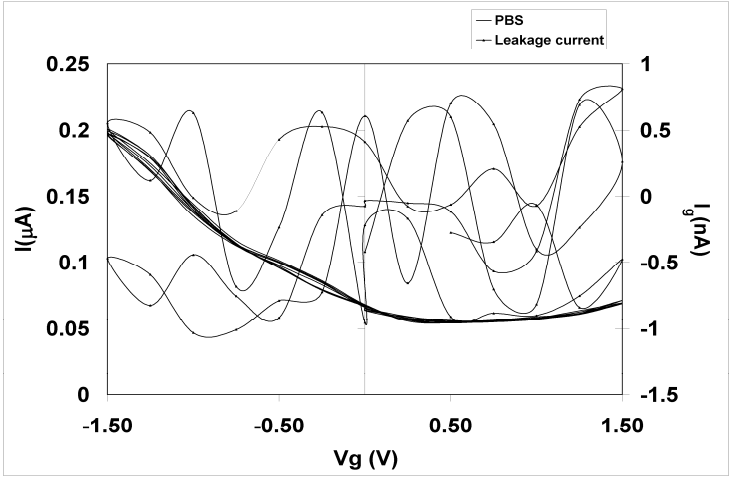

Figure 4-18. I-Vg curve showing the sensor response in PBS (left ordinate axis) and the leakage current (right ordinate axis). Three replicates are shown.

After adding a certain amount of HIgG to the silicone cell containing PBS, the recorded current is clearly reduced (see Figure 4-19). Three replicates are shown for both measures.

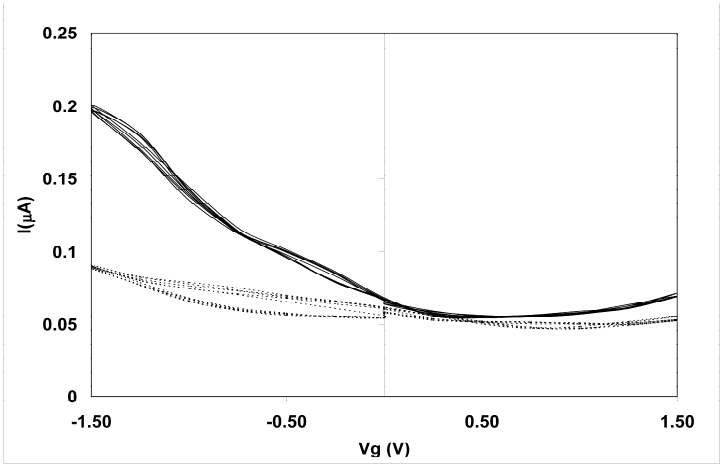

Figure 4-19. The different response of a CNTFET functionalized with anti-HIgG and Tween 20 to a PBS solution (straight line) or a HIgG solution (dotted line).

4.5 CONCLUSIONS

As expected, spontaneously and irreversibly non-specific binding of proteins on SWCNTs has been found, as reported previously.[13] Supramolecular attachment of antibodies to SWCNTs in order to obtain immunosensors is currently being investigated and a review on this topic has been published recently.[7] Different approaches to attaching the protein molecule as the receptor onto the SWCNTs have been reported. These are:

- Direct adsorption of the antibody molecule upon the SWCNTs' sidewalls by means of hydrophobic interactions. [14-16]
- Adsorption of a polymer coating over the SWCNTs and posterior binding of the antibody through covalent bonds to the polymer functional groups.[1, 17, 18]
- Adsorption of molecules containing bifunctional groups to the surface of the SWCNTs by means of pi-pi stacking with a posterior binding of the antibody molecules.[8, 9, 19]

Two different non-covalent approaches to immobilizing the antibody molecule onto the SWCNT have been undertaken in this thesis. In the first approach, the antibody is immobilized directly onto the SWCNTs. The antibodies are randomly oriented on the nanotube surface and non-selective binding is prevented by using Tween 20 to coat the surface of the SWCNT that remains free after the antibody immobilization. In the second approach, the nanotube surface is coated with a polymer; covalent forces then bind the antibodies. In this strategy, different molecules have been employed to immobilize the antibody properly. Glycine was used to block the free remaining amino groups of the polymer attached to the nanotubes.

With respect to the non-selective binding, both methodologies show a solution to avoid the non desired linking of interfering proteins on the nanotube. The BSA presence, used as a typical interference when studying HIgG, has not affected the sensor response in the previously described devices, since it could not reach the nanotube surface due to the fact that the carbon nanotube surface is protected against non-selective binding. Moreover, the selectivity of the sensor is basically provided by

the selectivity of the anti-HIgG, in this way, it does not recognize other proteins that might be present in the sample.

The antigen is successfully sensed even though the antibodies are randomly oriented on the nanotube surface in both approaches. The approach involving the PEI coating[18] shows that several functionalization steps keep the sensing abilities of the nanotube network intact, although, the amount of HIgG detected with this sensor is 10 mg/L. In contrast, the lowest concentration of HIgG of 1.25 mg/L is successfully detected when the SWCNTs are directly functionalized with receptor molecules.[14] This dissimilarity can be due to the distance between the SWCNTs and where the recognition event takes place. In the later approach, the recognition of the antigen by the antibody takes place close to the nanotube surface because the antibody is attached to the nanotube. In contrast, in the PEI functionalization procedure the antibodies are not directly linked to the nanotube surface and so the recognition event takes place slightly further away, which can affect the sensitivity of the nanotubes. Even so the PEI functionalization strategy shows that it is possible to use specific anchoring molecules between the SWCNTs and the receptor molecules while maintaining the SWCNTs' ability to be electrically disturbed.

CNTFET devices based on antigen-antibody interactions have been shown to be effective sensors. Although in this chapter the same antibody has been used for two different linkage procedures, the same strategies could be used for different antigen-antibody pairs. Future research on CNTFET based immunosensors should study analytical parameters such as repeatability, stability or reusability to verify whether this sensor could replace the systems currently used.

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UNIVERSITAT ROVIRA I VIRGILI
SENSORS BASED ON CARBON NANOTUBE FIELD-EFFECT TRANSISTORS
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5 Sensors based on CNTFET and ion selective membranes

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5.1 INTRODUCTION

ISFETs or CHEMFETs are one of the most interesting electrochemical sensors that have appeared in the last decades.[1] Although ISFETs can be built with different architectures,[2] they are based on the MOSFET technology. The replacement of the metallic gate in MOSFETs by a an electrolyte solution in contact with an specific membrane makes ISFETs sensitive towards the activity of a specific ion in a solution, as was previously described in Section 2.4. The membranes used in an ISFET are usually the same as those used for ion selective electrodes (ISEs).[3] ISFETs are classical sensing devices, but different technical problems have conditioned their application in non-academic fields such as the industrial processes. The most common problems are associated with the complexity of miniaturizing the necessary external reference electrode, and the encapsulation or the instability of the signal related to the ion-to electron transduction occurring at the interface between the sensing and transducing elements.

CNTFETs could overcome these limitations because they have been described in the literature as displaying a large range of sensing applications.[4-6] Usually, sensors based on CNTFETs ense relatively large specific molecules. As yet, there has been little literature on using CNTFETs to selectively sense small compounds in solution (e.g. ions), mainly because of the difficulty in effectively isolating nanotubes towards small interferent molecules. Zhao et al.[7] have recently published a study in which SWCNTs are functionalized in a non-covalent way with a pyrenecyclodextrin derivative in order to detect organic compounds of small molecular weight. This work shows that the target compounds are effectively linked to the functionalized CNTFET. However, no selectivity studies regarding possible interferences are shown.

Nowadays, different examples combining SWCNTs with polymeric membranes can be found in the literature. Polymer coatings have been used either to improve the characteristics of the CNTFET, enhancing the semiconducting properties of SWCNT (e.g. the modulation)[8-10] or for sensing purposes.[11-13] This latter report shows how the polymer coating acts as a layer which is sensitive towards the analyte of interest. It is known that some polymers have a certain reactivity to the compound to be detected. However, this kind of functionalization by a mere polymer coating has an

important drawback because it does not display a high degree of selectivity and many compounds can interfer with the target analyte response.

Crespo et. al.[14] were the first to report an effective coating for SWCNTs with a ion selective membrane for sensing a specific ion. In this study, they built a new type of potentiometric solid contact ISE based on a network of SWCNTs, which acts as an ion-to-electron transducer. They were able to detect potassium ions to a high degree of selectivity in the presence of other interfering ions.

Following the work of Crespo et al.,[14] we adapted this idea to CNTFETs. We used the classical ion selective membranes as an effective coating for SWCNTs to obtain a new type of ISFET. The objective was to assemble two different existing architectures, ISFETs and CNTFETs in only one device with enhanced performance characteristics.

5.2 ARTICLE: ION SENSITIVE FIELD-EFFECT TRANSISTORS USING CARBON NANOTUBES AS TRANSDUCING LAYER, ANALYST 2008

Ion Sensitive Field-effect Transistors Using Carbon Nanotubes as Transducing Layer

Cristina C. Cid, Jordi Riu*, Alicia Maroto, F. Xavier Rius

e-mail: jordi.riu@urv.cat

Department of Analytical Chemistry and Organic Chemistry

Rovira i Virgili University

C/ Marcel·lí Domingo s/n. 43007 - Tarragona. Spain

Tel: +34 977 55 84 91

Fax: +34 977 55 84 46

Keywords: Carbon nanotubes, field-effect transistor, ISFET, ion-to electron transducers, sensors, ion selective membrane

We report a new type of ion sensitive field-effect transistor (ISFET). This type of ISFET incorporates a new architecture, containing a network of single-walled carbon nanotubes (SWCNT) as the transduction layer, making an external reference electrode unnecessary. To show an example of application, the SWCNT based ISFET is able to detect at least 10^{-8} M of potassium in water using an ion selective membrane containing valinomycin.

