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Diplomarbeit

Titel der Diplomarbeit

Detection of drug precursors for amphetamine with QCM

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Magister der Naturwissenschaften

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Preface

This work is done in the chair of Chemical Sensors and Optical Molecular Spectroscopy from October 2008 till June 2009 under the supervision of O. Univ. Prof. Dr. Franz Ludwig Dickert at the Institute of Analytical Chemistry, University of Vienna, Währingerstraße 38, 1090-Vienna, Austria.

Acknowledgements

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I am much obliged to EU. Nanosecure Project for the financial support.

There are so many people, whom I always wanted to thank for their helpful and caring attitude, yet I could not do so properly. I am still unable to mention the names of all those; but I hope, they will understand that I never overlooked any of them. Many thanks are due to my friends in Vienna for their cheerful company and assistance. It was due to them that I felt at home in Vienna.

Special thanks should go to my friends: Dangen She and Yamin Zhou, who are always by my side and give me continuous encouragement.

I am at a loss of words to express the gratitude towards my father, my mother, my brothers, my sisters, and my dear Siyu. Their love encourages me to go always forward.

Contents

Chapter 1 Chemical Sensors

1.1 Introduction

Analytical chemistry is the oldest as well as the youngest branch of chemistry. It has a long history which could go back to the early chemistry time since the questions, for instance, what are the elements and chemicals that are present in the world around us, what are their fundamental natures, were asked all along by the early chemists.

In the last century physics and chemistry have experienced great improvements. New techniques emerged in an endless stream, such as, laser (the first working laser was demonstrated on 16 May 1960 by Theodore Maiman[1]), AFM (Binnig, Quate and Gerber invented the first AFM in 1986[2]). With the help of the new techniques in physics and chemistry analytical chemists have strived continuously to discover new analytical methods to improve the reliability of the analytical results. Analytical chemistry boomed in the last century, spectroscopy, mass spectrometry, crystallography, electrochemical analysis were widely used in Science. Currently, it has played critical roles in the understanding of basic science to a variety of practical applications, such as biomedical applications, environmental monitoring, quality control of industrial manufacturing, forensic science and so on.

Classic analytical chemistry is dominated by instrumental analysis. The performances, such as, sensitivity, selectivity, robustness, accuracy, are improved through the advances of the instruments. Nowadays, the classic analytical instruments have already achieved high performances and are widely applied. However, generally these analytical methods have the some disadvantages. They usually have big sizes and are not mobile, so normally they are located in the laboratories; the prices of the instruments are generally high; they are not easy to operate and need labor staffs that have professional

acknowledgement, which increases the analysis cost and they are not able to do the on-line-monitor of the industrial processes.

The trend of analytical chemistry today is to develop a new analytical method which is free of the above mentioned disadvantages. It is small, needs simple operation and possible to do real-time analysis. Chemical sensors meet exactly those requests. Besides, they are usually mass-produced and have much lower prices compared with the classical analytical instruments.

1.2 Chemical Sensors

1.2.1 Definition of Chemical Sensors and Basic Principles

Chemical sensors are small devices capable of continuously recognizing concentrations of chemicals constituents in liquids or gases and converting this information in real time to an electrical or optical signal.[3]

Principally, a chemical sensor consists of three parts: a sensitive layer, it contacts with the analyte and acts as the recognition system; a transducer, used to convert the chemical signals of the recognition system into an electrical or optical signal; a data evaluation electronics to calculate from the electrical or optical signal into the desired information, like concentration, temperature and pressure. The whole and continuous process is described as following[4]: after the analyte contacts with the sensitive layer, one of the physical properties of the sensitive layer changes, for example, mass, capacity or resistance. This change is then detected by the transducer. Immediately after, the transducer converts the change of physical property to an electrical or an optical signal. This electrical or optical signal is ultimately detected by data evaluation electronics, where the signal is operated and shown in a desired form. A simple scheme of chemical sensors is shown in Figure 1.

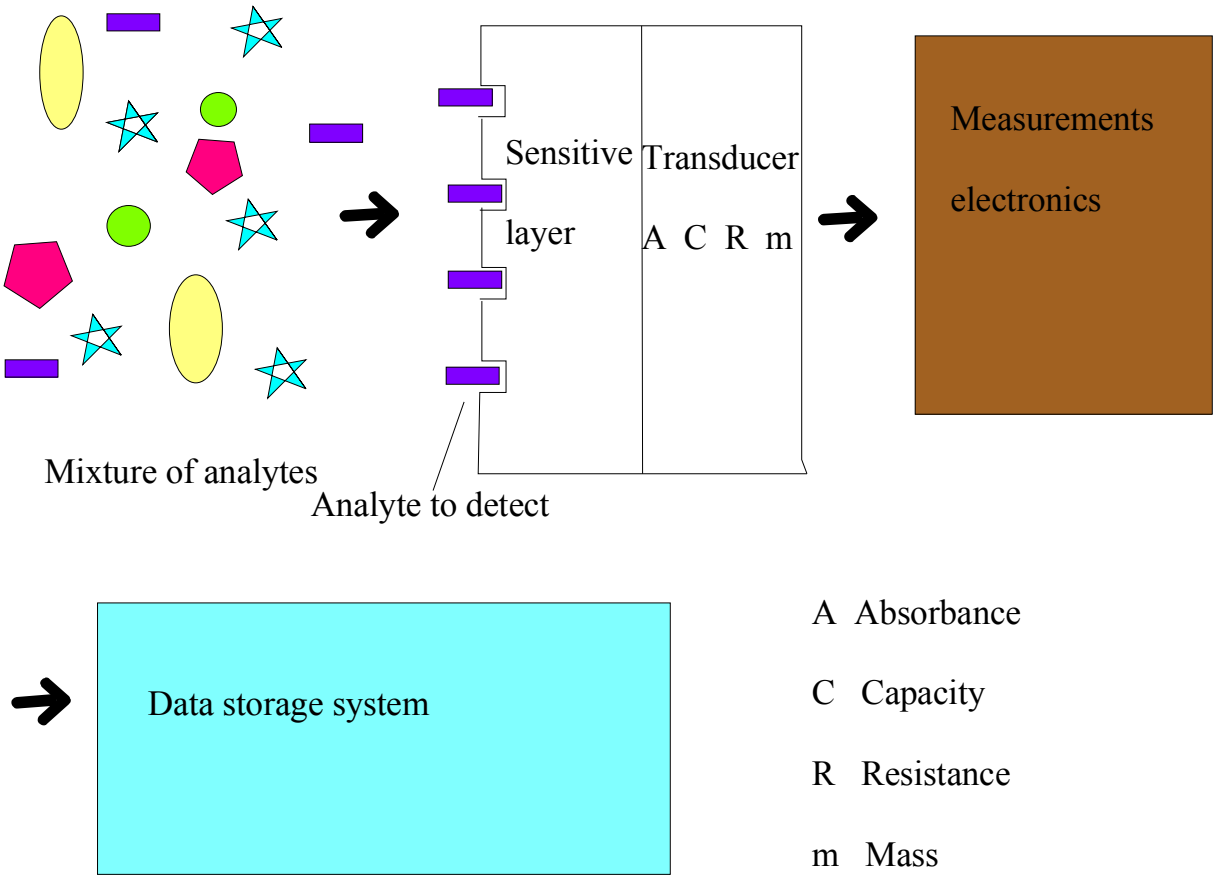


Figure 1.1 Scheme of a chemical sensor

1.2.2 History of Chemical Sensors

Chemical sensor is a relative new technique in analytical chemistry. pH electrode was invented as the first chemical sensor in 1922[4]. The second well-known chemical sensor is Clark electrode, also called oxygen electrode (invented by Leland Clark in 1962). Since 1970 the chemical sensors were gone rapid evolution due to the new applied transducer principles like piezoelectricity and the new ways of immobilizing the sensitive lays.

At present, there are many chemical sensors that are already commercial produced. The most applied chemical sensors include metal oxide

semiconductors, conducting polymers, quartz crystal microbalance, surface acoustic wave, and field effect transistors.

The trend is to develop various chemical sensors to replace classic analytical instruments in many fields, such as, by monitoring chemical quantities in the environment, in industrial processes, in safety techniques, and in medicine.

Tab 1.1 Most produced commercial chemical sensors[6,7,8,9]

Lambda Sensor	An electronic device that measures the proportion of oxygen (O_2) in the gas or liquid being analyzed. The most common application is to measure the exhaust gas concentration of oxygen for internal combustion engines in automobiles and other vehicles.
Taguchi Sensor	A widely used gas sensor. It is a metal oxide-semiconductor-chip that detects the reductive gas at the temperature higher than 200 °C by the change of electronic conductance
Clark Electrode	An electrode that measures oxygen on a catalytic platinum surface using the net reaction: $O_2 + 4\ e^- + 2\ H_2O \rightarrow 4\ OH^-$
Ion-selective Electrode (ISE)	It converts the activity of a specific ion dissolved in a solution into an electrical potential which can be measured by a voltmeter. The voltage is theoretically dependent on the logarithm of the ionic activity, according to the Nernst equation.

1.2.3 Typical Parameters of Chemical Sensors

There are many parameters that characterize a chemical sensor, e.g. detection limit, selectivity, specificity, drift, reproducibility, miniaturization, mechanical stability, response time, long time stability, compatibility and so on. In the following sections, some of these parameters are briefly discussed.

Drift

The slow change of the output signal with the same measured property is called drift. The sensitive layer and the transducer, both undergo changes which may lead to drift. For a chemical sensor it is optimal to have no or low drift.

Reproducibility

Reproducibility is an important parameter for a chemical sensor. When a chemical sensor is reproducible, it means that it shows over a long time the same output signal with the same measured property under the same system conditions. Owing to the continuous measurements during the processes reproducibility is essential for chemical sensors that are used to real-time monitor industrial processes.

Response time

Response time is the time that a chemical sensor takes to finish the process that is from the interaction of the analyte and the sensitive layer to the final shown output. Response time is very critical for a chemical sensor, especially for the chemical sensors that are applied in warfare conditions, on-line monitoring by industrial process and in medicine by operations since in these situations the analysis time factor is crucial. It depends greatly on the interaction between the analyte and the sensitive layer and thickness of the layer.

Sensitivity

Sensitivity S is defined as the change in signal Y on change of concentration (S=dY/dc). Sensitivity of chemical sensors depends on many factors, such as,

the property of the sensitive layer and the transducer, the analysis conditions. A good chemical sensor should have a linear relationship over a wide range of measured property.

Selectivity

A chemical sensor should have good selectivity to distinguish the analyte and the other components, which are together with the analyte in the sample.

Compatibility to the Ambiance

The trend in the future of chemical sensors is that they can be used directly and easily in all of the fields, such as, industry, environment, medicine, food, criminal proceeding. So chemical sensors should be compatible to the ambiance, like humidity, pressure, temperature, biological conditions, sterilization, explosiveness, radioactivity and so on.

Miniaturization

Miniaturization is the obvious advantage of chemical sensors compared with classic analytical instruments. Due to the mini-size of chemical sensors they are easy to carry hence mobile to apply.

Long Time Stability

From the commercial point a chemical sensor should have a good stability over a long time.

1.2.4 Types of Chemical Sensors

Based on the different physical principles of transducers the chemical sensors can be generally divided into three main groups: 1) electrochemical sensors 2) optical sensors 3) acoustic wave sensors or mass sensors.

Under each of the three main groups mentioned above there are many sub-groups. For example, metal oxide semiconductors based on conductivity change

and ion-selective electrodes based on potential change both belong to electrochemical sensors. In case of optical sensors the chemical information is transformed into different optical properties, such as, transmission, absorption, scatter, reflectance or fluorescence. For mass sensors there are two sub-groups: bulk acoustics and surface acoustics. The different sensor types according to different physical principles are listed in Tab 1.2

Table 1.2 Overview of sensing schemes and types of sensors[7,8,9,10]

Sensing scheme	Sensor type
Conductivity change	Metal oxide semiconductors
	Organic semiconductors
Potential change	Ion-selective electrodes
	Solid-state gas sensors
	Field-effect transistors
Current change	Amperometric sensors(oxygen and enzyme electrodes, immunosensors, solid state gas probes)
Change of resonance frequency	Piezoelectric crystal resonators, surface acoustic wave sensors
Change of optical properties	Transmission/absorption, scatter, reflectance, fluorescence, refraction, decay time, polarization
Thermal effects	Thermal/calorimetric sensors
	Pellistors

1.3 Task of Diploma Thesis

Drug abuse nowadays is becoming an important problem to the society and endangers psycho- and physical health of the people. So it is essential to do the drug analysis quickly and accurately.[10]

There are many classic analysis methods applied for drugs[11], such as LC-MS, NMR, which has high sensitivity and accuracy. But all the classic analysis methods have typically following disadvantages: they are not mobile, not easy to operate and are expensive.

There is a desired need to find some other analytical methods that are mobile, easy to operate, cheap and at the same time, also sensitive and accurate, which will probably replace the classic analysis methods. Chemical sensors have exactly those properties. So it is meaningful to develop chemical sensors to analyse drugs.

Based on the chemical structures the drugs can be divided into following groups[12]: alkaloide, β-phenylethylamine, amphetamine, katecholamine, tropanalkaloide, tryptamine, lysergsäureamide, triptane, xanthine, terpenoide, cannabinoide, salvinorine.

In this work there were three analytes: 1) ephedrine, it belongs to the group amphetamine; 2) phenylacetone, which is usually used as a precursor for the manufacture of amphetamine; 3) isosafrole, which is known as a precursor for the manufacture of MDP2P (3,4-methylenedioxy-phenyl-2-propanone). MDP2P is then used for the manufacture of MDMA (more commonly known as 'Ecstasy' or 'XTC'[13]). MDMA is also a member of amphetamine.

The work in hand was to study the strategies of the receptors based on molecular imprinted polymers for the three analytes: phenylacetone, isosafrole, ephedrine. QCM (quartz crystal microbalance) is employed as the mass sensitive transducer, which has the detect limit of ng.

Chapter 2 Quartz Crystal Microbalance

2.1 Introduction

Quartz crystal microbalance (QCM) is a plate of piezoelectric quartz crystal sandwiched between two gold electrodes. It is widely used as ultra sensitive mass sensors, by which the density down to a level of below 1ng/cm^2 can be detected. The sensitivity of the QCM is approximately 10^5 times higher than an electronic fine balance with a sensitivity of 0.01 mg. So QCM is capable of measuring mass changes as small as single layer of atoms.

