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Surface-immobilized Hairpin DNA Sensors  
for Direct and Specific Detection  
of Target DNA

Tanja Kjällman

**A thesis submitted in complete fulfillment of the requirements  
for the degree of Doctor of Philosophy,  
Department of Chemistry, The University of Auckland, 2009**



## Abstract

Gene-sensors show great promise as tools for various applications, such as clinical diagnosis, reliable forensic analysis, environmental monitoring, and biological research. There is a great demand for DNA sensors that are able to detect single-base mismatches, which are the most common genetic defects that need to be discriminated for medical diagnostic purposes. The development of label free, direct, and fast sensors can be essential in meeting that requirement. Current gene-sensing technology relies heavily on fluorescent labeling of samples but this approach suffers from the disadvantage of time-consuming, expensive and multi-stepped procedures, especially during the sample preparation stage. Although the use of fluorescent labels has overcome the hazards involved with radioactive markers, development of alternative approaches to the traditional assays is still vital to advance the area of DNA sensors.

The aim of this research was to develop a one-step sensor, offering direct and specific detection of a target DNA. Nanostructured materials, such as quantum dots (QDs) and self-assembled monolayers, together with hairpin structured DNA probes were applied and investigated for optical as well as electrochemical sensors. The properties of inorganic quantum dots (or nanoparticles), such as narrow and intensive emission spectra, resistance to photobleaching and a wide range of possible surface functionalities, give QDs a great potential as labels in biological sensing applications. Self-assembled monolayers provide well established and versatile platforms for biosensors and hairpin probes, which are able to discriminate single-base mismatches in the target sequences, are ideal components for DNA sensors.

Generally, the electrochemical sensors demonstrated a superior response compared to the optical sensors. The best prepared sensor showed sensitivity down to 4.7 fM of target and was capable of detecting single-base mismatches, fulfilling the requirements for a high-quality DNA sensor.

## Declaration

This is to certify that:

- 1) This thesis comprises only the authors original work, except where indicated below;
- 2) Due acknowledgment to all other material used has been made in the main text of the thesis.

My overall contribution to the work presented in this thesis is approximately 95%, based on the following:

Chapter 4

95 % The models for fitting of the acquired neutron reflectometry data were developed by Dr Ducncan McGillivray, from the Department of Chemistry, The University of Auckland. Dr McGillivray also carried out the polarized neutron reflectometry experiments at the NIST Center for Neutron Research, USA.

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## List of Symbols and Abbreviations

$\theta$	Angle
$\bar{P}$	Average height
$\alpha$	Charge transfer coefficient
$\varepsilon$	Extinction coefficient
$\omega$	Frequency
$\mu$	Micro, $10^{-6}$
$\Omega$	Ohm
$K$	Radiation intensity
$\eta$	Refractive index
$\rho$	Scattering length density
$\sigma$	Surface roughness
$\nu$	Sweep rate
$\lambda$	Wavelength
$\chi^2$	Chi-square (uncertainty)
$\Delta G$	Gibb's free energy
$\Delta H$	Enthalpy
$\Delta S$	Entropy
$^{13}\text{C NMR}$	Carbon nuclear magnetic resonance spectroscopy
$^{15}\text{N NMR}$	Nitrogen nuclear magnetic resonance spectroscopy
$^1\text{H NMR}$	Proton nuclear magnetic resonance spectroscopy
$A$	Absorbance / Area
A	Adenine
Å	Ångström
a	Atto, $10^{-18}$
$a$	Chemical activity coefficient
a.u.	Arbitrary unit
AC	Alternating current
ACCV	Alternating current cyclic voltammetry
AdTSV	Adsorptive transfer stripping voltammetry
AFM	Atomic Force Microscopy
$A_i$	Atomic weight