ISFET were first reported in 1970.[1] They are potentiometric sensors from the family of chemically modified field-effect transistors (CHEMFET),[2] and have several similarities to the well known ion selective electrodes (ISE).[3] ISFET are based on an ion sensitive and selective membrane that replaces the gate electrode in metal oxide field-effect transistors (MOSFET). Both an external reference electrode and the conductive solution that is in contact with the ion sensitive layer assure the closure of the electrical circuit and the presence of a field-effect transistor (FET). The membrane allows the selective detection of the target ions in the test solution. In spite of the numerous applications which have been developed, the future of ISFET is highly compromised by the difficulty of miniaturizing the necessary external reference electrode.[2, 4] Another technical problem is the instability associated with the interface between the membrane and the silicon based transducer due to the conversion of the ionic current to an electronic one.

Tans *et al*.[5] successfully integrated a SWCNT as the semiconductor channel into a FET to develop the first carbon nanotube field-effect transistor (CNTFET). As SWCNT are very sensitive to minimal variations in their surrounding environment, CNTFET have been used as platforms to design sensitive and selective chemical sensors.[6] Selectivity is achieved by chemically functionalizing the SWCNTs with specific receptors (e.g. proteins,[7] aptamers,[8] DNA[9, 10]) and by protecting them with polymer coatings to avoid the non specific binding of other molecules. Suitable polymer coatings can also be used not only to avoid the non specific binding but also for sensing purposes, although the main drawback in this case is the lack of selectivity towards the target analyte. Polymer coatings have also been used to improve the

characteristics of the CNTFET, enhancing the modulation of the semiconducting character of SWCNT.[11, 12] Looking at the sensing purposes, Star *et al.*[13] developed a CNTFET sensitive to the relative humidity by functionalizing non-covalently a semiconducting SWCNT with the commercial polymer Nafion. In this case, the sensing mechanism was based on the capacity of Nafion to shield the gate voltage when the relative humidity increases. Kaempgen *et al.*[14] coated SWCNT networks electrochemically with the conducting polymer polyaniline to develop a potentiometric pH sensor. SWCNT were not used as part of CNTFETs but as a conductive support so that the polyaniline could detect the pH change by transforming the ionic conductivity to electronic conduction. So far CNTFET have been mainly applied either as gas sensors or as biosensors to detect medium or large biomolecules (such as proteins or DNA) in the presence of solutions which have low concentrations of small ions (which they use, for instance to regulate pH or the ionic strength). In this communication we functionalize SWCNT with an ion selective polymeric membrane to be able to detect small ions (in this case K^+). The instrumental response is not affected with the presence of high concentrations of other small ions such as Li^+ and Na^+.

The design of the CNTFET devices, unlike those based on the MOS technology, incorporates the nanotubes at the surface of the devices. In these FET, the semiconductor channel consists of a layer of SWCNT linking the source and drain electrodes and the capacitor is established between the layer of SWCNT and the backgate electrode that is integrated into the device. Both conducting layers are separated by a dielectric film of thermally grown SiO_2 (500nm thick) (Fig. 1a). The output signal is the electrical current flowing through the semiconducting channel that is being influenced by the presence of both the electrical and electrochemical potentials. Therefore, although sharing some basic principles, CNTFET have a different architecture and materials compared to traditional ISFET, and even the recorded instrumental signal is also different. Moreover CNTFET use an internal electrode which makes an external reference electrode unnecessary.

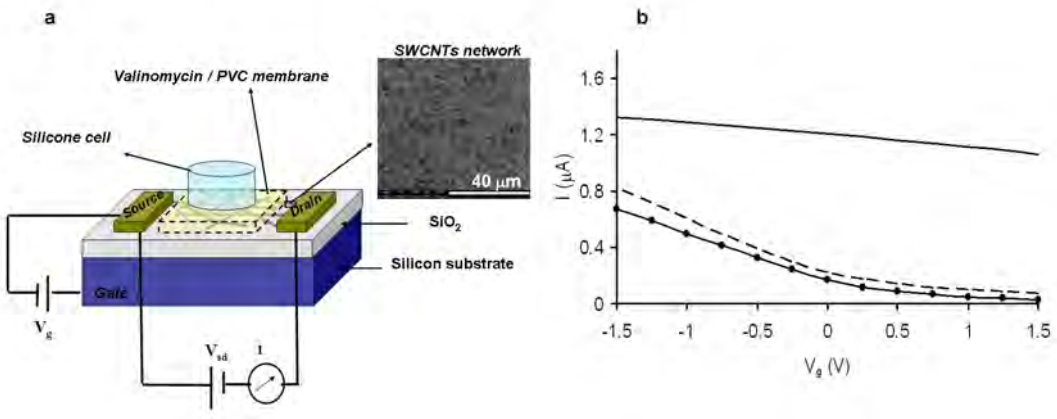

Figure 1. (a) Setup of the device. A network of SWCNT connects the source and drain electrodes. An ESEM image of the density of the network is shown. SWCNT are covered with the PVC membrane containing valinomycin. The gate voltage is applied through the Si layer. Liquid measurements are taken using a silicone cell. **(b)** Source-drain current (I) vs. gate voltage (V_g) of a typical SWCNT based ISFET after each step. V_{sd} = 0.25 V. As-grown nanotubes (——); SWCNT covered by the valinomycin/ PVC membrane (– –); SWCNT plus the membrane in contact with a 10^{-7} M solution of KCl (–●–).

The network of SWCNT that form the channel of the FET studied here was grown by chemical vapour deposition (CVD),[15] using iron nitrate in isopropanol as the catalyst. The CVD was done at 900 ºC for 20 minutes with 600 sccm of methane and 200 sccm of hydrogen. Source and drain electrodes contacted the channel and were screen printed with Electrodag 1415M from Acheson industries (Europe) Ltd. The ion selective membrane was prepared as by Michalska *et al.*[16] (2% w/w valinomycin, potassium tetrakis (4-chlorophenyl) borate (60 mol % relative to valinomycin), 66% of dioctyl sebacate with poly (vinyl chloride) (PVC)). The membrane was casted over the surface by using a spin coater (30 μL of membrane, 3000 rpm, 1 min). The thickness of the selective membrane was measured with an environmental scanning electron microscope (ESEM) for 10 independent devices. The average was found to be 17 μm, with a standard deviation of 1 μm for these 10 independent devices. Test solutions were introduced into a silicone liquid cell (volume of 5 μl) located on top of the ion selective membrane. Neither the liquid cell nor the solution was in contact with the source and

drain electrodes (Fig. 1a). By applying a difference of potential between source and drain electrodes (V_{sd}), electrical current (I) flowed through the network of SWCNT. The overall semiconducting character of the SWCNT network meant that by applying a second potential between the source and gate electrodes (V_g), a modulation of the electrical current was obtained. A further modulation of the electrical current took place due to the electrochemical potential arising in the interface membrane-solution.[17] In any case no electrical potential is directly applied to the test solution. Therefore the solution remains unbiased in all the experiments.

Fig. 1b shows the device's recorded current at a constant source-drain voltage V_{sd} = 0.25 V, when the gate voltage was swept between -1.5 and 1.5 V. The values shown in Fig. 1b were the average of three replicates. We can see that the raw SWCNT network shows a slight p-type semiconductor behavior.[18] After casting the membrane a decrease in the electrical current and a change in the semiconductor character are observed. This effect is attributed to the adsorption of the PVC membrane components onto the walls of the carbon nanotubes by means of hydrophobic interactions. Similar behavior has been observed with molecules containing aliphatic chains such as Tween 20.[19] When a solution containing 10^{-7} M of K^+ is in contact with the ion selective membrane covering the SWCNT, the signal further decreases. This fact can be explained by the presence of the electrochemical potential generated at the membrane/sample interface.[17] This electrochemical potential depends on the activity of K^+ ions in the test solution and it is transmitted to the membrane/SWCNT interface since the diffusion within the membrane phase can be neglected.[17] This potential operates in the same way as the electrically produced gate potential, i.e., positive gate voltages cause the valence band shifting down away from the Fermi level, leading to higher difficulties for the electrons to reach the conduction band and thus less conducting states.[20] The device's response when potassium is present is higher at negative gate voltages, therefore, the measurement of the potassium solutions is set at V_g = -1.5 V and V_{sd} = 0.25 V.

We studied the sensitivity of the device by recording the current with increasing concentrations of K^+ in the cell solution. Fig. 2 shows the decrease of the electrical current after adding increasing concentrations of K^+. The device is able to detect concentrations of 10^{-8} M of K^+. The current signal shows a non-linear change along the

concentration range (Fig 2. inset). The system becomes practically saturated at 10^{-5} M of K^+ where the chemical modulation effect on the electrical current through the SWCNT network is no longer effective. The sensor always displays time responses of a few seconds. The error bars in the inset of Fig. 2 are obtained from the range of the stabilized source-drain current.