According to the 'Sauerbrey equation'[14] (developed by G. Sauerbrey in 1959) the resonance frequency of piezoelectric crystal quartz is inversely proportional to the total thickness of the quartz plate when the sensitive layer is a rigid, uniform and thin film. The total thickness of the quartz plate increases when a mass is deposited onto the crystal surface. So a direct relation between the deposited mass on the crystal surface and the resonance frequency of quartz exists. At first QCM was only applied under vacuum and in gas phase as an analysis tool. In the late 80's, it was recognized that QCM could also be operated in liquid phase, if proper measures are taken to overcome the consequences of the large damping. With the development of QCM applied in liquid system interests towards this technique increase dramatically.

A typical setup for the measurement with QCM contains water cooling tubes, the retaining unit, frequency sensing equipment, an oscillation source, a measurement and recording device. QCM is a member of a wider class of acoustic wave sensors. All the acoustic wave sensors are based on the principle of piezoelectric effect. So it is important for us to understand piezoelectric effect firstly.

2.2 Quartz as Piezoelectric Materials

2.2.1 Piezoelectric Effect

The piezoelectric effect[15] describes the phenomena that some crystals could produce electricity when pressure is applied in certain crystallographic directions. It was firstly demonstrated in 1880 by the brothers Pierre Curie and Jacques Curie. At the time they carried out experiments with crystals of tourmaline (a crystal silicate mineral compounded with elements such as aluminium, iron, magnesium, sodium, lithium, or potassium), quartz, topaz (a silicate mineral of aluminium and fluorine with the chemical formula $Al_2SiO_4(F,OH)_2$), cane sugar, and Rochelle salt (sodium potassium tartrate tetradydrate) and found, that quartz and Rochelle salt exhibited the phenomena of piezoelectricity obviously.

There are positive and negative electrical charges in a piezoelectric crystal. Normally they are randomly positioned, so the crystal is electrically neutral. under normal conditions. But when a mechanical pressure is applied in certain crystallographic directions, this neutrality will be destroyed. The positive and negative electrical charges shift across the crystal and then generate a voltage in the crystal. How intensively and in which direction die electrical charges shift depends on the direction of the mechanical pressure.

Converse piezoelectric effect is the phenomena that when an electrical field is applied on the piezoelectric crystal the mechanical deformation in the crystal will be created. It shows the opposite effect of piezoelectric effect. Whether the crystal is compressed or expanded depends on the polarity of the electrical field. So when an alternating voltage is employed on piezoelectric crystal an oscillating deformation will be created.

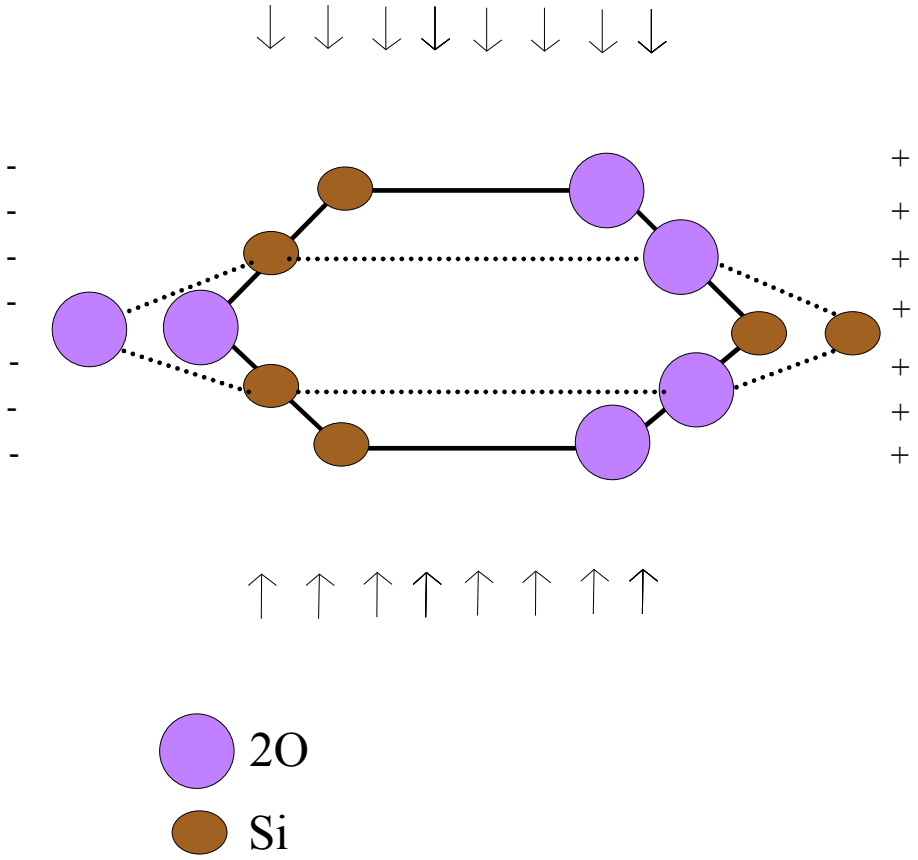


Fig 2.1 Figure of the piezoelectric effect

The relation between the electric field and the caused mechanical deformation(oscillation mode: thickness shear) in the crystal is shown in the equation below:

$$E = \delta \left(\frac{\Delta x}{x}\right)$$

E: electric field strength
x: thickness of the quartz
Δx: changes of the thickness
δ: piezoelectric constant (typical value: $10^9 – 10^{11}$ Vm^{-1})

Piezoelectricity did not receive many interests in the beginning. The first quartz crystal controlled oscillator was not described until 1921 which was based on X-cut crystal. X-cut[16] crystal is sensitive to the temperature, which greatly limits its

application. Since AT-cut crystal was introduced in 1934, which has nearly zero frequency drift with temperature around room temperature, applications of quartz crystal increased dramatically.

2.2.2 Piezoelectric Materials

Piezoelectric materials can be divided into 2 main groups: crystals and ceramics. Two well-known piezoelectric material[17] are quartz (SiO_2) and lithium tantalate ($LiTaO_3$). Other materials which have commercial potential are langasite (lanthanum gallium silicate, chemical structure: $A_3BC_3D_2O_{14}$, A, B, C and D indicate particular cation sites), zinc oxide (ZnO_2). They are applied for different purposes.

The choosing criterion of piezoelectric materials include: temperature dependence, attenuation, sensitivity and so on. Crystalline α-quartz is by far the mostly applied material for QCM. Langasite and gallium-orthophosphate are investigated as alternatives to quartz, mainly for use at high temperatures[18,19.]

2.2.3 Piezoelectric Property of α-Quartz

Crystalline α-quartz[20], which is the mostly applied piezoelectric material for QCM, is stable when the temperature is less than 573 °C. It transforms to β-quartz by the temperature of more than 573 °C. The structure of Crystalline α-quartz is shown in Fig.2.2

The x-axis, which is through one edge of the hexagonal prism of the crystal quartz, is perpendicular to the z-axis (optical axis). When the pressure in the direction of x-axis is applied on the crystal quartz an electrical field, which is also in the direction of x-axis, will develop. Hence x-axis is called electrical axis. This phenomena is named longitudinal piezoelectric effect. When an electrical field in the direction of x-axis is applied the y-axis of the crystal quartz will be elongated. So y-axis is named mechanical axis.

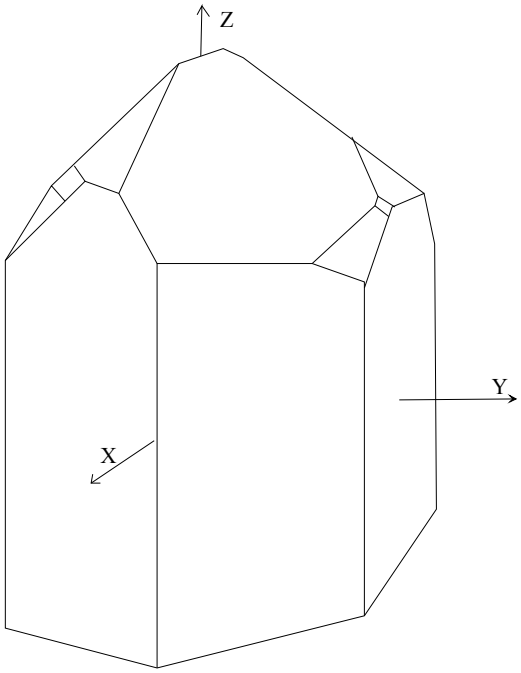


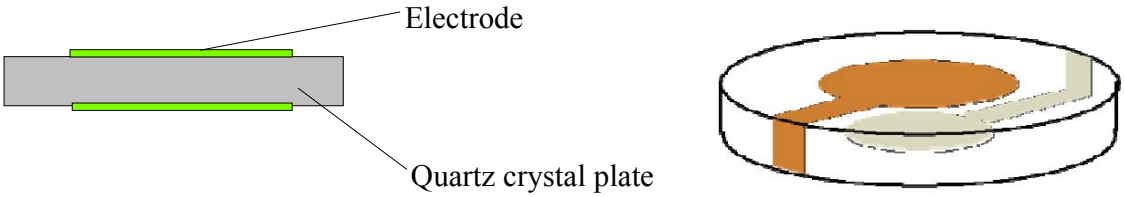
Fig. 2.2 α-Quartz crystal

If we apply the pressure in the direction of y-axis an electrical field, which is along the x-axis, will develop, but with an opposite sign. This phenomena is called transversal piezoelectric effect.

2.3 Crystal Oscillator

In this work crystal oscillator is a thin quartz plate with a defined cutting angle (AT-cut) sandwiched between two gold electrodes. When the electrodes are connected to an oscillator and an AC voltage is applied to the electrodes the quartz crystal starts to oscillate at its resonance frequency due to the piezoelectric effect.

The resonance frequency of quartz crystal depends on many factors, for instance, temperature, elasticity of the materials, the moving mass and primarily the crystallographic cut. Generally AT-cut quartz crystal is applied for QCM, due to its nearly zero frequency drift with temperature around room temperature. AT-cut means the plate of crystal is cut from the quartz crystal in the following way: 32.5° towards the z-axis and 122.5° towards the y-axis.



Side look Overlook

Fig. 2.3 Quartz crystal resonator used for QCM, metalized with gold electrodes

There are four different vibration modes[21]:

- flexural vibration (1kHz- 30kHz)
- stretching vibration (30kHz- 150kHz)
- surface shear vibration (150kHz- 1MHz)
- thickness shear vibration (1MHz- 50MHz)

The resonance frequency increases from flexure shear oscillation mode to thickness shear oscillation mode. Among these four different oscillation modes of quartz crystal thickness shear is mostly discussed by QCM and its resonance frequency is given by the following equation:

$$f_0 = \frac{C_Q}{2 d_Q} = \frac{N}{d_Q} \quad \text{.....(1)}$$

f_0 resonance frequency by standard temperature

C_Q acoustic velocity inside the quartz crystal(3340 m s^{-1})

d_Q thickness of the quartz plate

N frequency constant(1670 Hz m)

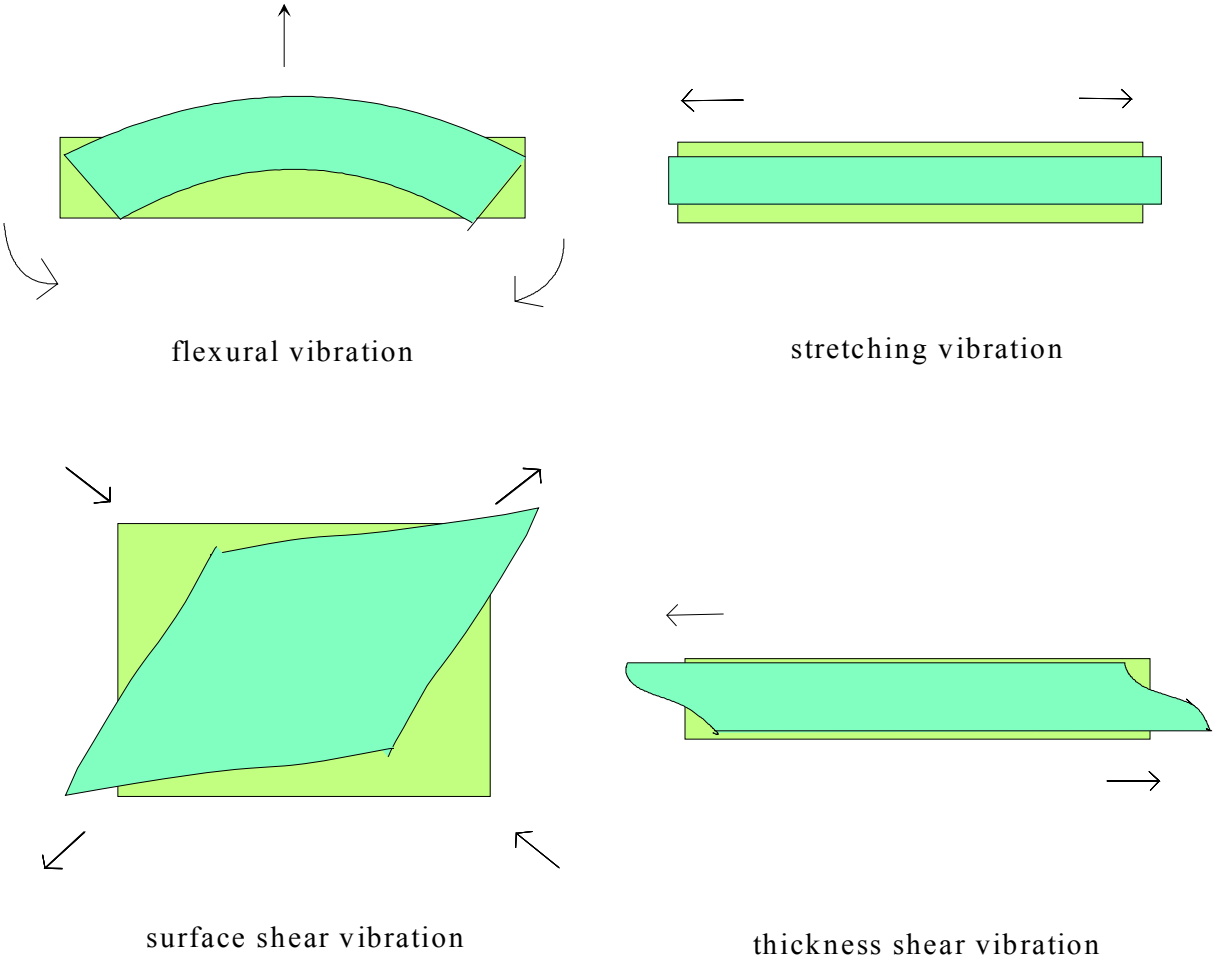


Fig. 2.4 Four different oscillation modes of the quartz crystal

The thickness of quartz plate could not be less than 0,08 mm, otherwise it will be mechanical instable. So the maximal resonance frequency is about 50 MHz. QCM applied in this work has a resonance frequency of 10 MHz.