ANSTO	Australian Nuclear Science and Technology Organisation
ATR-FTIR	Attenuated total reflection fourier transform infrared
$b_i$	Scattering length of nucleus $i$
$c$	Complementary
$C$	Concentration
C	Cytosine
$c$	Speed of light in vacuum
CCD	Charge-coupled device
$C_d$	Double layer capacitance
cm	Centimeter
CM	Contrast matching
Compound A	Biotin N-hydroxysuccinimide ester
Compound B	N-(13-Amino-4,7,10-trio- atridecanyl) biotinamide
Compound C	11-mercaptoundecanoyl- N-hydroxysuccinimide ester
$C_p$	Heat capacity
CPE	Constant phase element
CV	Cyclic voltammetry
Cy3	Indocarbocyanine
$D$	Diffusion constant
$d$	Thickness
Da	Dalton (mass unit)
DC	Direct current
DHLA	Dihydrolipoic acid
DMF	N,N-dimethylformamide
DNA	Deoxyribonucleic acid
$d_p$	Depth of penetration
DPV	Differential pulse voltammetry
ds	Double-stranded
DSBA/	((5-(6,8-Diaza-7-oxo-3-Ligand 2 thiabicyclo[3.3.0]oct-2-yl)-N[7-(3-{{2-(N{7-[5-(6,8-diaza-7-oxo-3- thiabicyclo[3.3.0]oct-2-yl)pentanoylamino] heptyl}-arbamoyl)ethyl] disulfonyl}propanoyl- amino)heptyl] pentanamide))
DSC	Differential scanning calorimetry
dT	Thymine deoxyribonucleotide
$E$	Energy

$E^\circ$	Standard potential
ECL	Electrogenerated chemiluminescence
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
EDS	Energy-dispersive spectrometry
EIS	Electrical Impedance Spectroscopy
F	Faraday's constant
f	Femto, $10^{-15}$
FC	Fully complementary
G	Guanine
h	Hour
$h$	Planck's constant
HAD	Hexadecylamine
HOMO	Highest occupied molecular orbital
HPP	Hairpin probe
HRP	Horseradish peroxidase
Hz	Hertz
$I$	Current
ICCP	Intensified charge couple device
IR	Infrared
IS	Immobilization strategy
$K_a^0$	The heterogeneous standard charge transfer rate constant
Ligand 1	8-Thio-3,6-dioxaoctanol
ln	The natural logarithm
LUMO	Lowest unoccupied molecular orbital
$m$	Mass
m	Milli, $10^{-3}$ / multiplet / meter
M	mol l <sup>-1</sup> / mega $10^6$
MAA	Mercaptoacetic acid
MB	Molecular beacon
MCB	4-Mercaptobutan-1-ol
MCH	6-Mercapto-1-hecanol
ML	Monolayer
MM	Mismatch
m-PEG	Methyl poly(ethylene glycol)

mSAM	Mixed self-assembled monolayer
MUA	11-Mercaptoundecanoic acid
$n$	Amount
n	Nano, $10^{-9}$
$N_A$	Avogadro's number
NC	Non-complementary
NCNR	NIST Center for Neutron Research
NDL	National Device Laboratories
NIST	National Institute of Standards and Technology
NMR	Nuclear magnetic resonance spectroscopy
NN	Nearest-neighbor
NP	Nanoparticle
NR	Neutron reflectometry
ODN	Oligonucleotide
p	Pico, $10^{-12}$
$P$	Power of transmitted radiation
$P_0$	Power of incident radiation
PBS	Phosphate buffered saline
PCR	Polymerase chain reaction
m-PEG	methyl-Poly(ethylene glycol)
PEO	Poly(ethylene oxide)
$P_i$	Height at each measured point
$\rho_i$	Mass density
PL	Photoluminescence
PNR	Polarized neutron reflectometry
pPy	PolyPyrrole
q	Quadruplet
QD	Quantum dot
$Q_z$	Momentum transfer
$R$	Resistance
R	The universal gas constant
$R_a$	Roughness average
$R_{ct}$	Charge transfer resistance
$R_f$	Faradic impedance

RMS	Root mean square
RNA	Ribonucleic acid
rpm	Revolutions per minute
$R_s$	Solution resistance
s	Singlet
SAM	Self-assembled monolayer
SEM	Scanning electron microscopy
SLD	Scattering length density
ss	Single-stranded
SSC	Saline-sodium citrate
STM	Scanning tunneling microscopy
$T$	Temperature
T	Thymine
t	Triplet
TEM	Transmission electron microscopy
TGA	Thioglycolic acid
$T_m$	Melting temperature
TM	Tapping-mode
TOP	Tri-n-octylphosphine
TOPO	Tri-n-octylphosphine oxide
UV-vis	Ultraviolet-visible spectroscopy
$V$	Potential
V	Volt
$v_f$	Volume fraction
$W_0$	Warburg impedance
$Y$	Admittance
$Z$	Total impedance
$z$	Zepto, $10^{-21}$
$Z'$	Real impedance
$Z''$	Imaginary impedance