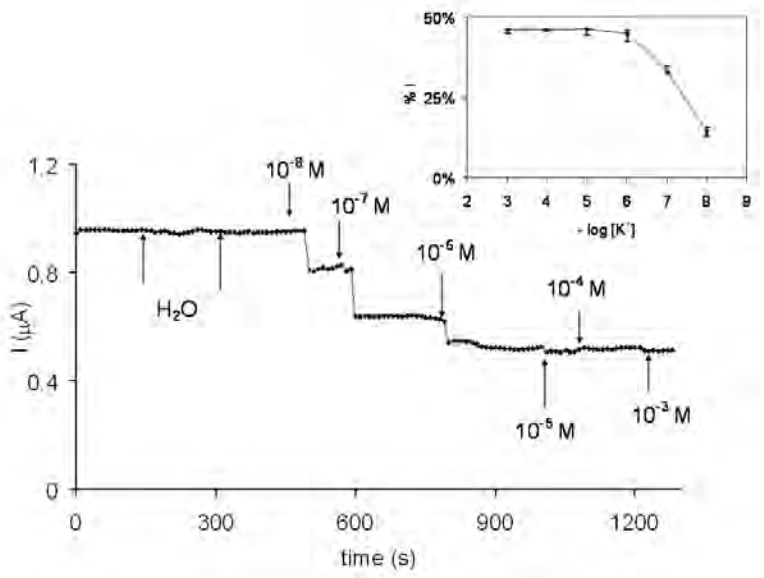

Figure 2. Time dependence of the source–drain current (I), at V_g = -1.5 V and V_{sd} = 0.25 V, on increasing concentrations of K^+. Arrows indicate the addition points and the total ion concentration in the cell. The inset shows the relative change of the source-drain current versus the negative logarithm of the concentration of K^+. The error bars are obtained from the range of the stabilized source-drain current. A progressive saturation of the device is observed from 10^{-5} M.

Fig. 3 shows the selectivity of the device in the presence of sodium and lithium ions. First, we recorded the change of the electrical current with 10^{-7} M of K^+. Afterwards, increasing concentrations of the interfering ion (i.e. Na^+ or Li^+) were added to the cell and the electrical response was recorded. Fig. 3 shows that the electrical current decreases significantly for 10^{-7} M of K^+. No appreciable changes of the electrical current were observed until the respective solutions in the silicone cell reached 10^{-3} M for sodium (Fig. 3a) and 10^{-4} M for lithium (Fig. 3b). These results

show that the concentration of sodium and lithium has to be at least three orders of magnitude higher in order to interfere with potassium. The ion selective membrane then effectively isolates the SWCNT network from the presence of other ions and makes our devices selective to potassium. Therefore, the ion selective membrane covering the SWCNT operates in a twofold manner: 1) it generates the electrochemical potential due to the different activities of the ion in the test solution and the membrane; and 2) it is an isolating layer, which effectively shields the SWCNT from the presence of the small charged ions or polar molecules in the test solution.

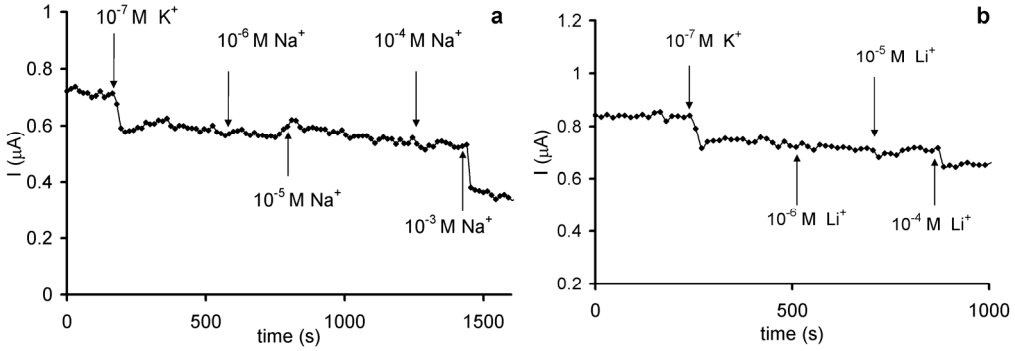

Figure 3. Change of the source–drain current (I), at V_g = -1.5 V and V_{sd} = 0.25 V in presence of interfering ions: **(a)** increasing concentrations of Na^+ in the presence of 10^{-7} M of K^+; **(b)** increasing concentrations of Li^+ in the presence of 10^{-7} M of K^+. Arrows indicate the addition points and the total concentration of the ion in the cell.

We have shown that ISFET based on a transducing layer made of a SWCNT network have a different architecture from the conventional ISFET based on CMOS technology. Because of the presence of carbon nanotubes and the architecture of the device, the external reference electrode is integrated as an internal electrode. This is an effective way of miniaturizing the ISFET technology. The advantages of this SWCNT based ISFET device are obvious. On the one hand, a reference electrode does not have to be used. On another hand, the inherent high sensitivity of the SWCNT to the charge transfer confers a higher analytical sensitivity on the new SWCNT based ISFET. The lowest amount of K+ detected by our device is two orders of magnitude lower than the detection limits reported for ISFET sensors of potassium (~10-6 M)21. Moreover, the extraordinary capacity to promote electron transfer between heterogeneous phases provides stability to the instrumental response. The new SWCNT based ISFET allows

the development of miniaturized devices. Future work will involve thoroughly characterizing the new devices by assessing their most relevant performance characteristics and comparing them with classical ISFET.

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5.3 ADDITIONAL RESULTS

5.3.1 SWCNT based ISFET preparation

The source and drain electrodes, separated by about 5 mm, were screen-printed with silver ink, and the gate electrode was a layer of aluminium on the back side of silicon. A SWCNT network acted as the semiconductor channel of the FET (Figure 5-1). A solution of the PVC membrane coated the entire SWCNTs' surface. The thickness of the membrane is about 17 µm and a Section can be imaged with ESEM (Figure 5-1). Liquid measurements were performed with a 5 µl home-made silicone cell placed on top of the membrane between the metal electrodes. The solution and the silicone cell were not in contact with the source and drain electrodes in any of the experiments.

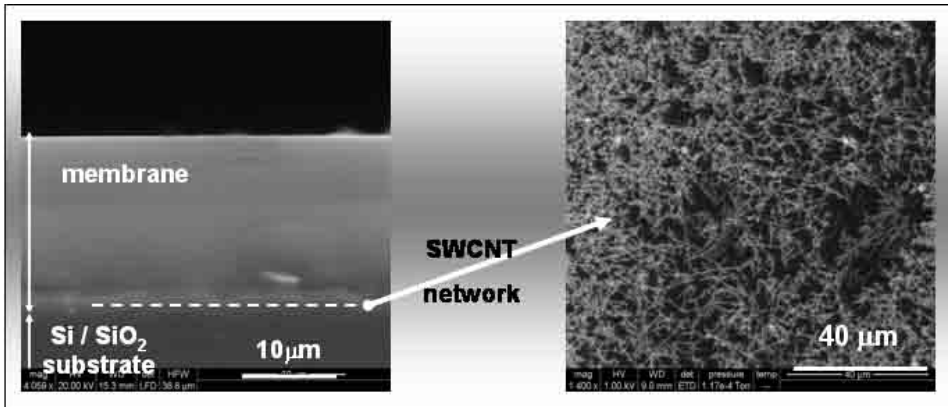

Figure 5-1. ESEM images from a SWCNT network (right) and a transversal Section of the Si/SiO_2 substrate coated with the polymeric membrane (left). Spotted lines indicate the position of the SWCNTs (observed as a slight change of color tone in the left image).

5.3.2 Selectivity coefficients

Although our device is not based on amperometry, it measures the conductance between the source and drain electrodes of the CNTFET. Therefore, we used the procedure described by Maccà *et al.*[15] based on amperometric measurements to

estimate the selectivity coefficients. The values obtained within this method were log K_{K^+/Na^+} = - 3.8 and log K_{K^+/Li^+} = - 3.2.

Using the same membrane composition as in this chapter, Michalska et al.[16] obtained the following values for potenciometric selectivity coefficients using ISEs: log $K^{Pot}(_{K^+/Na^+})$ = - 2.9 and log K^{Pot} $(_{K^+/Li^+})$= - 3.2. Our values of the selectivity coefficients are within the same magnitude order as those reported by Michalska et al. However, it should be mentioned that these selectivity coefficients can not be compared exactly because they have been obtained by two different procedures.

5.3.3 Regeneration

The membrane of the sensor, similarly to the ion-selective electrodes, can be readily regenerated. This 'conditioning' process consists of reequilibrating the concentration of the ions in the ion-selective membrane. This involves immersing the sensor in deionized water for about 20 min, and after it has been rinsed vigorously, it can be used again to make a test measurement. Therefore, the SWCNT based ISFET can be used in repeated cycles of measurements, as can be observed in Figures 3a and 3b of the paper included in this chapter. The electrical current after the final measurement in Figure 3a is less than 0.4 μA, and after the sensor has been properly rinsed, the electrical current greatly recovers and gives a current value which is similar to the initial one. Furthermore, adding the same concentration of K^+ to this regenerated device gives a similar change to the signal in both cases (about 0.1 μA). This is the basis for research into the regenerating the sensor so it can be used multiple times.