One of the many factors that affect the resonance frequency is temperature. The temperature dependence of resonance frequency is expressed in the following equation:

$$f = f_0 \left(1 + \alpha(T-T_0) + \beta(T-T_0)^2 + \gamma(T-T_0)^3\right)$$

f_0 : resonance frequency by standard temperature T_0

f: resonance frequency by working temperature T

α, β, γ: temperature coefficient

2.4 Crystal Oscillator in an oscillating circuit

It is proven to be convenient to use an equivalent circuit for the calculation of the crystal oscillator in an oscillating circuit.

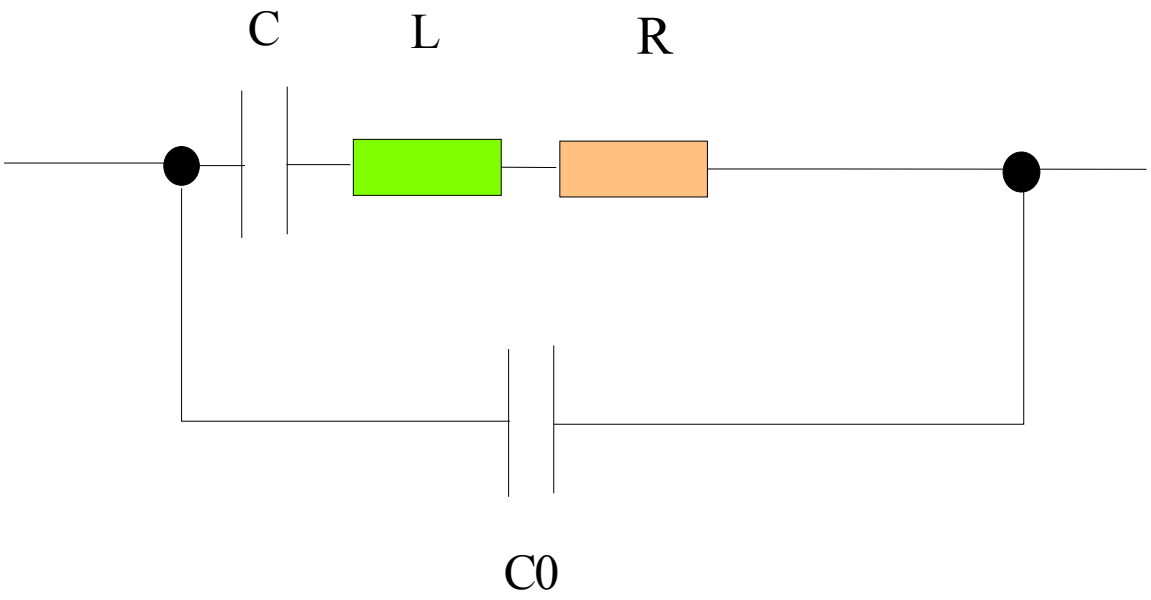


Fig. 2.5 An equivalent circuit of the crystal oscillator

L: inductivity	mechanically vibrating mass
C: dynamic capacitance	elastic behavior of the resonator
R: resonance	dynamic vibration losses
C0: static capacitance	capacity between the two electrodes

With the neglect of the resistance there are two eigenfrequency resulted for the quartz crystal plate: series resonance frequency

$$f_s = \frac{1}{2\pi\sqrt{LC}}$$

and, parallel resonance frequency

$$f_p = \frac{1}{2\pi\sqrt{LC}}\sqrt{1+\frac{C}{C0}}$$

In Fig.2.6 the series resonance and the parallel resonance are displayed and also the secondary resonances, which are caused by different oscillation modes.

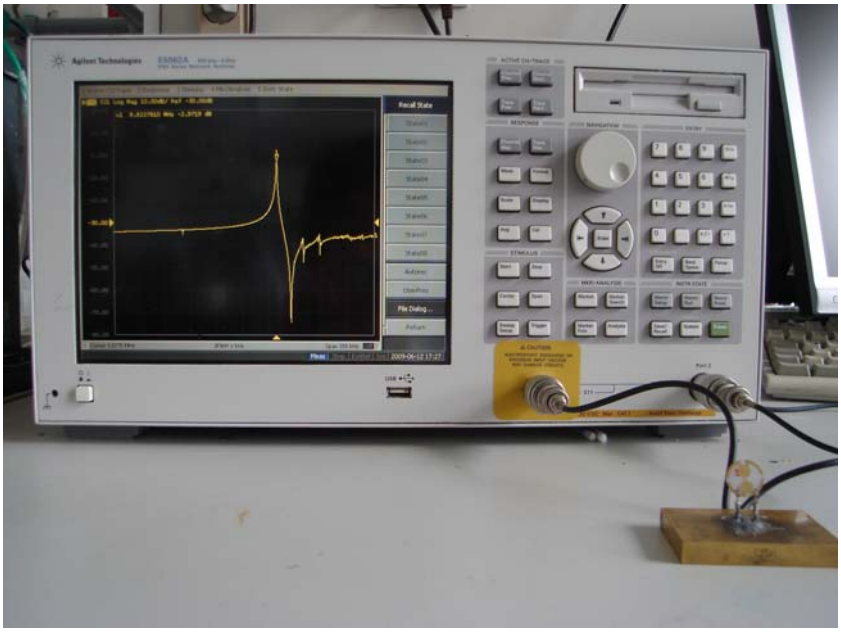


Fig. 2.6 Damping and phase spectrum of a 10 MHz-QCM

2.5 QCM as mass sensitive device

The resonance frequency of the quartz crystal plate is dependent on its thickness. The sensitive layer of a mass Δm, which is deposited on the electrodes of the quartz , bring a thickness of Δd to the quartz crystal plate. Thus this sensitive layer leads to a change of resonance frequency of the quartz. Quartz with electrodes can then be applied as a mass sensitive device[22,23,24] .

$$\frac{\Delta f}{f_0} = \frac{-\Delta d}{d} = \frac{-\Delta m}{\rho d A} \quad \text{.....(2)}$$

Δf	change of resonance frequency
f_0	fundamental frequency of quartz
Δm	change of deposited mass on electrodes
ρ	density of the sensitive layer
d	thickness of the quartz ($d_0+\Delta d$)
A	area of the electrode

The equation (1), which was mentioned in 2.3, is inserted in the above equation (2), the Sauerbrey equation is then derived:

$$\Delta f = \frac{-2 f_0^2 \Delta m}{\rho C A}$$

Δ f is proportional to ($-f_0^2 \Delta$ m). So there is a linear relation between the change of the resonance frequency and the change of the added mass and also between the change of the resonance frequency and the quadrate of the fundamental resonance frequency. The mass sensitivity can be greatly improved by the advancement of the fundamental frequency of quartz crystal.

QCM used in this work has a fundamental resonance frequency of 10.00 MHz. Its sensitivity is calculated:

$$\Delta f / \Delta m = -0.95 \text{ Hz/ng}$$

2.6 QCM in Liquid Phase

In this work QCM was applied in liquid phase, where the density and the viscosity of the liquid have great influences on the resonance frequency and the damping of QCM. Hence, the model of oscillating circuit that is applied in gas phase (2.4) is not valid for liquid phase any more.

The liquid, which adheres to the quartz plate, also oscillates. This oscillation of the liquid causes a fluctuation in the medium and damps the oscillation of quartz. In other words, the oscillation will propagate in the liquid phase. The propagation of the oscillation in the medium is greatly dependent on the viscosity of the medium. When the liquid phase is water, the length of propagation is about 0.25 μm.

It is known that in the case of gas phase if the polymer layer is inelastic it oscillates with the same amplitude as the quartz and it leads to a decrease in resonance frequency of QCM. And in the case of liquid phase, the situation is more complicated. The resonance frequency and the damping of QCM in liquid phase can be considerably affected by many factors. Propagation of the oscillation is an important factor among them. The propagation of the oscillation causes the increase of the thickness, which induces a decrease of the resonance frequency.

$$\Delta\nu = -2.26*10^{-6}(\nu_0^2\Delta m+\nu_0^{3/2}\sqrt{\rho_l \Delta \eta_l})$$

η_l : viscosity of the liquid
ρ_l : density of the liquid
ν_0 : eigenfrequency of the quartz in the air

Other factors by liquid phase, which affect the measurement of QCM, e.g. the swelling of the polymer layer caused by the contact with the liquid, lead to decrease of the resonance frequency.

An equivalent circuit of QCM[27], where mass and liquid are loaded, is shown in Fig.2.8 L_{liq} represents the oscillating part of the liquid, L_m represents the oscillating mass, R_{liq} represents the increase of the damping due to the viscosity of the liquid. R_p results from the quartz.

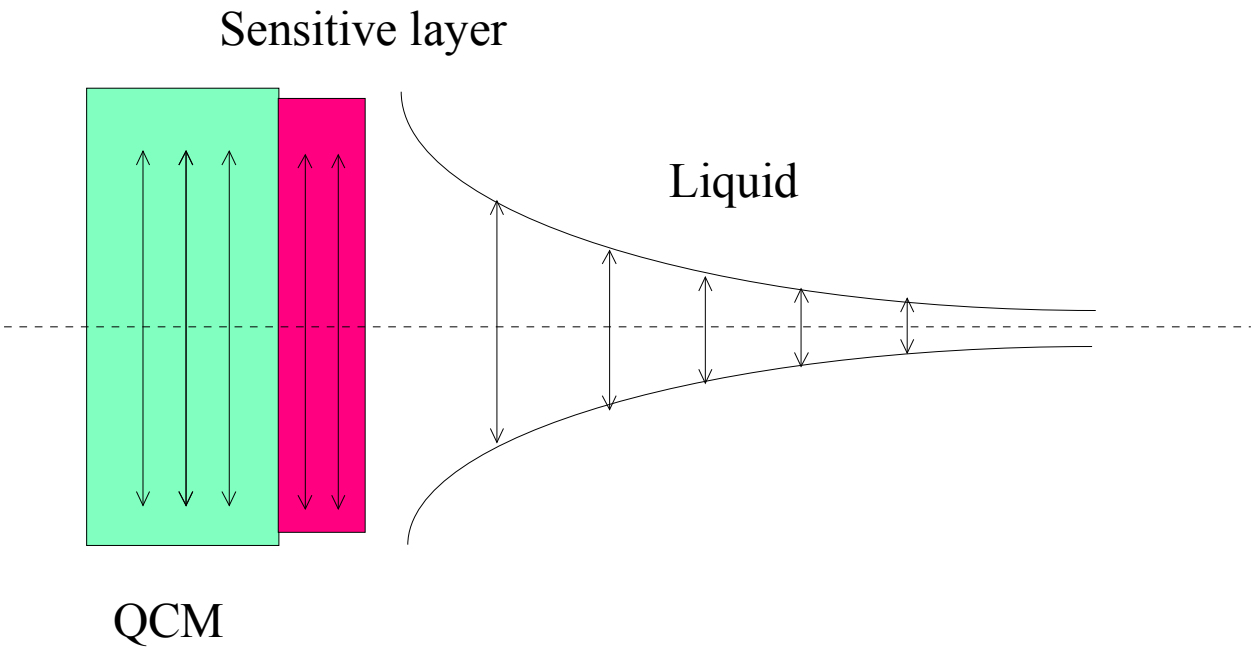


Fig 2.7 Propagation of oscillation of QCM in a viscous medium

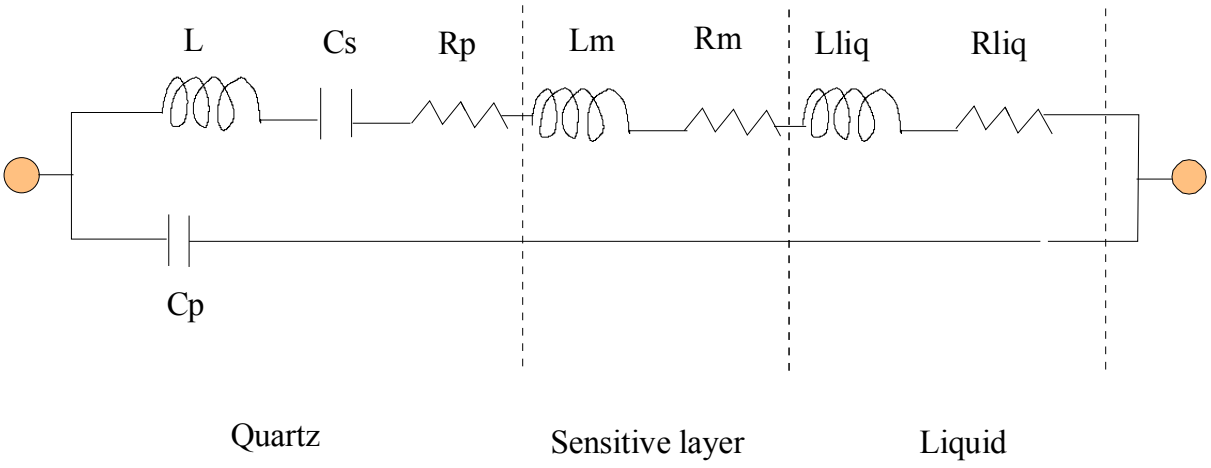


Fig. 2.8 An equivalent circuit for QCM loaded of mass in liquid phase

2.7 Manufacturing of QCM

QCM in this work was a α-quartz crystal plate (AT cutting) coated with gold electrodes. The gold electrodes were deposited on the quartz crystal plate with screen printing technique. It is consisted of screen manufacture and printing procedure.

For the screen manufacture the desired shape of the electrodes was made in a sieve by optical lithographical procedure. It made up of following steps: firstly, a UV sensitive polymer (Azocol Poly plus S of KIWO) was plastered evenly on the silk filter, which was already been stuck on a metal framework. The silk filter was then kept in the dark for 30 minutes. Later the desired area of the silk filter was exposed under the UV lamp for 30 seconds, immediately after, the not-exposed part was washed by hot water. The finished screen was finally dried in the air.