5.4 CONCLUSIONS

In this study we have developed a new type of ISFET based on CNTFETs, which incorporates both a transducing layer made of a network of SWCNTs and an ion selective membrane. The ion selective membrane is placed on the SWCNT network, and thus isolates the SWCNTs from the solution while maintaining their inherent sensitivity and selectivity and their ability to detect the target ions.

In the present device architecture, SWCNTs act as efficient transducers. After equilibrating the ions in the aqueous sample with the polymeric membrane, the ionic current through the membrane is transformed into an electronic current along the SWCNTs. The extraordinary capacity of SWCNTs to promote electron transfer provides an effective transduction, which in turn gives a highly stable signal output.

The miniaturization of ISE technology is very much related to the efforts to minimize the reference electrode, which is a basic element when using ISEs. ISFETs based on SWCNTs have a clear and important advantage over ISEs, since the whole sensing device can be miniaturized because no reference electrode is needed in these new sensors.

An ion selective membrane is used as an effective isolation layer on SWCNTs, thus preventing small molecules in the sample, such as other ions, from interfering with the response. Using the membrane also makes the CNTFETs highly selective towards the target ion.

To evaluate the real capacity of ISFETs based on SWCNTs, their performance characteristics (sensitivity, selectivity coefficients, detection limits, etc.) must be assessed and then compared with those of classical ISFETs. Although the detection limits of ISFETs based on SWCNTs have not been established by this study, the ISFETs based on SWCNTs were able to detect a much smaller quantity of potassium than current ISFET based sensors.[13] This may be related to the extreme sensitivity of SWCNTs because they act as an active transducer element, without being in contact with the solution to be analyzed.

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6 Sensors based on CNTFET for detecting a gaseous analyte

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6.1 INTRODUCTION

Analysis of gases is a topic of permanent interest due to the implications for both human health and the environment. Special attention should be paid to some of the most common gas pollutants that can be found in the atmosphere. For example, gases such CO_2, CO, SO_2, NO_2, etc. are atmospheric contaminants and monitoring them is crucial to preserve the health of the population. Chemical gas sensors are mainly based on electrical or optical techniques.[1] The most representative example of commercial gas sensors are metal-oxide gas sensors.[2] Currently available gas sensors suffer from different problems, such as high working temperatures, high response times or lack of selectivity.[3, 4]

Nanostructured materials have become very popular as components of newly developed gas sensors.[3, 4] Different nanostructured materials have been used to assemble sensors with better parameters than the current ones. This is the case, for example, with the metal[5] or metal oxide nanoparticles used in chemiresistor sensors.[6] CNTFETs have also been used as sensitive chemical sensors.[7, 8] SWCNTs perform as the semiconducting channel of the field effect transistors. They are very sensitive towards changes in their local environment, so can easily detect the presence of gas molecules. Kong *et al*.[9] were the first to report that the electrical conductivity of a CNTFET was sensitive to various gases such as ammonia or nitrogen. Up to now, the behavior of SWCNTs has been tested by exposing them to several gases, such as NH_3, NO_2, H_2, CH_4, CO, SO_2, H_2S, and O_2, although these experiments are usually carried out with 'pure' gases, that is, a gas sample diluted into an inert solvent gas. Since the samples contain only one analyte, the experiments reported do not take into account selectivity towards other particular gases. In air, SWCNT conduction is made through positive carriers (holes), because O_2 withdraws electrons from the surface of the SWCNT. Therefore, SWCNTs in air show a p-type behavior.[10, 11] Depending on the electronegativity properties of the gas molecules, their effect upon bare SWCNTs will be different and the hole conduction of SWCNTs can be enhanced or decreased. Electrodonating gas molecules, such as NH_3, will provide electrons to the p-type SWCNTs and thus decrease the sensor conductance. In contrast, electroattractive gases, such as NO_2, will enhance SWCNT conductance by increasing the amount of electronic holes for conduction (Figure). The effect on

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conductivity when SO_2 molecules adsorb over the surface of bare SWCNTs[12] is similar to that produced by NO_2 because both NO_2 and SO_2 are electronattractive molecules.[13] Sensors based on nanotubes which detect SO_2 are scarce.[14] Suehiro et al. reported MWCNT sensitivity to SO_2. The results obtained in this work were inconsistent with an electronactractive species such as SO_2, and no further explanation was given.

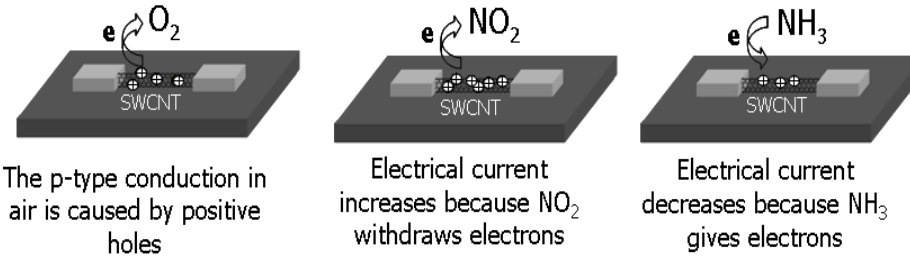

Figure 6-1. Effect on the electrical conduction of a bare SWCNT upon exposure to gas molecules.

The knowledge of how to successfully link the specific receptors involved in a molecular recognition event with CNTFETs led to a new CNTFET based sensor for determining a given gas molecule. To this end we used a synthetic receptor, that is, a square-planar platinum (II) complex of the N,C,N'-terdentate-coordinating monoanionic "pincer", which is known to be highly selective towards SO_2 molecules (see Section 2.3.1). This platinum complex, linked in a suitable manner to the SWCNTs' surface, will target the CNTFET based sensor's selectivity at one specific gas molecule.

The functionalization process has to take into account interference from other gases because those gases which are known to react with bare SWCNTs can disturb the response signal. For this reason, by functionalizing SWCNTs with a polymer coating and deactivating the remaining reactive functional groups, SWCNTs are sufficiently protected from possible interference from other gas molecules. The functionalization process described below results in a CNTFET based sensor which is highly selective towards a single gaseous analyte.

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This chapter describes for the first time the development of a CNTFET based sensor functionalized with a synthetic receptor. This is able to discriminate between SO_2 and other gaseous interferences (including gases of similar electronegative character) that might be found in the sample to be analyzed.

6.2 ARTICLE: SELECTIVE DETECTION OF SO_2 AT ROOM TEMPERATURE BASED ON FUNCTIONALIZED SINGLE-WALLED CARBON NANOTUBE FIELD-EFFECT TRANSISTORS

Selective Detection of SO_2 at Room Temperature Based on Organoplatinum Functionalized Single-Walled Carbon Nanotube Field Effect Transistors

Cristina C. Cid[1], *Giselle Jimenez-Cadena*[1], *Jordi Riu*[1]*, *Alicia Maroto*[1], *F. Xavier Rius*[1],

Guido Batema[2], *Gerard van Koten*[2]

[1]Department of Analytical and Organic Chemistry, Rovira i Virgili University, 43007 Tarragona, Spain

[2] Chemical Biology & Organic Chemistry, Debije Institute for Nanomaterials Science, Faculty of Science, Utrecht University, 3584 CH Utrecht, The Netherlands

12 Pages
5 Figures

*Please address correspondence to:
Jordi Riu
Department of Analytical and Organic Chemistry
Universitat Rovira i Virgili
Campus Sescelades
C/ Marcel·lí Domingo s/n
43007 – Tarragona
Catalonia – Spain

Tel.: +34 977 558 491
Fax.: +34 977 558 446
e-mail:jordi.riu@urv.cat

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ABSTRACT

We report a field effect transistor (FET) based on a network of single-walled carbon nanotubes (SWCNTs) that for the first time can selectively detect a single gaseous molecule, SO_2, in air by chemically functionalizing the SWCNTs with a selective synthetic receptor for SO_2. The synthetic receptor is a square-planar NCN-pincer platinum (II) complex (NCN is the *N,C,N'*-terdentate-coordinating monoanionic $[C_6H_3(CH_2NMe_2)_3\text{-}2,6]^-$ ligand) to which SO_2 selectively binds. Because of the strong electronwithdrawing character of SO_2, it withdraws negative charge from the synthetic receptor thus affecting the electronic properties of the functionalized SWCNTs. The minimum concentration detected is 0.05% SO_2 in air at room temperature. Interferences like NO_2, CH_4 and CO_2 need to be present in a higher concentration than SO_2 to give a significant response.

Keywords: nanotechonology, sensors, carbon nanotubes, SO_2, gas

In recent decades, interest in gas detection has considerably increased because of the environmental problems caused by atmospheric contamination and because of the high toxicity of some industrial facilities. Interest in SO_2 monitoring has increased because of its highly reactive nature and relative abundance. SO_2 is usually determined using chromatography, electrochemical analysis and spectroscopy, most of these techniques being combined with solution-absorbing pre-treatment chemical analysis. These techniques are expensive, time-consuming, and require sophisticated measuring equipment.[1] SO_2 has also been determined with chemical sensors using different detection systems, but these suffer from different problems such as high working temperatures (especially in sensors based on metallic oxides), lack of selectivity, high response times or low sensitivity.[2-4] To overcome many of these problems, nanostructured materials have been incorporated into new sensors. But despite the immense potential shown by these new materials some performance characteristics of the sensors, such as selectivity, are not always well defined, especially when detecting gaseous substances.[5, 6] Single-walled carbon nanotubes (SWCNTs) are nanostructures with outstanding electrical and mechanical properties. Tans *et al.*[7] reported the first field effect transistor based on a single semiconducting SWCNT. Kong *et al.*[8] found that the electrical conductivity of these carbon nanotube field effect transistors (CNTFETs) was sensitive to various gases such as ammonia or nitrogen dioxide and

that these CNTFETs can thus operate as sensitive chemical sensors.[9, 10] These sensors are based on CNTFETs in which the conductor channel can be either a single semiconducting SWCNT or a network of SWCNTs.[11] However, a high selectivity of CNTFET devices towards a single gaseous molecule is still an unsolved problem. A functionalization process with a specific receptor to obtain a selective CNTFET gas sensor has not yet been developed. In this communication we report for the first time a field effect transistor based on networks of SWCNTs as the transducing layer and an aryl platinum (II) complex[12] as a specific receptor to selectively and quantitatively detect a single gaseous molecule, SO_2, in gaseous samples at room temperature. This CNTFET obtains a linear relationship between instrumental response and gas concentrations, which opens the way to quantitatively detecting SO_2 in gaseous samples.

The disadvantage of the CNTFETs reported so far in the literature and based on non-functionalized SWCNTs is that, although they can be very sensitive gas sensors,[8, 13, 14, 15] they are not selective because they are sensitive to many gases.[5, 6] Two main strategies have been applied so far to improve the selectivity of these CNTFETs as gas sensors: a) coating SWCNTs with a polymer and b) decorating SWCNTs with metal nanoparticles. As an example of the first strategy, SWCNTs have been coated with polyethylene imine (PEI), a polymer showing alkaline properties, to detect acidic gases such as CO_2[16] or NO_x[17]. These acidic gases are able to react with the amino groups of PEI and to decrease the conductance of the functionalized SWCNTs. Selectivity between different acid gases is not achieved, although gases which are not able to donate or share electrons are effectively discriminated. In the second strategy, Star *et al*.[18] showed that a sensor array consisting of multiple CNTFET devices with different catalytic metallic nanoparticles adsorbed onto the SWCNTs presented selectivity towards several gases. The sensing mechanisms of CNTFETs applied to gas detection that are described in the literature can be explained with two main approaches.[19] One is based on the modification of the Schottky barrier due to the adsorption of the target compound onto the metal-nanotube junction,[13, 20] while the other one is based on the charge transfer due to the adsorption of the target compound onto the nanotube' sidewalls.[11, 21] Both mechanisms can be distinguished by passivating the metal-nanotube junction. Even though the gas molecules can penetrate through the pinholes of

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the passivation layer, the response time increases when the sensing mechanism is caused by the modification of the Schottky barrier.[13]

The CNTFET described in this communication for the selective detection of SO_2 in air is built using a three step functionalization process. In the first step, the SWCNTs are coated non-covalently with a layer of PEI that is irreversibly adsorbed over the whole surface of the SWCNTs. The polymer coating offers suitable functional groups for a further covalent binding of the receptor. The second step incorporates the synthetic receptor to selectively detect SO_2. In our case the receptor is the platinum complex [PtI(4-$COONC_4O_2H_2$-2,6-$(CH_2NMe_2)_2$-C_6H_2] that selectively reacts with SO_2 by forming a coordinated bond between the platinum and sulphur atoms at room temperature.[12, 22] The platinum complex is linked to the PEI-coated SWCNT network by a reaction between the amino groups of the polymer and the succinimide ester of the platinum complex (Fig.1a). The third step of the functionalization process consists of blocking the remaining free amino groups of PEI that may not have reacted with the platinum complex and which could give rise to interferences by reacting with gaseous substances other than SO_2. For this reason we use the blocking molecule N-acryloxysuccinimide (NAS). This molecule reacts with the remaining free amino groups of PEI (Fig.1b) and prevents interferences as a result of possible acid-base reactions with an interferent gas (for example with acidic gases such as CO_2 or NO_2). In this way, the unique recorded interaction between the CNTFET and the test samples is between the SO_2 and the specific receptor complex.

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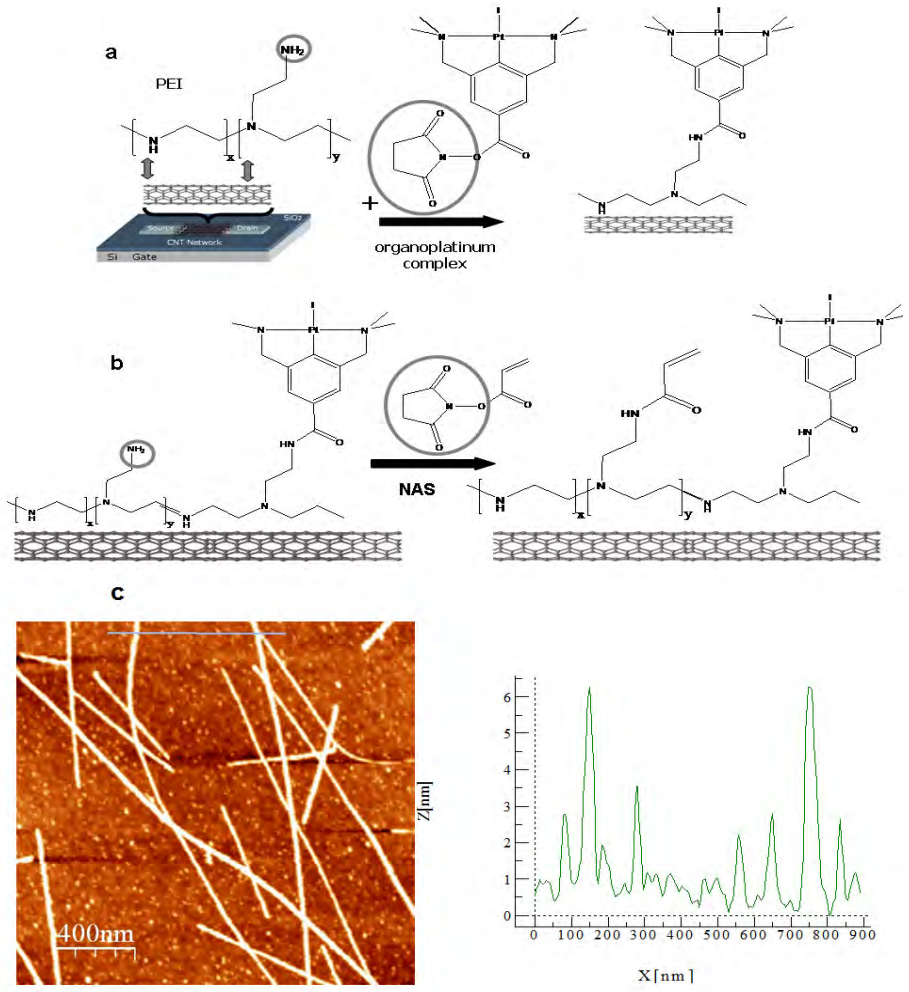

Fig.1: (a) Functionalization process of SWCNTs with PEI and the platinum complex. (b) Reaction of the remaining free amino groups of PEI with the blocking molecule NAS. (c) Atomic force microscope (AFM) image of a typical SWCNT network obtained by CVD (left). The height of the functionalized SWCNTs is between 5.5 and 6 nm (right).

Our CNTFET contains a network of SWCNTs grown using the chemical vapour deposition (CVD) method. The diameter of the SWCNTs is between 1.7 and 2 nm. The density of the network (see Fig.1c) that connects the source and drain electrodes of the CNTFET is similar in all the devices and has several parallel pathways. The height of the completely functionalized SWCNTs (i.e. after linking the platinum complex to the PEI-coated SWCNTs) is between 5.5 and 6 nm (Fig.1c), what

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indicates that the height of the PEI coating and the platinum complex is about 3.5 - 4 nm. Fig.2 shows the electrical characteristics of a device for each functionalization step at a constant source to drain voltage, Vsd = 0.25 V at room temperature. The gate voltage (Vg) was swept between -5 and 5 V using a semiconductor parameter analyzer (Agilent E5270A). Fig.2 shows the average values of three instrumental replicates. We can see that the as-grown SWCNT network shows a p-type semiconductor behaviour.[23] Because the network grown by CVD is made of both metallic and semiconducting nanotubes,[24] the conductance in the off state will be governed by the conductance of the metallic ones (Fig.2). Low on/off ratios are observed (Fig.2a) which are characteristic of networks with a gap distance of 2.5 μm between source and drain electrodes.[25] The non-covalent coating of PEI changes the semiconductor behaviour of the SWCNTs' network from p-type to n-type (Fig.2a) because of the electron donating ability of the amine groups of PEI.[26] Fig.2b shows the current versus gate voltage characteristics for a functionalized CNTFET before and after exposure to 1.8 % v/v of SO_2 in an air atmosphere. When SO_2 is present in the atmosphere, the platinum complex reacts reversibly to form a coordination bond between the metallic centre and the sulphur atom (Fig.3). This reaction changes the geometry of the metallic centre from square planar to square pyramidal and creates a steric effect between the methyl groups of the nitrogen atoms and the SO_2 molecule coordinated in the apical position of the complex.[27, 28]

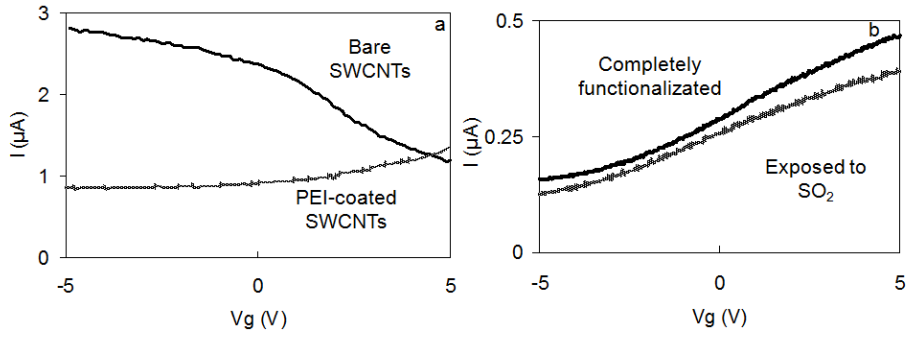

Fig.2: (a) Gate dependence of the source-drain current of bare SWCNTs and after adsorbing PEI onto the SWCNTs. (b) Source-drain current (I) versus gate voltage (Vg) of the completely functionalized CNTFET device in air (0 % of SO_2) and after exposure to an SO_2 concentration (1.8 % v/v). Source to drain voltage was set at 0.25 V.