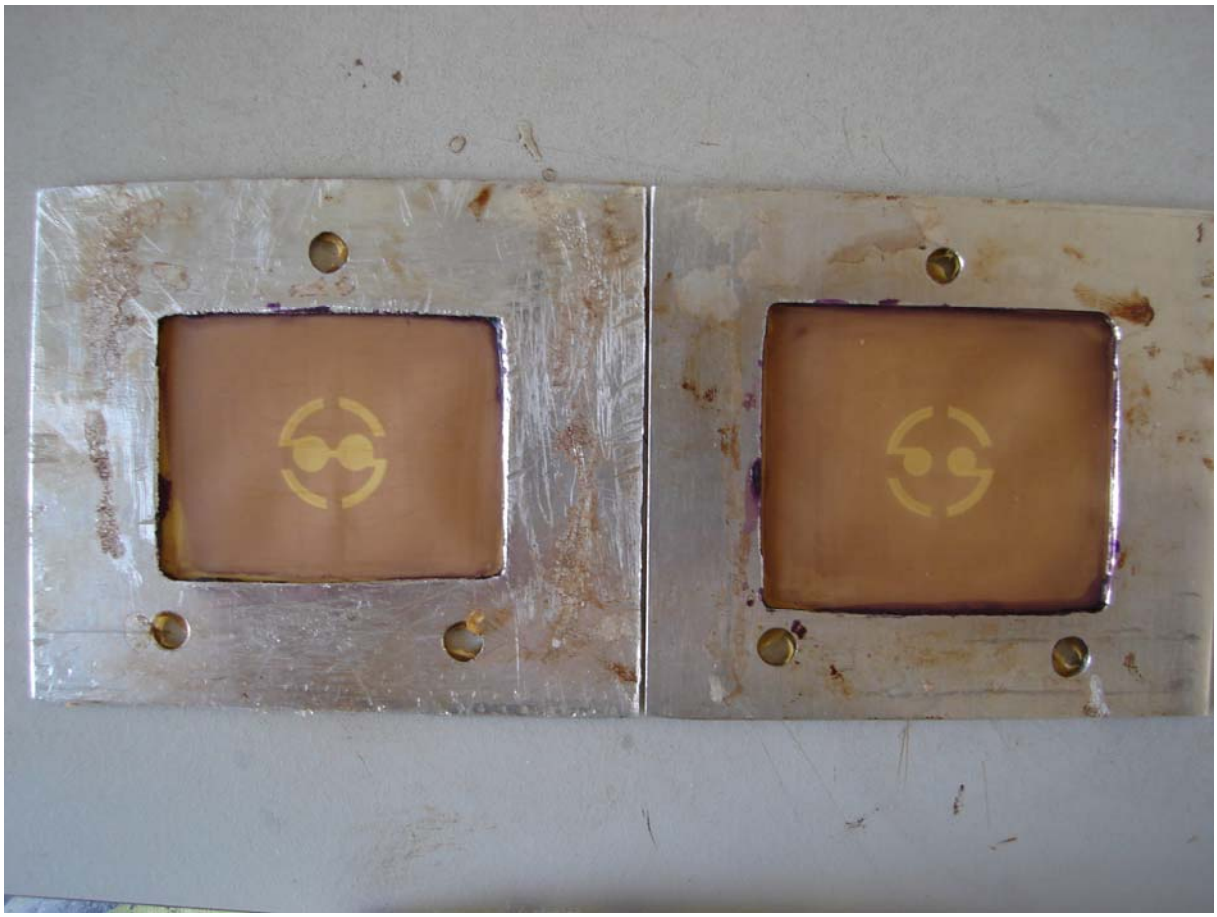


Fig 2.9 Sieves showing the geometry of electrodes**.**

For the printing procedure the quartz crystal plate and the sieve were adequately positioned by the application of vacuum. Then the gold paste was spread with a blade on the sieve finely in order to get a very thin layer of gold on the sieve. For the last step, the quartz was baked in the oven by 400°C for 2 hours. During time the organic components of the gold paste were burn out totally, only the gold electrodes were left on the quartz crystal plate.

The same procedure was applied for the electrodes on the other side of quartz. It is worth noting that the temperature of the oven could not be too high. With a temperature of higher than 500°C, the structure of the quartz changes, which lead to a change of resonance frequency.

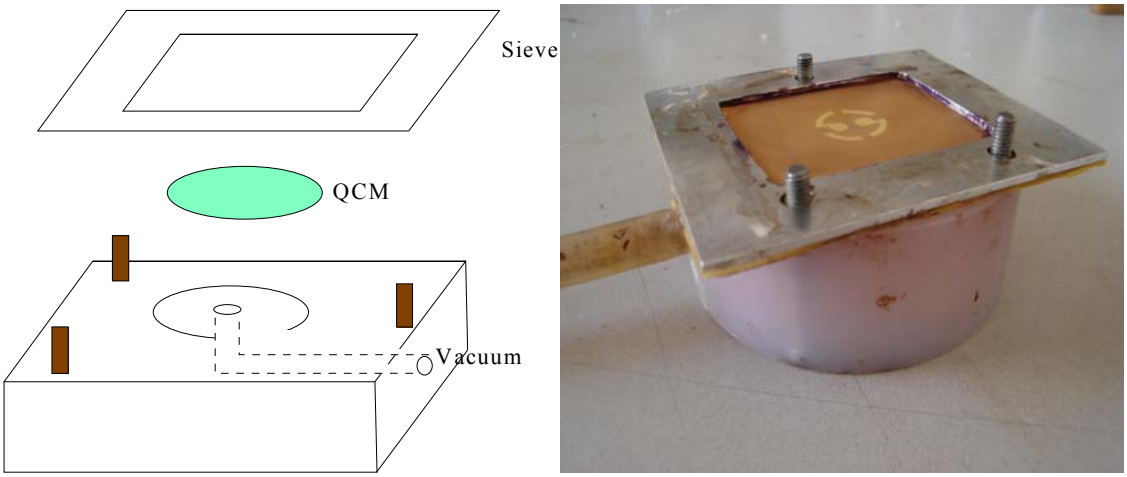


Fig 2.10 Screen printing technique used to deposit the gold electrodes.

The thickness of the gold electrodes can be estimated from the decrease of the resonance frequency according to the following equation:

$$d = \frac{\Delta m}{\rho_{Au} A} = -4.42*10^{-9} \left[\frac{g}{Hz\, cm^2} \right] \frac{\Delta f}{\rho_{Au}}$$

Due to the facts that the oscillation of quartz is only limited to the electrode area (Fig 2.11) and the field of quartz by each electrode oscillates with each individual resonance frequency, more than one electrode can be deposited on the quartz. In this work, two electrodes were deposited on the quartz. One is working electrode and the other one reference electrode. The typical data of QCM applied in this work are listed in Tab 2.1.

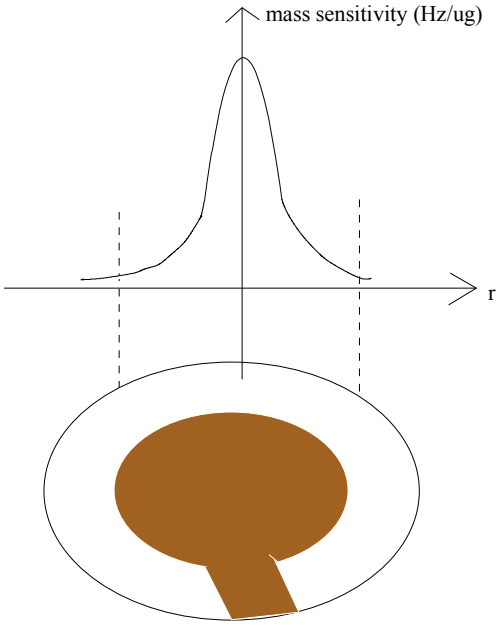


Fig 2.11 Mass sensitivity in the field of electrode.

Tab 2.1 Table of typical data of QCM applied in this work

thickness of quartz	0.167 mm
resolution	0.1 Hz
sensitivity	951 Hz/μg
detection limit	0.6 ng
effect of thickness of layer	40 nm/kHz
resonance frequency	10 MHz

2.8 Oscillating Circuit

Quartz was setup in an oscillating circuit in order to be in resonance of oscillation. In this work an oscillation circuit soldered in SMD architecture was applied.

The oscillating circuit was made up of three parts: a power supply, an oscillator circuit and a switch. The details are not described. Diagrams of power supply and oscillator circuit are shown as following:

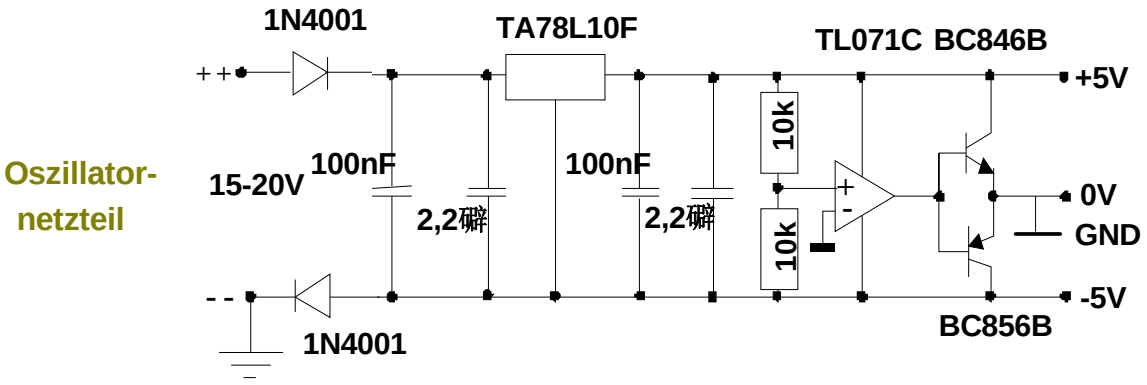


Fig. 2.12 Diagram of power supply

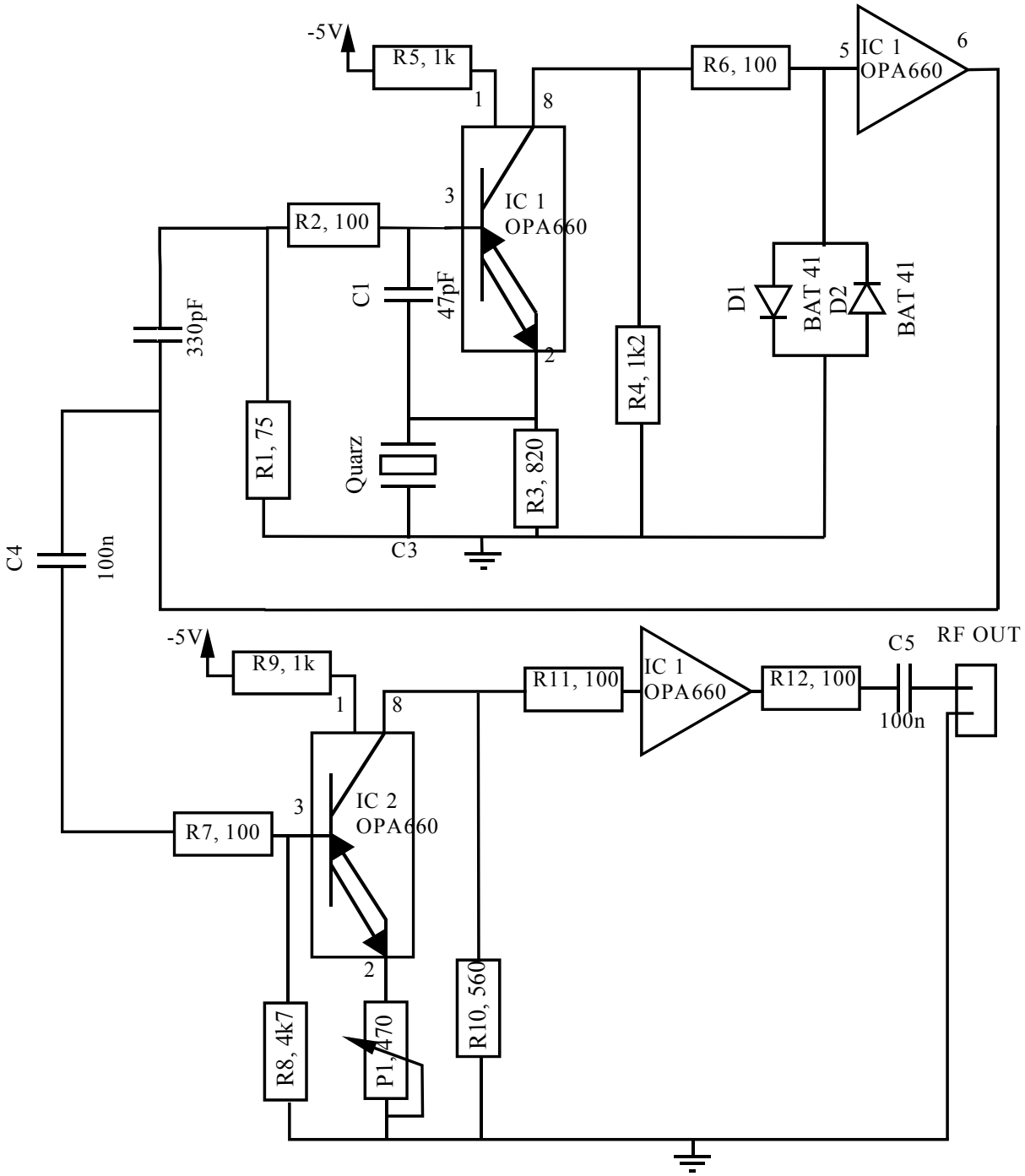


Fig. 2.13 Diagram of oscillator circuit

Chapter 3 The Strategy of Receptor

The quality and utilizability of chemical sensors are determined primarily by the properties of the coatings. e.g. the covalent and non-covalent interactions between the receptor and the analyte; the robustness of the receptor to the physical or chemical disturbance; the porosity of the receptor, which determines the possibility of diffusion of analytes and the dynamics of the responding behaviour. Thus, the synthesis of layers is essential to the chemical sensors.

There are many strategies for the manufacture of receptors, which are listed in Tab 3.1. Molecular imprinted polymer will be discussed in more detail.

Tab 3.1 Strategies of Receptor

Interaction	Grade of Recognition	Selectivity	Assembly
Ad- and Absorption on Polymer layer	low	low	purchasable
Host-Guest Complex	low	low	synthesis demanded
Molecular Imprinted Polymer	high	high	on-chip

3.1 Molecular Imprinted Polymer

3.1.1 History

In nature there are numerous examples of effective molecular recognition. Interactions between enzymes and substrates or antibodies and antigens are highly selective interactions. Emil Fischer is the first one who proposed the

concept of lock-key-principle[25], which is the basic principle for the molecular recognition with high sensitivity.