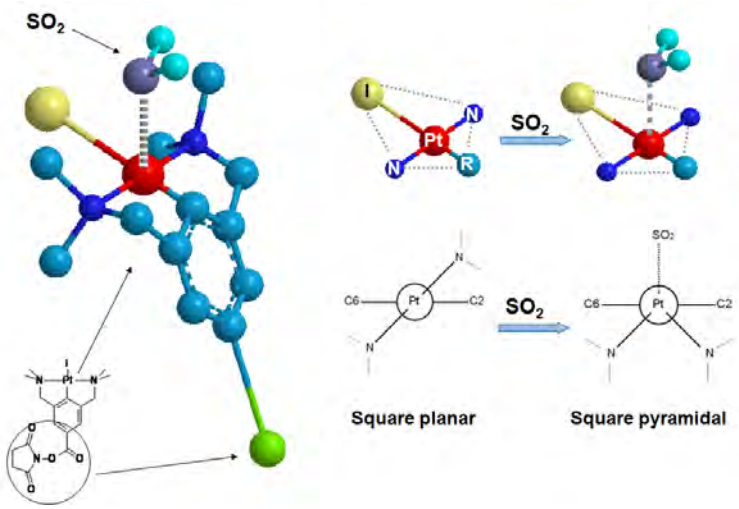

Fig.3: Representation of the complex formed between the platinum complex and the SO_2 (left). The platinum complex acts as a receptor reacting with SO_2 to form a coordination bond between the metallic centre and the sulphur atom. The receptor structure changes from a square planar to a square pyramidal state (right).

The decrease in the electrical current after the exposure of the functionalised CNTFETs to SO_2 can be explained by the strong electronwithdrawing character of SO_2. When SO_2 interacts with the platinum complex, the SO_2 withdraws a negative charge from the receptor and thus affects the n-type PEI-coated SWCNTs. Since the n-type SWCNTs have electrons as major carriers, the electron withdrawing effect decreases the conductance of the CNTFETs.[16, 17] The charge transfer through single bonds has been described by Liu *et al.* [29] and Huang *et al.*[30] who explain the charge transfer process between Au substrates and SWCNTs bridged by aliphatic compounds. However, a second mechanism could be considered and the change in the carrier mobility of the CNTFET could also result from the modification of the Schottky barrier due to the adsorption of the target compound on the metal-nanotube junction.[16, 31] Fig.2b shows that the device's response to SO_2 was higher at positive gate voltages, leaving the negative Section less affected. For on-time measurements the gate voltage was set at + 5 V, with the Vsd fixed at 0.25 V.

Control experiments were carried out to show both that the receptor was correctly anchored to the substrate and that the changes in the instrumental response

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were only due to the interaction between the platinum complex and SO_2. In this way, we functionalized SWCNTs with PEI and subsequently with NAS, but not with the platinum complex. These CNTFET devices were subsequently exposed to up to 10 % v/v of SO_2, CO_2 and NO_2, with no significant change to the electrical current (data not shown). Therefore, the platinum complex is needed to generate an electrical response upon the addition of SO_2. In this way we proved, at the same time, that the functionalization with PEI and NAS effectively shields the SWCNTs from the interaction of acid gases such as CO_2 or NO_2, and that the decrease in the electrical current is only observed when the synthetic receptor and the SO_2 interact.

To determine the response time of the CNTFET, the electrical current of the CNTFET was followed during the exposure to several concentrations of SO_2. Fig.4 shows how the electrical current decreases for increasing concentrations of SO_2 in an air atmosphere in the gas cell at room temperature (at Vsd = 0.25 V and Vg = 5 V). Response times range from 16 min at lower concentrations of SO_2 to 8 min at higher concentrations. Before each new addition of SO_2 we always checked that the electrical current was stabilized giving rise to the horizontal Sections seen in Fig.4. The inset in Fig.4 shows a linear dependence for the electrical current along the concentration range. The sensitivity (calculated as the slope of the fitted straight line) was –0.028 μA/(% v/v) with an standard deviation of 0.004 μA/(% v/v). The range of concentrations of SO_2 detected with this CNTFET was from 0.25 % to 1.8 % v/v, which was similar, for instance, to the concentrations of CO_2 detected by Star *et al.* in a PEI-coated CNTFET device.[16] The minimum concentration of SO_2 that we were able to detect with our CNTFET devices was 0.05 %. We always used the same CVD parameters, however, the density of the network of SWCNTs and the sensitivities may change slightly for different devices. Nevertheless, we were able to detect concentrations of SO_2 of the same order of magnitude using different CNTFET devices.

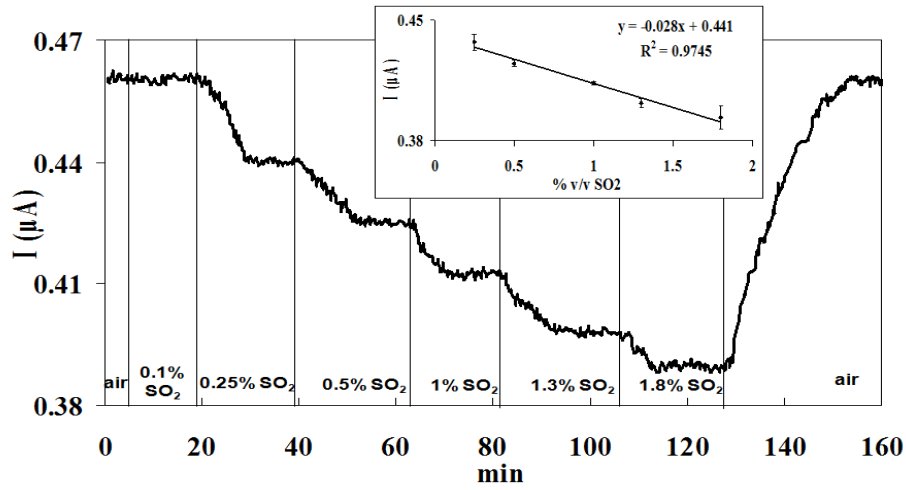

Fig.4: Time dependence of the source–drain current (I), at Vg = +5 V and Vsd = 0.25 V, for increasing concentrations of SO_2. Vertical straight lines define the composition over the time in the gas cell. The inset shows the source-drain current versus the concentration of SO_2. The error bars were obtained with two measurements with the same device in two consecutive days.

We can see in Fig.4 that the CNTFET was successfully regenerated in only 25 minutes by re-exposing it to air at room temperature.[27, 28] The following day the CNTFET was again exposed to the same increasing concentrations of SO_2. The electrical current for that day (data not shown) was recorded in a similar way to that shown in Fig.4. The inset of Fig.4 shows the average of the two values of the electrical current obtained for each concentration of SO_2 taken on two consecutive days with the same sensing device. The error bars (inset in Fig.4) show the difference between these two measurements on these two different days. Similar electrical current values are then obtained after regenerating the CNTFET. This regeneration might be achieved even faster by using other mechanisms to release the SO_2 from the complex formed with the receptor.[22] The recovery time of our devices was similar to that observed for other functionalized CNTFETs. [17, 32] The recovery time of the baseline after regeneration could be explained by the process involving the reversibility of the reaction between the receptor and SO_2.

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The selectivity was checked using other gases such as CH_4, CO_2 and NO_2 that might be found in the same samples together with SO_2 and that can also contribute to environmental problems.[33] As has been previously indicated,[16] sensors using polymer coated CNTFETs need to eliminate the cross reactivity between similar gases (CO_2, SO_x, NO_x) to be able to discriminate among them. For these reasons these gases have been used as interferent compounds. Fig.5 shows the selectivity of the device in the presence of CH_4, CO_2 and NO_2 against the response for SO_2. Increasing concentrations of the interfering gas (i.e. CH_4, CO_2 or NO_2) in an air atmosphere were added to the gas cell in the absence of SO_2 and the electrical current was recorded at Vg = 5 V and Vsd = 0.25 V. Fig.5 shows that the electrical current did not significantly change for CH_4 even up to a concentration of 15 % v/v. No appreciable changes in the electrical current were observed for successive additions of either CO_2 or NO_2 until the concentration reached a value of 10 % and 5 %, respectively. In any case, these changes cannot be attributed to the interaction of CO_2 or NO_2 with the amino groups of PEI, since one of the previously described control experiments showed that a device properly functionalized with PEI and NAS (without the platinum complex) did not respond to CO_2 or NO_2. The change in the electrical current after the addition of over 10 % v/v of CO_2 and over 5 % v/v of NO_2 could be related to a low interaction between either CO_2 or NO_2 and the platinum complex. The platinum complex is known to react with I_2,[22] but I_2 is usually found in extremely low concentrations in gaseous samples. Water does not affect the CNTFET as it can also be used in aqueous solutions. The blocking molecule (NAS) effectively shields the PEI-coated SWCNT network from the presence of other gases such as CO_2, CH_4 or NO_2. The presence of the platinum complex makes our devices selective to SO_2 because a higher concentration of other gases is needed to cause a significant and similar response to that produced by SO_2. Therefore, the proposed chemical functionalization of SWCNTs operates in a twofold manner: 1) the synthetic receptor makes the CNTFET selective for SO_2 and 2) the functionalization process together with the NAS blocking step shields the CNTFET device from interfering gases.

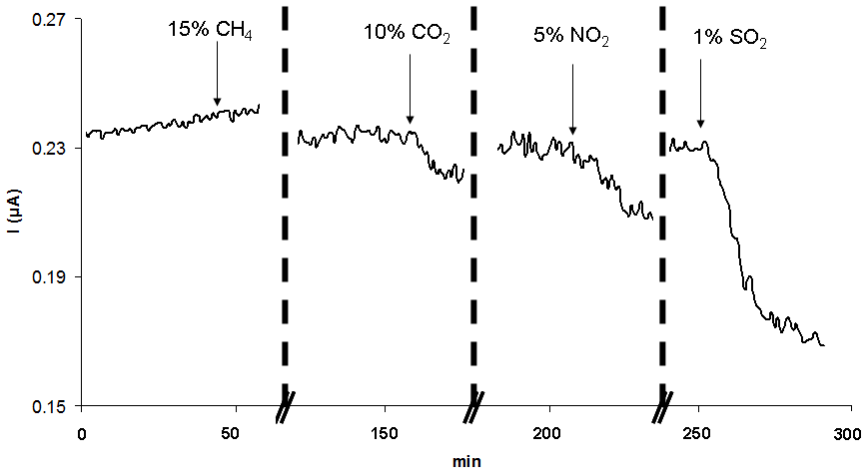

Fig.5: Change of the source–drain current (I) at Vg = +5 V and Vsd = 0.25 V in the presence of interfering gases. Increasing concentrations of CH_4, CO_2 and NO_2 were added. Vertical dotted lines describe the gas cell composition over time. A 15% v/v CH_4 did not affect the base signal; a 10% v/v of CO_2 makes a change in the current of 10 nA and a 5% v/v of NO_2 of 20 nA. These two experiments for interfering gases are compared to the 1% v/v of SO_2 that reduces the CNTFET current to 60 nA.

In this paper we describe a CNTFET device for selectively and quantitatively detecting a single gaseous molecule, SO_2, at room temperature by means of a synthetic receptor. The CNTFET is based on a reversible interaction between a platinum complex and SO_2. The SWCNTs have been non-covalently functionalized with a polymer (PEI) with functional groups to be accessible for a desired receptor without damaging the SWCNT's electrical properties. The complete functionalized network of the SWCNTs is properly blocked because other acidic gases show no significant interaction with amine groups of PEI. The platinum complex is selective to SO_2 because a higher concentration of interfering gases is needed to obtain a significant response. The sensing mechanism could involve either a modification of the Schottky barrier due to the absorption of the target compound on the metal-nanotube junction or a modification of the charge transfer when SO_2 is coupled to the platinum complex. This strategy could be used for detecting other gaseous molecules by functionalizing the CNTFETs with a suitable receptor. Moreover, the CNTFET devices functionalized with the platinum complex could be used as a device to detect SO_2, not only selectively, but also quantitatively.

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EXPERIMENTAL

Fabrication of CNTFET: The network of SWCNT that forms the channel of the CNTFET was grown by chemical vapour deposition (CVD) over Si substrates with a layer of SiO_2 (500 nm thick) on top as described previously [34]. Source and drain electrodes (5 x 10 μm) were patterned by using optical lithography (Cr/Au 2/30 nm thick, respectively). The gap distance between the electrodes was 2.5 μm. The Si substrate was used as a gate electrode.

Functionalization process: The devices with the SWCNTs and the electrodes were first submerged overnight in a 20% w/v aqueous solution of PEI (high molecular weight, water-free, from Sigma Aldrich, Tres Cantos, Spain). A monolayer of polymer is irreversibly adsorbed on the sidewalls of the nanotubes [26, 35]. The devices were then rinsed thoroughly with water to remove the non-specific adsorbed polymer over the sample surface, and dried with nitrogen. The platinum complex acting as the specific receptor for SO_2 was synthesized according to a literature procedure [36]. To anchor the platinum complex to the PEI-coated SWCNTs, the devices were soaked in a solution of 3 mg/mL of the platinum complex [$PtI(4\text{-}COONC_4O_2H_2\text{-}2,6\text{-}(CH_2NMe_2)_2\text{-}C_6H_2$] in dichloroethane and allowed to react (amide bond formation with the NH_2 group of PEI) for 3 hours at room temperature. The devices were rinsed thoroughly with dichloroethane and water and dried with nitrogen. The last step of the functionalization process consisted of blocking the remaining amino groups of PEI that did not react with the platinum complex. The devices were immersed in a solution of 3 mg/mL of NAS (from Sigma Aldrich, Tres Cantos, Spain) in water for 2 hours at room temperature. Afterwards, the devices were rinsed with water and dried with nitrogen.

SO_2 measurements: The completely functionalized CNTFET device was then placed in a gas cell and exposed to SO_2 in an air atmosphere. The gas assays were performed at room temperature at a relative humidity of 30 - 40 %. SO_2 (99.98 %), NO_2 (98.5 %), CO_2 (99.8 %) and CH_4 (99.0 %) were purchased from Carburos Metálicos (Barcelona, Spain).

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6.3 CONCLUSIONS

A new sensor has been developed which uses SWCNTs as transducers in FETs and a synthetic organoplatinum complex as a receptor indirectly linked to the SWCNTs. This sensor is able to determine SO_2 at room temperature with low response times and correctly regenerates after its re-exposure to the atmosphere.

Polyethylenimine, a polymer coating for SWCNTs, offers suitable functional groups for anchoring the synthetic receptor, and furthermore isolates SWCNTs from possible interaction with other gaseous substances. The amino groups of polyethylenimine are converted to less reactive groups using a blocking molecule, N-acryloxysuccinimide. This process prevents acid gases from interfering with the sensor.

CNTFET based sensors allow gaseous substances to be determined at room temperature by means of a suitable functionalization process. The SO_2 sensor reported in this work shows no or few cross-reactivity with gases such as CO_2 or CH_4 that could be found in the exhaust combustion gas samples when analyzing for SO_2. Nitrous gases are identified as the only possible interferences when found at high concentrations.

This functionalization strategy could be used for sensing many gaseous analytes, if the appropriate receptor is anchored to the SWCNTs. CNTFET based sensors are promising candidates for overcoming the current limitations of gas sensors, not only because of the working temperature, but also because the high selectivity and the short response times.

Currently, there are no studies in the literature dealing with the detection of small analytes using CNTFET with consistent experimental selectivity. The original strategy shown in this work, with a systematic chemical functionalization of SWCNTs, could serve to open different pathways in order to obtain highly selective CNTFETs sensors useful for gas and liquid samples, including those directed towards detecting small molecules.

6.4 REFERENCES

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7 General Conclusions

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The present chapter contains the main conclusions of this thesis. Specific conclusions regarding the individual procedures carried out during the thesis have been discussed at the end of each chapter. This Section has two conclusions: first, the scientific conclusions directly related to the work carried out, and second, a personal analysis of the attributes and skills acquired during this four year period, given that the main objective of the doctoral thesis is to train the PhD student to become a full researcher.

7.1 SCIENTIFIC CONCLUSIONS

CNTFET-based sensors are a relatively new kind of sensor. Random networks of SWCNTs synthesized using the CVD method show semiconductor electrical behavior and can thus be integrated as the semiconductor channel in FETs. Consequently, SWCNTs are the key element of CNTFETs. The new structure of the transistors based on SWCNTs allows nanotubes to be integrated at the surface of the devices, thus exploiting SWCNTs' sensitivity to changes in their environment. This is the basis of the sensing part of the sensor. This thesis has shown that CNTFETs can be used for the successful selective detection of different types of target analytes. These can be biomolecules such as antigens, small compounds such as cations or gas-phase compounds such as SO_2.

SWCNTs are highly sensitive to changes in their immediate chemical environment however, at the same time, this property gives them very low selectivity. One of the main problems of using bare SWCNTs in analytical sensors is the fact that they interact with many types of analytes. This chemically non-selective interactivity is closely related to the presence of a shell of π electrons surrounding the walls of the SWCNTs. Proposals for solving this lack of selectivity include both the non-covalent and covalent coverage of the SWCNTs as well as functionalizing these with specific receptor molecules, thus mimicking the process of molecular recognition events.