The lock-key-principle has been widely used in chemistry. For example, the cavity compounds[26,27,28,29,30,31] such as crown ether, cyclodextrine, calixarenen and cyclophane. They are with high sensitivities but generally cost much. So another approach which is based on the lock-key concept has been investigated, so called molecular imprinting. The first example of molecular imprinting is attributed by M.V.Polyakov in 1931[32] who studied the polymerization of sodium silicate with ammonium carbonate. And this material was at the first time used for separation of dyes in 1949. The first molecular imprinted polymer for protein was developed by Mosbach in 1985 using silane monomers for molecular imprinting and enzymes entrapment in polysiloxane coated porous silica.

Currently, molecularly imprinted materials have already been applied in many fields. They are often used as selective supports in liquid chromatography, solid phase extraction, capillary electrophoresis and chemical sensors. These materials offer the advantage of being relatively easy and inexpensive to prepare and also of being very stable.

3.1.2 Imprinting Process

There are two distinct imprinting approaches[33] which one can follow. One approach, which has been developed primarily by Wulff and co-workers, is the so-called covalent or pre-organised approach in which the interactions between the analyte and the functional monomers in the pre- polymerisation assembly are covalent in nature. A polymerisable derivative of the analyte is prepared by forming covalent bonds with suitable monomers and this is subsequently copolymerised with a cross linking monomer. Extraction of the analyte from the network requires this covalent bonds to be cleaved, and they are reformed upon subsequent analyte bonding.

Another approach has been developed by Mosbach and co-workers who rely on the formation of a pre-polymerisation complex between functional monomers and the template through non-covalent bonds such as ion pairs, hydrogen bonds or π-π interactions. The template can be removed simply by solvent extraction. Rebinding of the analyte to the polymer is also non-covalent in nature.

The covalent and the non-covalent imprinting approaches each have their own merits and drawbacks. The covalent approach may yield binding sites which are better defined, is not always easy or practical. The non-covalent approach, on the other hand, requires no chemical derivatization step, and is therefore much more general in nature and applicable to a considerably wider range of analytes. Although the binding sites may be not heterogeneous, rebinding kinetics are more favourable. Indeed, because of its inherent simplicity, the non-covalent approach tends to be the method of choice.

Imprinting process[34,35] is generally consisted of four steps: 1) the target molecule and polymerisable solution (contains functional monomers) are mixed together 2) a complex between a functional monomer and the template (target molecule) is formed 3) Polymerisation: the functional monomers are then polymerized to form an imprinted matrix, so called molecular imprinted polymer. Generally crosslinker, initiator, porogen are added to this step 4) At last the template molecule is removed from the MIP leaving behind a cavity that has a complementary size and shape of the template molecule. So the leaving cavity in MIP can work as a sensitive binding site for a template molecule. The procedure of the manufacture of molecular imprinted polymer (non-covalent) is shown in Fig 3.1.

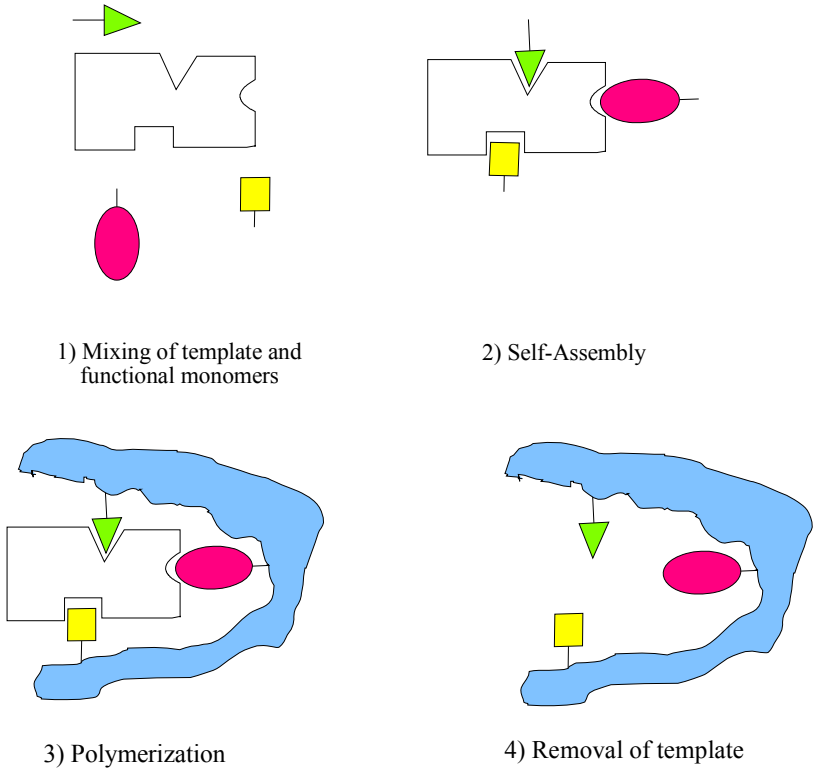


Fig 3.1 Procedure of Molecular Imprinted Polymer

3.2 Polyurethane

Polyurethane[36,37,38,39] is a polymer containing the urethane linkage, -RNHCOOR'- and produced by the polyaddition reaction of a monomer containing at least two isocyanate functional group (R-(N=C=O)n $\geq$ 2)with another monomer containing at least two hydroxyl group (R'-(OH)n $\geq$ 2.) in the presence of a catalyst and other additives. Polyurethane is favourable for wetting due to its hydrophilicity.

The physical and chemical characters of the monomers influence the final physical and chemical properties of the polyurethane. In other words, polyurethane with different properties can be achieved by using different monomers. Force field studies can reveal that the types and amounts of monomers and crosslinkers determine the size and shape of the hollows in molecular imprinted polymer and the geometry of the template determines the selectivity of layer.

Since in the three analytes there are no pronounced functional groups only non-covalent interactions exist between the analytes and the monomers during the polymerization. It is revealed that the week non-covalent interactions, such as, hydrogen bonds, van der Waals interaction, are sufficient to induce specific orientation of the templates during the process of polymerization, which leads to a specific cavities for analytes.

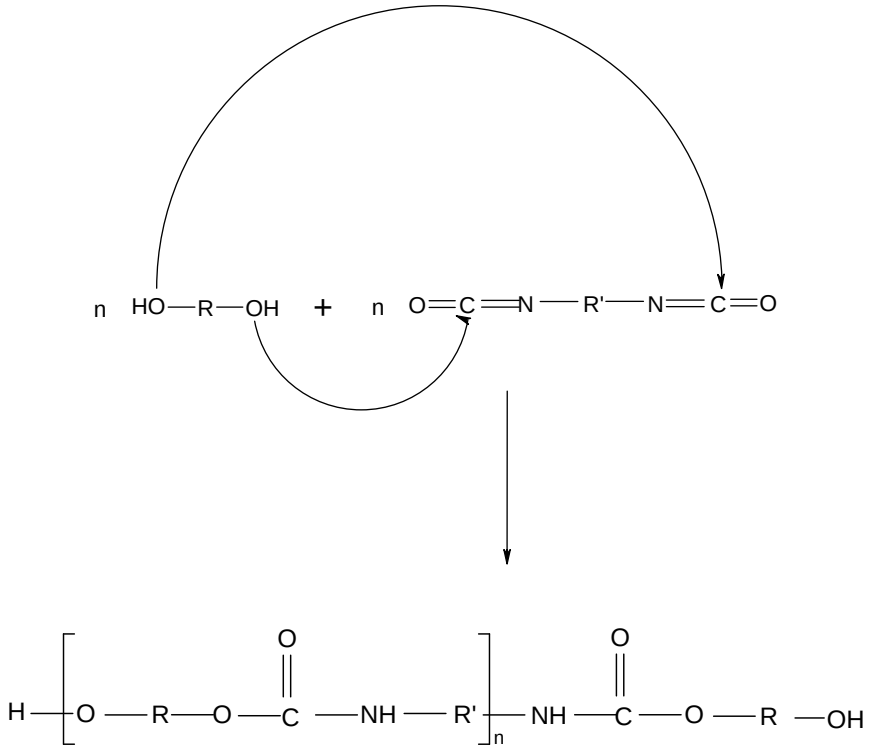
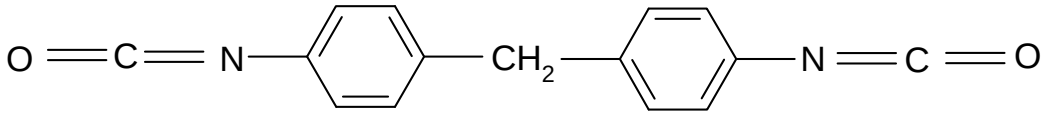
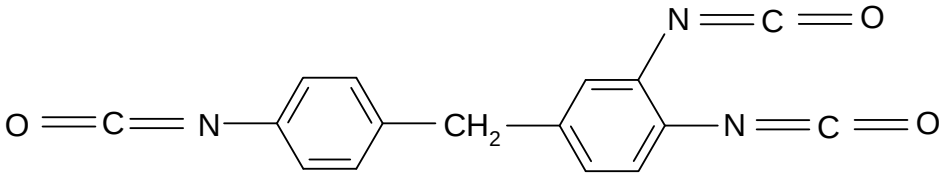


Fig 3.2 Formation of polyurethane

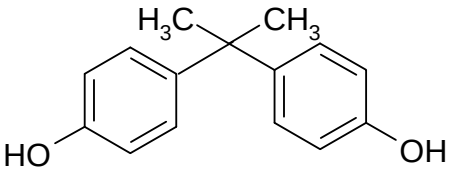
In this work, all of the three analytes contain benzene ring. Aromatic monomeric compounds were chosen to synthesize molecular imprinted polyurethanes in order to provide an good interaction between the analytes and the monomers. Mixture of diphenylmethane diisocyanate and diphenylmethane triisocyanate(30%), bisphenol A as diol and phloroglucinol as crosslinker were applied.



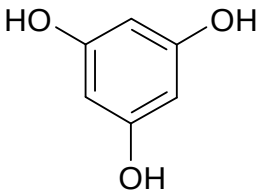
diphenylmethane diisocyanate



diphenylmethane triisocyanate



bisphenol A



phloroglucinol

Fig 3.3 Structures of Monomers of Polyurethane

In the process of manufacture, water is strictly avoided. Water reacts with isocyanate to form foam due to the produced carbon dioxide.

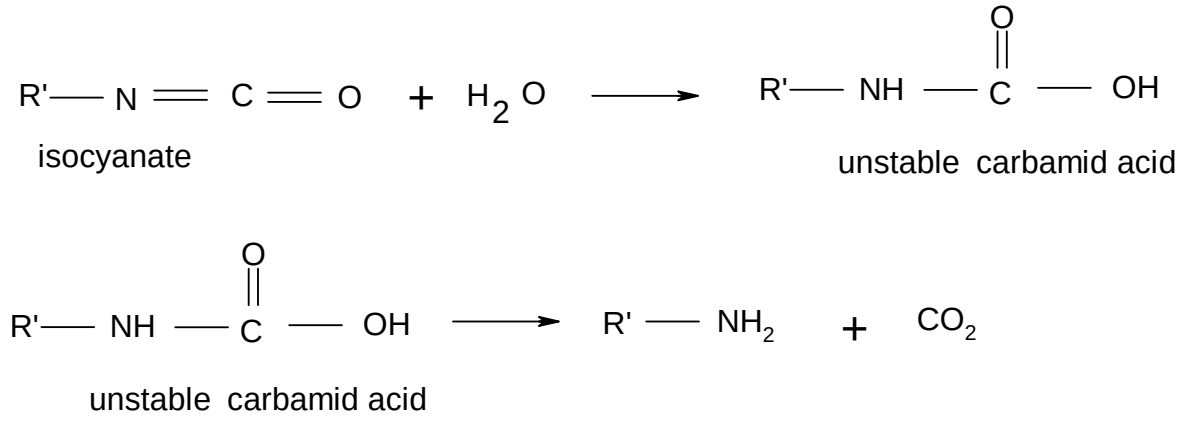


Fig 3.4 Reaction of isocyanate and water

The monomers and 5% template were weighed in a 2 ml eppendorf tube, 200µl THF was added as solvent and 10 µl pyridine as catalyst. The mixture was heated in water bath by 70 °C till the gel point arrived. It was then diluted with THF to the desired concentration for the coating.

Table 3.2 Amounts of Monomers for Polyurethane

Monomers	Amounts
diphenylmethane diisocyanate (MDI)	80,3 mg
bisphenol A	95,6 mg
phloroglucin	23,9 mg
template	10 mg
pyridine	10 µl

3.3 Poly-4-vinylphenol

In this work, poly-4-vinylphenol[40] polymer was also applied. For the process of manufacture 4.4 mg phluoroglucinol and 10% template were added to the mixture of 41 mg diphenylether-4,4'-diisocyanate and 59 mg poly-4-vinylphenol. Then it was dissolved in 200 µl THF and heated by 70°C until gel point arrived. This poly-4-vinylphenol solution was diluted with THF to the desired concentration for the coating.

Table 3.3 Amounts of Monomers for poly-4-vinylphenol

Monomers	Amounts
diphenylmethane diisocyanate (MDI)	41mg
phloroglucin	4,4 mg
Poly-4-vinylphenol	59 mg
template	10 mg

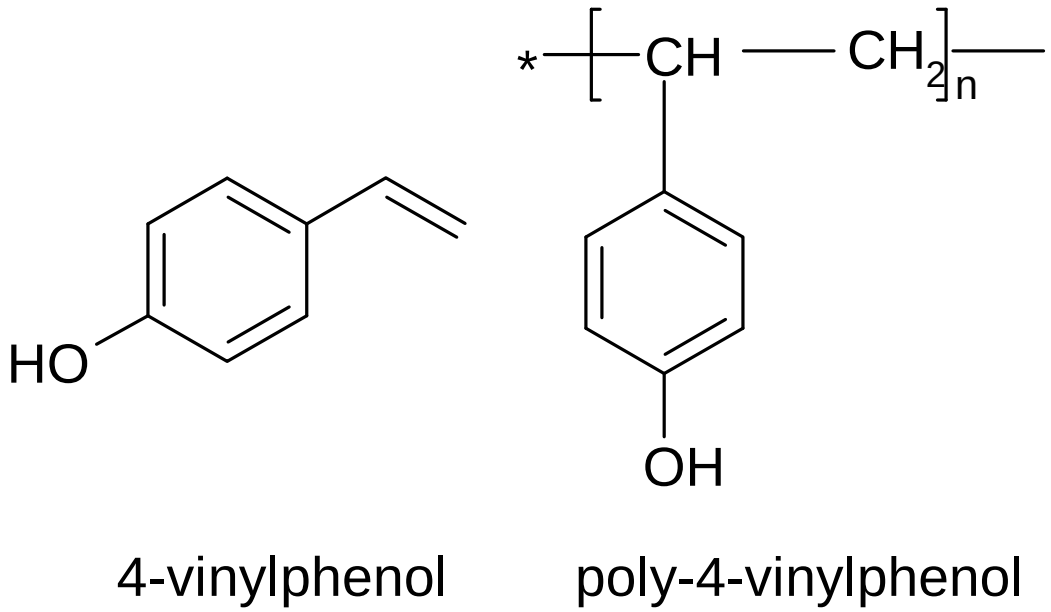


Fig 3.5 Poly-4-vinylphenol

3.4 Spin-coating

Spin coating is a procedure that is applied to coat a thin, flat film of polymers onto the electrode of QCM. An excess amount of a copolymer solution is applied to electrode of QCM, which is fixed in a spinner. The spinner rotates at a high rate continuously until the desired thickness of the polymer film is achieved.

The solvent of the polymer solution is usually volatile so it evaporates during the spinning. Films with different thicknesses are achieved using

polymer solutions with different concentrations and different spinning rate. Thin films with thicknesses below 10 nm are possible by spin-coating process.

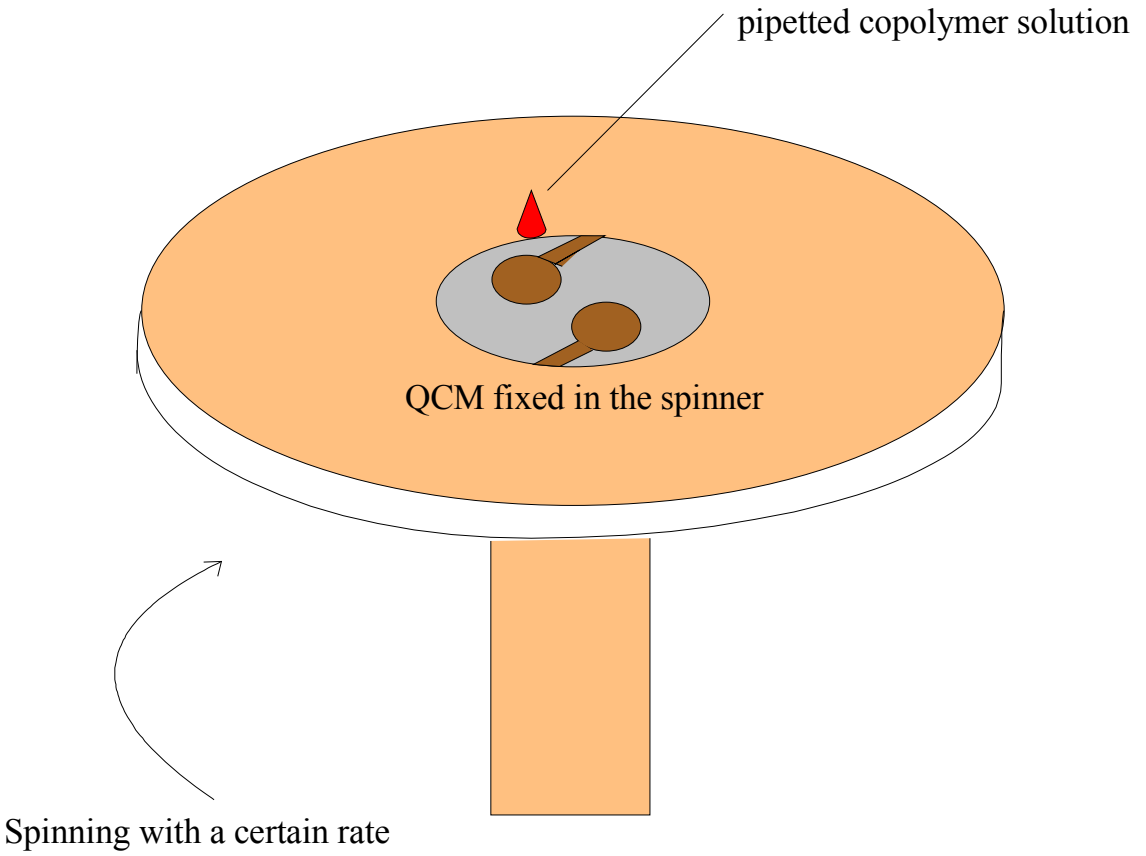


Fig 3.6 Spin-coating on QCM

Chapter 4 Experiment

4.1 Introduction of Analytes

In this work, four precursors of drugs were planned to analyse: phenylacetone, isosafrole, PMK and ephedrine. The first three substances have the related structures and they are the precursors for the group of amphetamine. Ephedrine is self a member of amphetamine and also applied as a precursor for other drugs. They are introduced in detail in the following sections.

4.1.1 Ephedrine

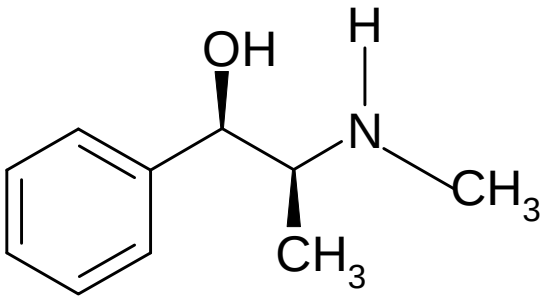
Ephedrine is a sympathomimetic amine commonly used as a stimulant, appetite suppressant, concentration aid, decongestant, and to treat hypotension associated with anaesthesia.[41] It is thought to be a member of the group of amphetamine.

In traditional Chinese medicines, the herb má huáng (麻黄, Ephedra sinica) contains ephedrine and pseudoephedrine as its principal active constituents. The production of ephedrine in China has become a multi-million dollar export industry.[42] Since ephedrine is the precursor for N-Methylamphetamin, which is strictly controlled in Europe, the delivery of ephedrine is in Europe limited.

Chemically ephedrine exhibits optical isomerism and has two chiral centers. The structure of one diastereomer is shown below:

(1*R*,2*S*)-2-(methylamino)-1-phenylpropan-1-ol is one diastereomer of ephedrine, which is marketed widely. And in this work 98% (1*R*,2*S*)-(-)-

ephedrine was applied. It was purchased from Sigma-Aldrich Logistik GmgH and used as received.



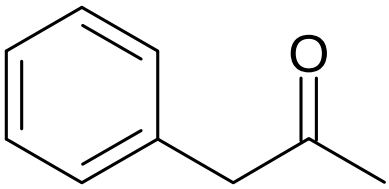
IUPAC name of ephedrine:
(1R,2S)-2-(methylamino)-1-phenylpropan-1-ol

Tab 4.1 Chemical properties of ephedrine(1R,2S)

Molecular formula	$C_{10}H_{15}NO$
Molar mass(g/mol)	165.23
State	solid
Melting point(°C)	36
Boiling point(°C) by 760mmHg	255
PKs	10.252
Solubility in Water by 20°C (g/L)	50

4.1.2 Phenylacetone

Phenylacetone is an organic compound and sometimes abbreviated as P2P. It is a clear oil, which has a strong odor. Normally it is used in the manufacture of amphetamine and methamphetamine.[43] Due to the illicit uses in clandestine chemistry, it is a controlled substance. The structure of phenylacetone is shown below:



Systematic (IUPAC) name: 1-phenylpropan-2-one

Tab 4.2 Chemical properties of phenylacetone

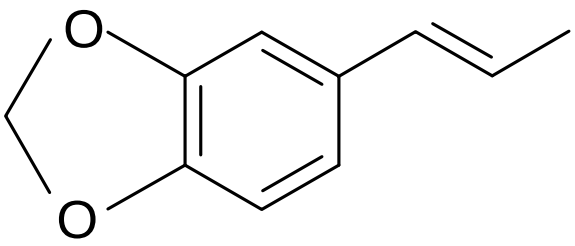
Molecular formula	$C_9H_{10}O$
Molar mass(g/mol)	134.2
State	liquid
Melting point(°C)	-15
Boiling point(°C)	216
Density(g/mL) by 20°C	1.003
Solubility in Water by 20°C (g/L)	5.2

In this work, phenylacetone was purchased from Sigma-Aldrich Logistik GmgH in the highest available purity and was used as received.

4.1.3 Isosafrole

Isosafrole is an aromatic liquid and commonly obtained by isomerizing the plant oil safrole, which is typically extracted from the root-bark or the fruit of sassafras plants. It is the precursor of Piperoylmethylketone. Due to the illicit uses in clandestine chemistry, it is a controlled substance.

There are two isomers: cis-isosafrole and trans-isosafrole. The structure of trans-isosafrole is shown below:



trans- isosafrole
Systematic (IUPAC) name:

(*E*)-5-(Prop-1-enyl)benzo[*d*][1,3]dioxole

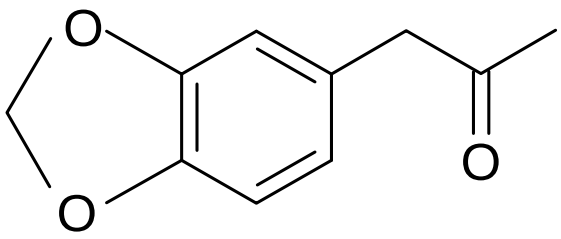
Tab 4.3 Chemical properties of isosafrole(97% cis/trans-mixture)

Molecular formula	C10H10O2
Molar mass (g/mol)	162.188
State	liquid
Flash point (°C)	113
Boiling point (°C)	253
Density (g/mL) by 20°C	1.116
Water solubility (g/L)	0.045

In this work, 97% cis/trans-mixture isosafrole was purchased from Sigma-Aldrich Logistik GmgH and used as received.

4.1.4 Piperonylmethylketone

Piperoylmethylketone is another name of 3, 4-Methylendioxyphenylpropan-2-on and abbreviated as PMK or MDP2P. MDP2P is used as the precursor of MDMA (commonly known as 'Ecstasy'). Its chemical structure is shown below:



Systematic (IUPAC) name:
3,4-methylenedioxy-phenyl-2-propanone

Tab 4.4 Chemical properties of MDP2P

Molecular formula	C10H10O3
Molar mass(g/mol)	178.185
State	liquid
Melting point(°C)	68.69
Boiling point(°C)	275.9
Density(g/mL) by 20°C	1.211
Water solubility(g/L)	2,7

In this work, MDP2P has been synthesized from isosafrole. The synthesis of MDP2P is shown in the next section.

4.2 Synthesis of MDP2P

4.2.1 Route of Synthesis

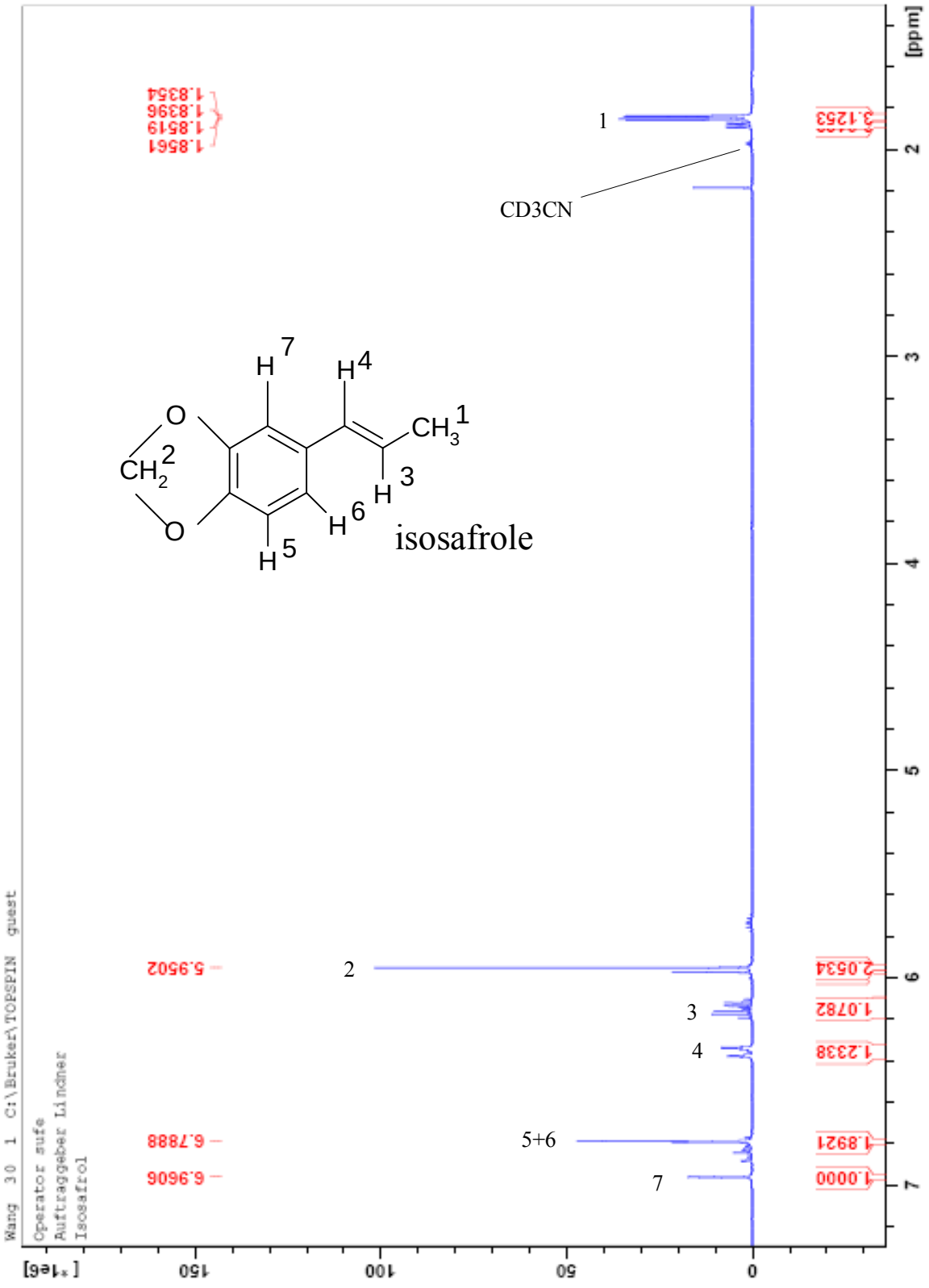
MDP2P is most commonly synthesized by oxidizing isosafrole using the Wacker oxidation[44] or peroxyacid oxidation[45]. In this work peroxyacid oxidation was applied. The route of synthesis is described as following:

29 g of hydrogen peroxide(35%), 136 g of formic acid(88%) and 20,5 g of water are mixed together and are well stirred. A solution of 32,4 g isosafrole in 120 ml acetone is added dropwise to the mixture and with cooling to keep the mixture from exceeding 40°C. After stirring for 16h at room temperature, the mixture was concentrated under vacuum without heating. The crude product was dissolved in 55ml of methyl alcohol, treated with 240g of 15% sulfuric acid and heated for 3h. After cooling, the reaction mixture was extracted with diethyl ether. Organic layers were washed with water and then with dilute sodium hydroxide. Solvent was removed by rotary evaporation. The residue was distilled under vacuum to PMK as pale yellow oil. At last NMR spectroscopy was done to measure the purity of PMK. NMR spectrum is shown in the following page.