Different molecular recognition approaches can be applied when using CNTFETS to selectively detect several kinds of analytes. The target analytes can be at a low concentration in different phase systems (gaseous, liquid, and dry). The classic antigen-antibody interaction was studied for the first time using a CNTFET based

sensor involving HIgG and anti-HIgG. Sensors based on CNTFETs and functionalized properly with anti-HIgG molecules as the receptors, detected the target antigen in the nM range, and also showed no cross reactivity with the other important protein, BSA. The target HIgG was detected both in liquid and dry environments, with two different experimental functionalization procedures.

In another research line, one of the sensors reported in this thesis combined an ion selective membrane with an SWCNT network for the first time. This structure generates a new type of ISFET device which combines the properties of the CNTFETs with the sensing properties of ion selective membranes. The clear advantage that this type of sensor offers compared to the traditional ISFETs is the possibility of miniaturizing the entire device without using an external reference electrode.

The challenge faced throughout this thesis was to develop a CNTFET gas sensor to demonstrate that CNTFET work well not only with liquid samples but also with gas samples. In chapter 6 an organoplatinum complex is used to detect SO_2 at room temperature, again employing molecular recognition in the gas phase as the basis of a CNTFET sensor. This complex is highly selective towards the SO_2 molecule, and thus gives a high degree of selectivity to our CNTFET based sensor. The functionalization of the SWCNTs with the receptor complex and, at the same time, the blockage of the remaining free active sites of the polymer-coated SWCNTs, provides a robust system where other gaseous analytes cannot interfere with the sensor response. In this way, the receptor, which is usually employed in solution, has been linked to the solid-phase of the transductor achieving a sensor that is remarkably selective and operates at room temperature, unlike other gas sensors using CNTFETs.

A large variety of new sensors operating in different media (liquid or gas), could be designed with enhanced performance characteristics by defining a strategy for immobilizing suitable receptors on the SWCNTs' surface so that they preserve their inherent recognition properties. Therefore, the future of sensors based on CNTFET and molecular approaches is promising, as long as the main drawbacks could be overcome, such as the synthesis of nanotubes of different chiralities, the reproducible growth (or deposition) of the nanotubes onto the silica substrates, the different sensitivities shown among different CNTFET devices, etc. Although this work has estimated some of the

main performance parameters such as sensitivity, selectivity or short range stability, many other analytical parameters (long term stability, precision, robustness, etc.) should also be evaluated to fully appreciate the potential of CNTFETs as marketable sensors. For example, SWCNT based ISFET have been shown to detect concentrations of potassium ions comparable to or even lower than the minimum amount reported for the existing ISFETs. This fact has to be investigated further to check if the network of SWCNTs coupled to the ion selective membrane is better than the current membrane limits of detection because of its different transduction mechanism.

The overall methodology of sensing using CNTFET based sensors has to be applied in different fields. These applications will necessarily involve thorough validation schemes using suitable references to trace the results obtained with these new kinds of sensors.

7.2 ACQUISITION OF ATTRIBUTES AND SKILLS

During my PhD studies, in addition to acquiring scientific knowledge, I have also acquired certain attributes that will help me to develop my career in the future.

In this thesis I have outlined the development of my research project. First I have focused on learning the main features of what for me was a new field—nanotechnology—and how this field is related to analytical chemistry, which was my specific research area. To do this I studied the literature extensively in order to understand the concepts and terminology involved. Second, I selected and reviewed the literature I found in order to obtain what was most useful for my own work. This has helped me to develop critical reading skills for evaluating the relevant literature. Moreover, I have acquired the ability to initiate research projects and to define the framework and variables involved.

These skills enabled me to perform my experimental work, which involved understanding what SWCNTs were, developing a CNTFET-based sensor for detecting a specific target analyte, and gaining the ability to critically evaluate my results, both within and across a changing disciplinary environment. The experimental work of this thesis has been conducted in collaboration with other members of the research group, and so I have learned to work as a member of a team. I also supervised the research work of a foreign research student on an Erasmus project in our laboratory, thus learning the skills needed to plan and supervise a specific research project.

I have taken several master's and doctorate courses after which I was awarded the official master's degree in Nanoscience and Nanotechnology. At the same time, I have attended several congresses where I had to present and discuss our scientific results. Moreover, I have written up and published the results of our work in international scientific journals and in a book chapter. Through these scientific contributions, I have acquired the ability to communicate results effectively both orally and in writing, and have gained an understanding of the relevance and value of my research to the national and international scientific communities.

Finally, all these skills are combined with a respect for truth, intellectual integrity and the ethics of research.

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Annex I: Contributions to the scientific community

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JOURNAL ARTICLES

Authors: Cid, Cristina C.; Riu, Jordi; Maroto, Alicia; Rius, F. Xavier
Year: 2008
Title: Carbon Nanotube Field-effect Transistors for the Fast and Selective Detection of Human Immunoglobulin G
Journal: The Analyst
Volume: 133
Pages: 1005-1008

Authors: Cid, Cristina C.; Riu, Jordi; Maroto, Alicia; Rius, F. Xavier
Year: 2008
Title: Ion Sensitive Field-effect Transistors Using Carbon Nanotubes as Transducing Layer
Journal: The Analyst
Volume: 133
Pages: 1001-1004

Authors: Cid, Cristina C.; Riu, Jordi; Maroto, Alicia; Rius, F. Xavier
Year: 2008
Title: Detection of Human Immunoglobulin G at physiological conditions with chemically functionalizated carbon nanotube field-effect transistors
Journal: Current Nanoscience
Volume: 4
Pages: 133-137

Authors:: Cid, Cristina C.; Jimenez-Cadena, Giselle; Riu, Jordi; Maroto, Alicia; Rius, F. Xavier; Batema, Guido; van Koten, G.
Year: 2008
Title: Selective detection of SO2 at room temperature based on functionalized single-walled carbon nanotube field-effect transistors
Journal: Submitted

Authors: Cid, Cristina C.; Riu, Jordi; Maroto, Alicia; Rius, F. Xavier

Year: 2008

Title: Biosensors based on CNT network field-effect transistors

Book series: Methods in Molecular Biology: Carbon Nanotubes

Editors: Burghard, M. and Balasubramanian, K.

Publisher: The Humana Press Inc.

CONGRESS CONTRIBUTIONS

Contribution Type: Poster
Authors: Cid, Cristina C.; Jiménez-Cadena, Giselle; Riu, Jordi; Maroto, Alicia; Rius, F. Xavier,
Batema, Guido; van Koten, Gerard
Year: 2008
Title: Selective detection of SO_2 at room temperature based on functionalized carbon nanotube field-effect transistors
Congress: II Workshop Nanociencia y Nanotecnología Analíticas
Place: Tarragona (Spain)

Contribution Type: Poster
Authors: Cid, Cristina C.; Riu, Jordi; Maroto, Alicia; Rius, F. Xavier
Year: 2007
Title: Carbon nanotube based ion selective field-effect transistors
Congress: Trends in Nanotechnology 2007
Place: San Sebastián (Spain)

Contribution Type: Oral communication
Authors: Cid, Cristina C.; Riu, Jordi; Rius, F. Xavier
Year: 2005
Title: Sensors based on carbon nanotubes and antigen-antibody recognition
Congress: Second World Congress on Synthetic Receptors
Place: Salzburg (Austria)

Contribution Type: Poster
Authors: López, I.; Cid, Cristina C.; Riu, Jordi; Rius, F. Xavier,
Year: 2005
Title: Analytical sensors based on carbon nanotubes and molecular recognition
Congress: II Nanospain Workshop
Place: Barcelona (Spain)

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Annex II: Glossary

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Term used	Definition
Ab	Antibody
AFM	Atomic force microscope
Ag	Antigen
CB	Conduction band
CHEMFET	Chemical sensitive field-effect transistor
CMOS	Complementary metal oxide semiconductor
CNT	Carbon nanotube
CNTFET	Carbon nanotube field-effect transistor
CVD	Chemical vapor deposition
Da	Dalton
DOS	Density of states
EIA	Enzyme immunosorbent assay
ELISA	Enzyme-linked immunosorbent assay
ESEM	Environmental scanning electron microscope
eV	Electron volt
FET	Field-effect transistor
GA	Glutaraldehyde
HIgG	Human Immunoglobulin G
I	Electrical current
IgG	Immunoglobulin G
Ionophores	Small hydrophobic molecules that dissolve in lipid bilayers and increase their permeability to specific inorganic ions.
ISE	Ion selective electrode
ISFET	Ion sensitive field-effect transistor
IUPAC	International union pure applied chemistry
MIP	Molecular imprinted polymer
MOSFET	Metal-oxide-semiconductor field-effect transistor
MWCNT	Multi-walled carbon nanotube
NAS	N-acryloxysuccinimide
nm	Nanometer (10^{-9} m)

PBS	Phosphate buffered saline solution
PEI	Polyethyleneimine
PVC	Poly (vinyl chloride)
QD	Quantum dot
r.p.m.	Revolutions per minute
sccm	Square cubic centimeter
SEM	Scanning electron microscope
SWCNT	Single-walled carbon nanotube
Valinomycin	Potassium ionophore
VB	Valence band
Vg	Gate-to-source voltage
Vsd	Source-to-drain voltage
μm	Micrometer (10^{-6} m)

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Carpe diem