4.2.2 NMR Spectrums of Isosafrole and PMK

Spectra of isosafrole and PMK were measured due to TMS (at zero) and CD_3CN was the solvent. The spectra of isosafrole and of PMK were compared with the spectra of them from the NMR spectrum data bank. Therefore, signals in the spectra could be marked with corresponding H atoms in the molecules. After comparing the spectrum of isosafrole with the spectrum of PMK the purity of PMK could be estimated.

By circa 7ppm there was a typical signal of isosafrole, which showed also in the spectrum of PMK but with a 80% smaller intensity. It could be read that the most of isosafrole has reacted into PMK but there was still approximately 20% of isosafrole, which has not reacted, in the end-product. So it is estimated that the purity of PMK is less than 80%. Due to the low purity of PMK, the analysis of PMK has not been done in this work.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1.8519
1.8561
1
3.1253
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H 7
H 4
O
CH2 2
CH3 1
H 3
O
H 6
H 5
isosafrole
5.9502
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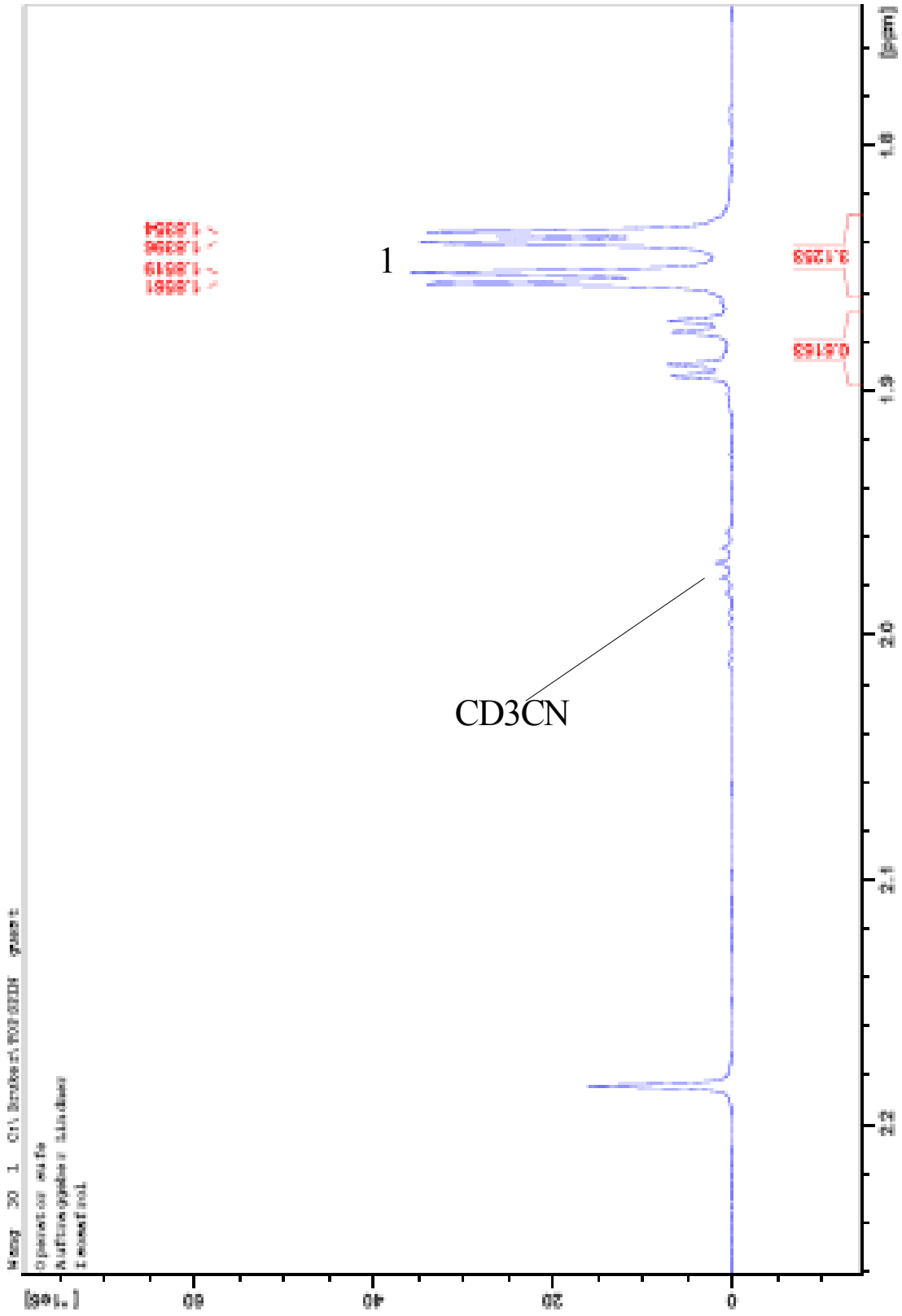
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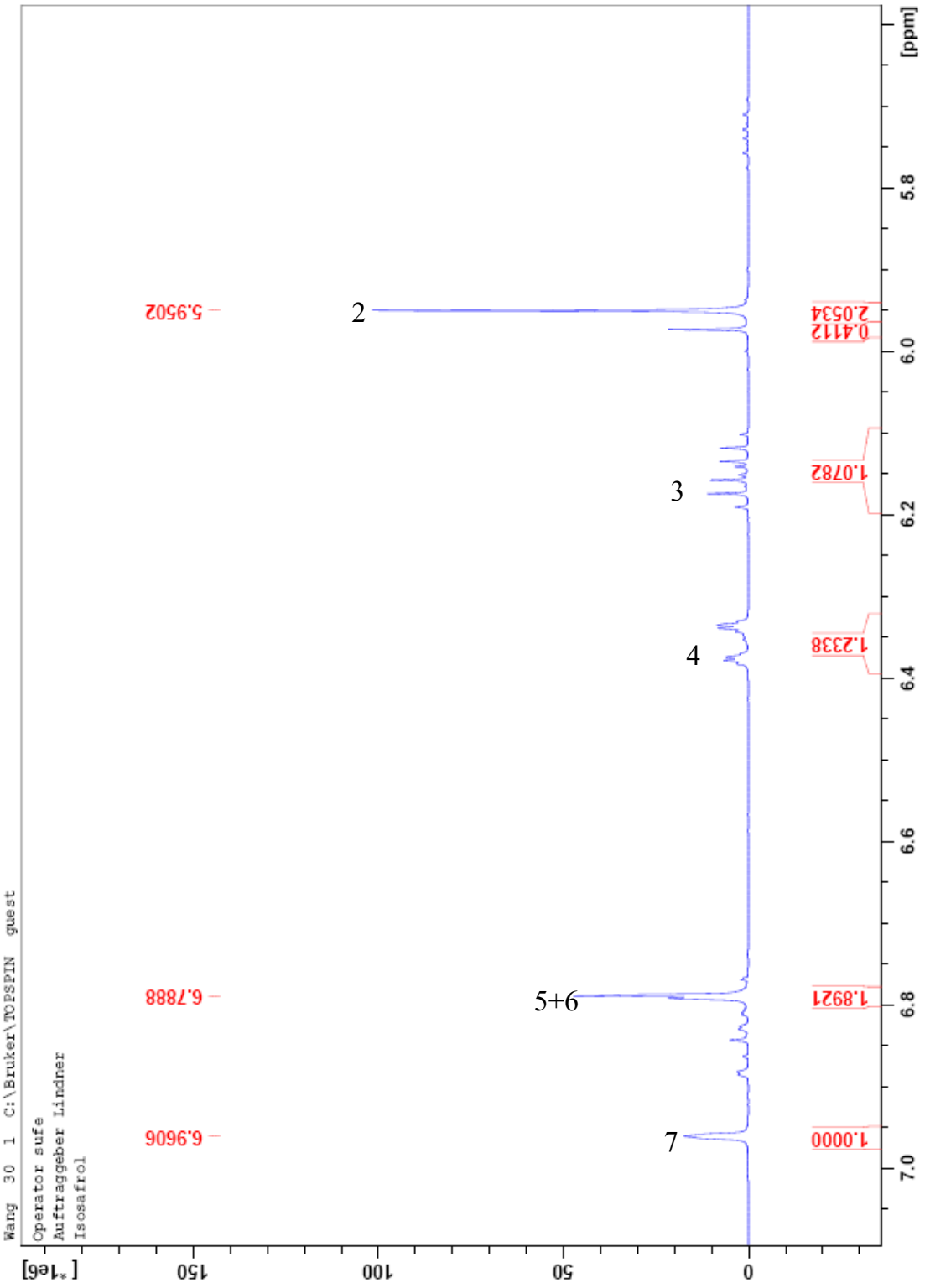
CD3CN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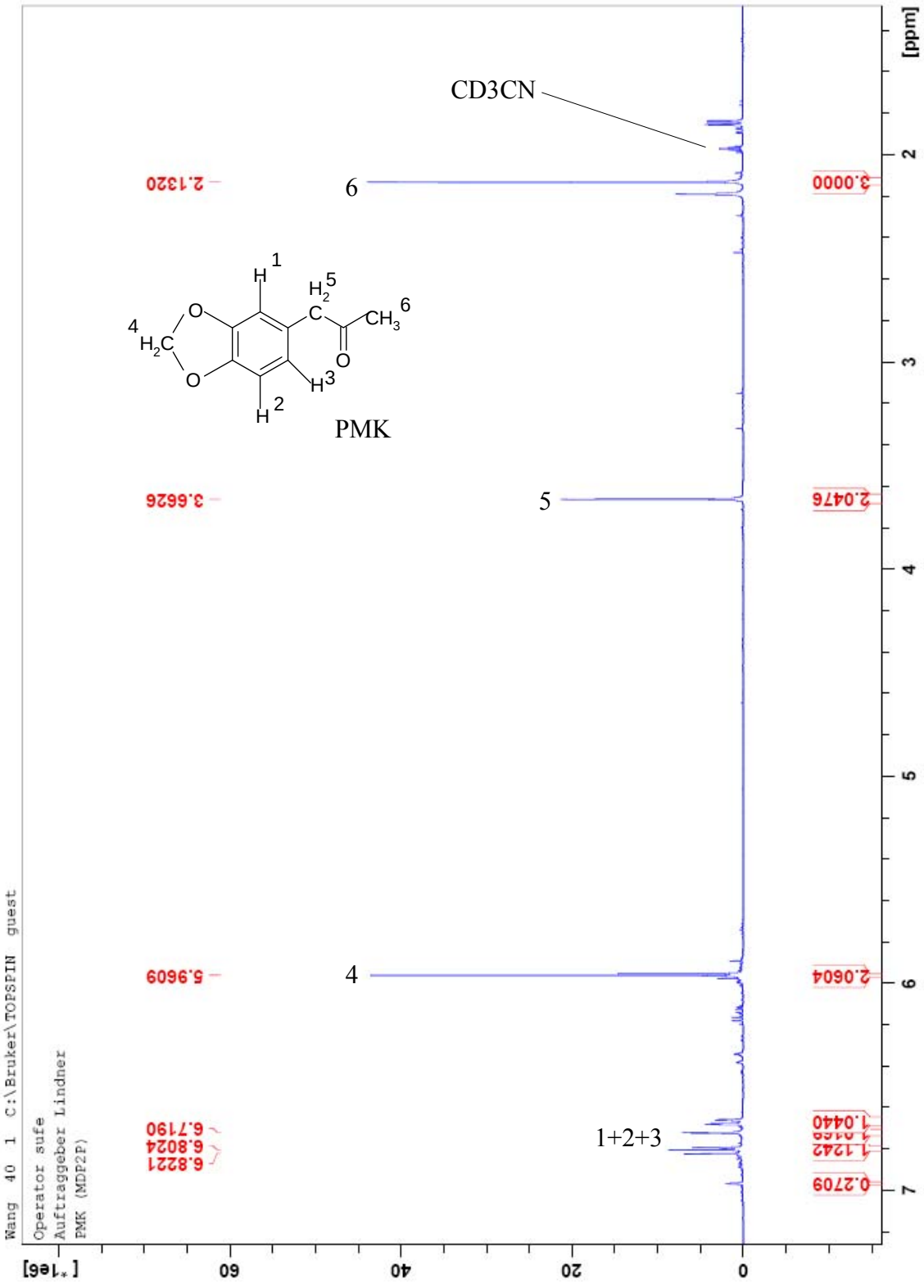
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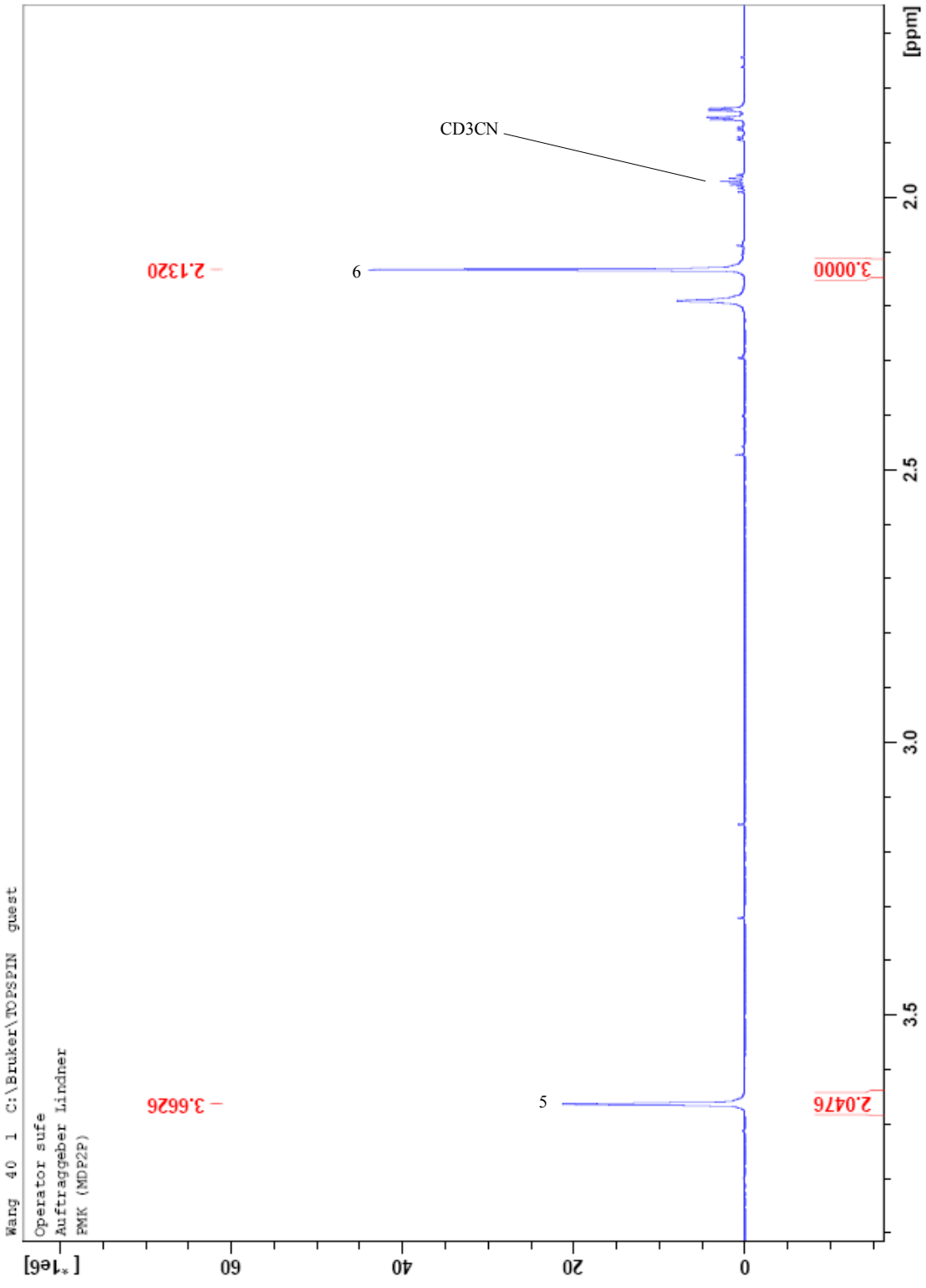
PMK (MDP2P)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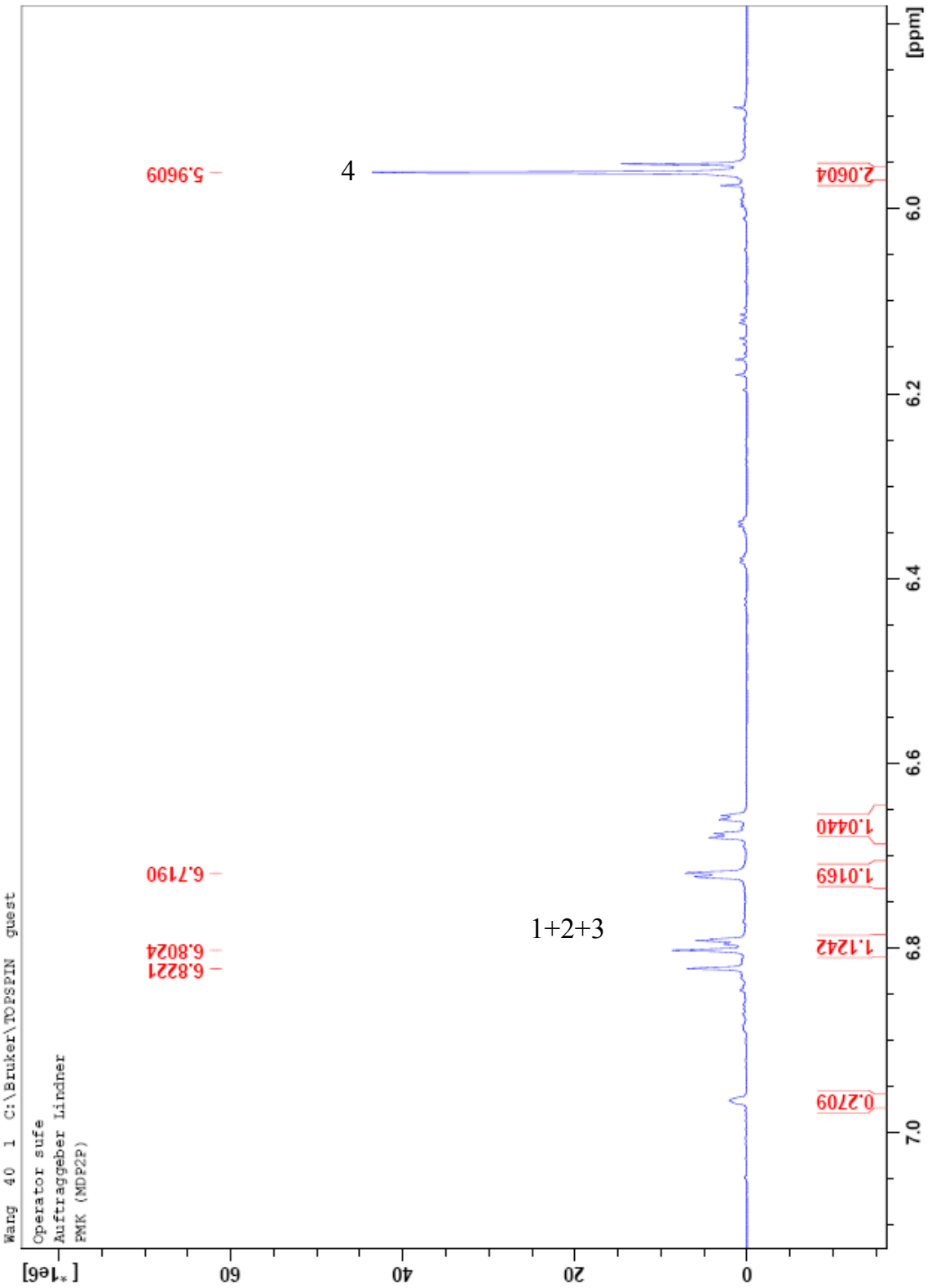
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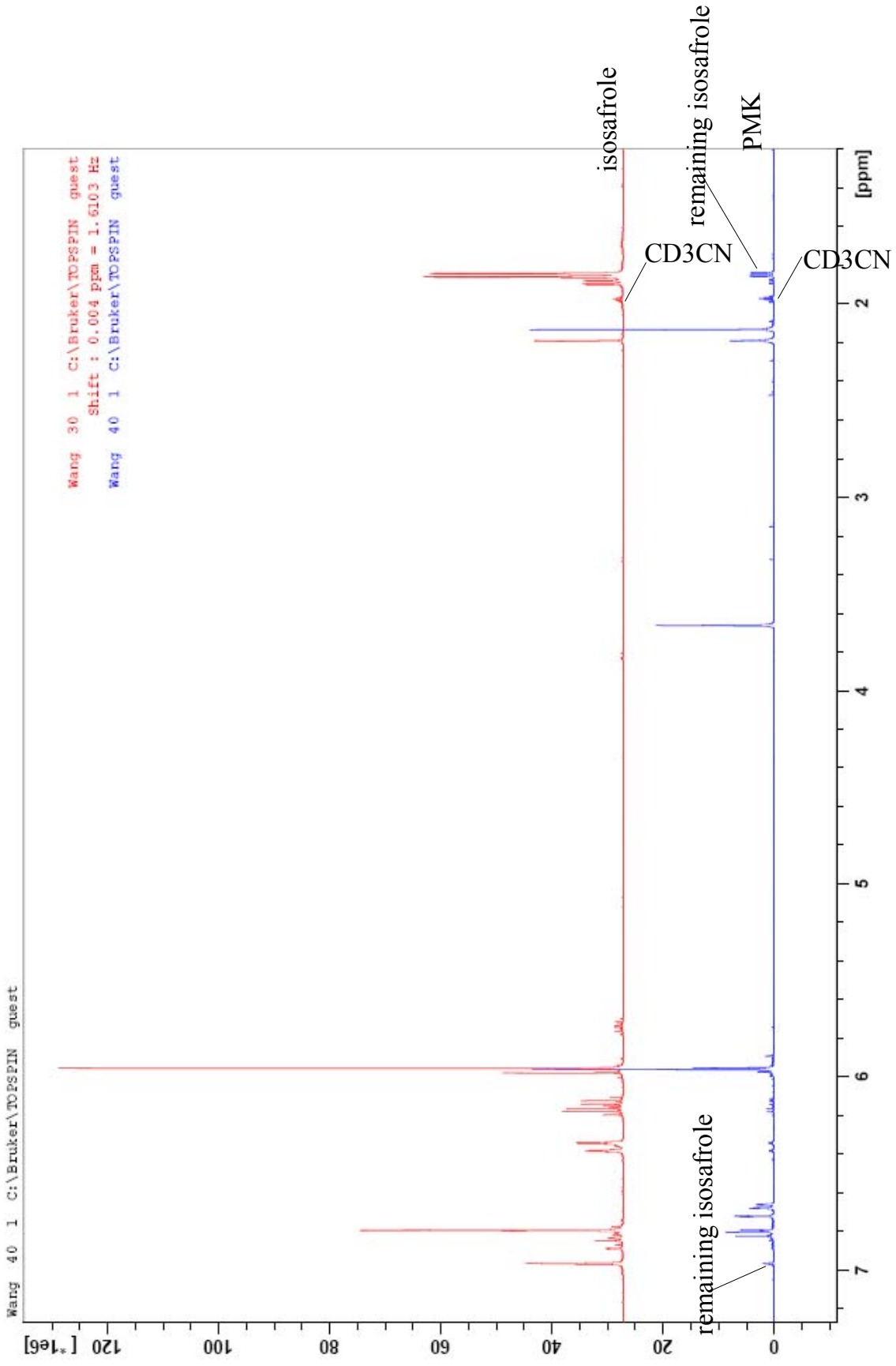
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remaining isosafrole
PMK
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CD3CN
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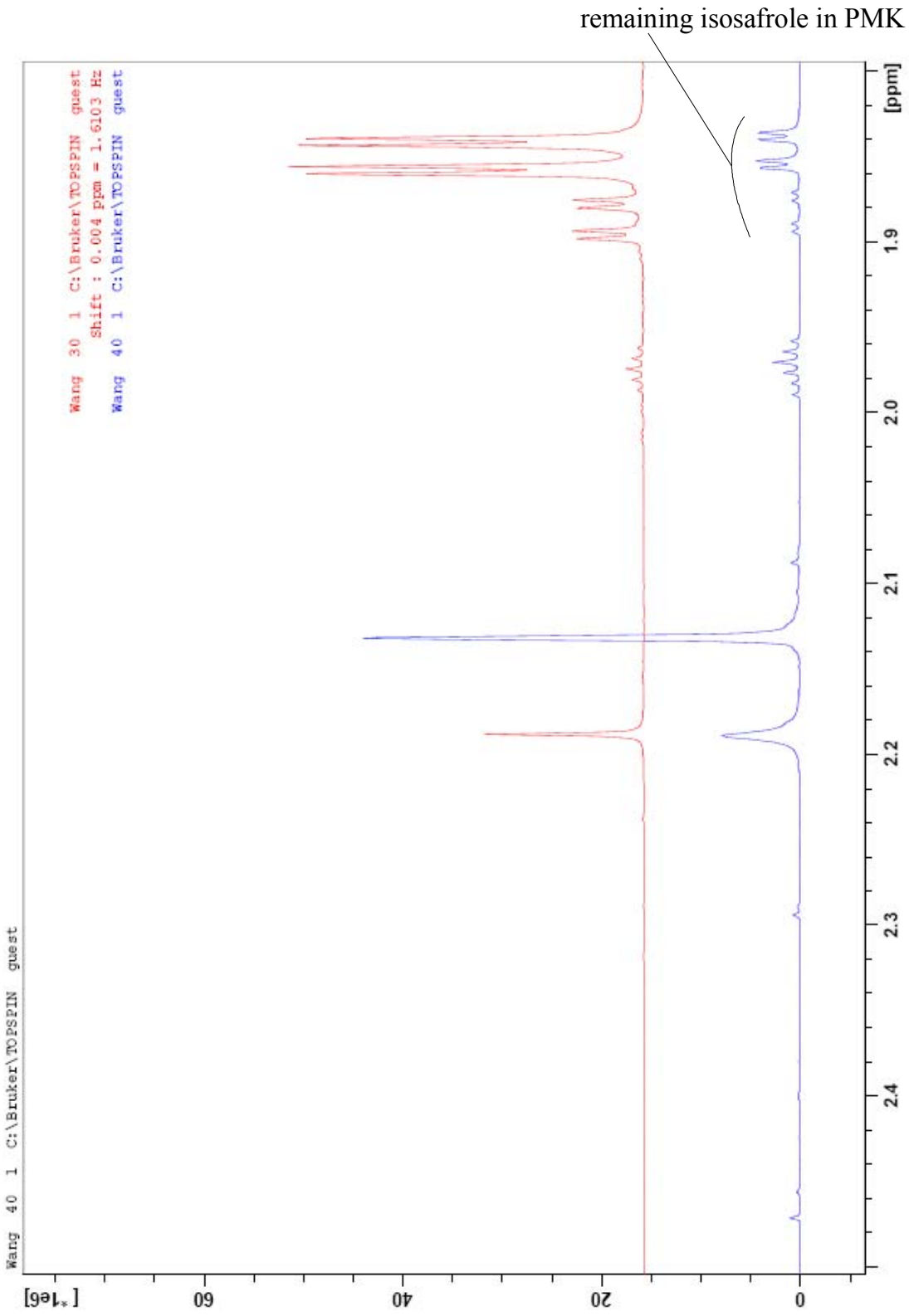
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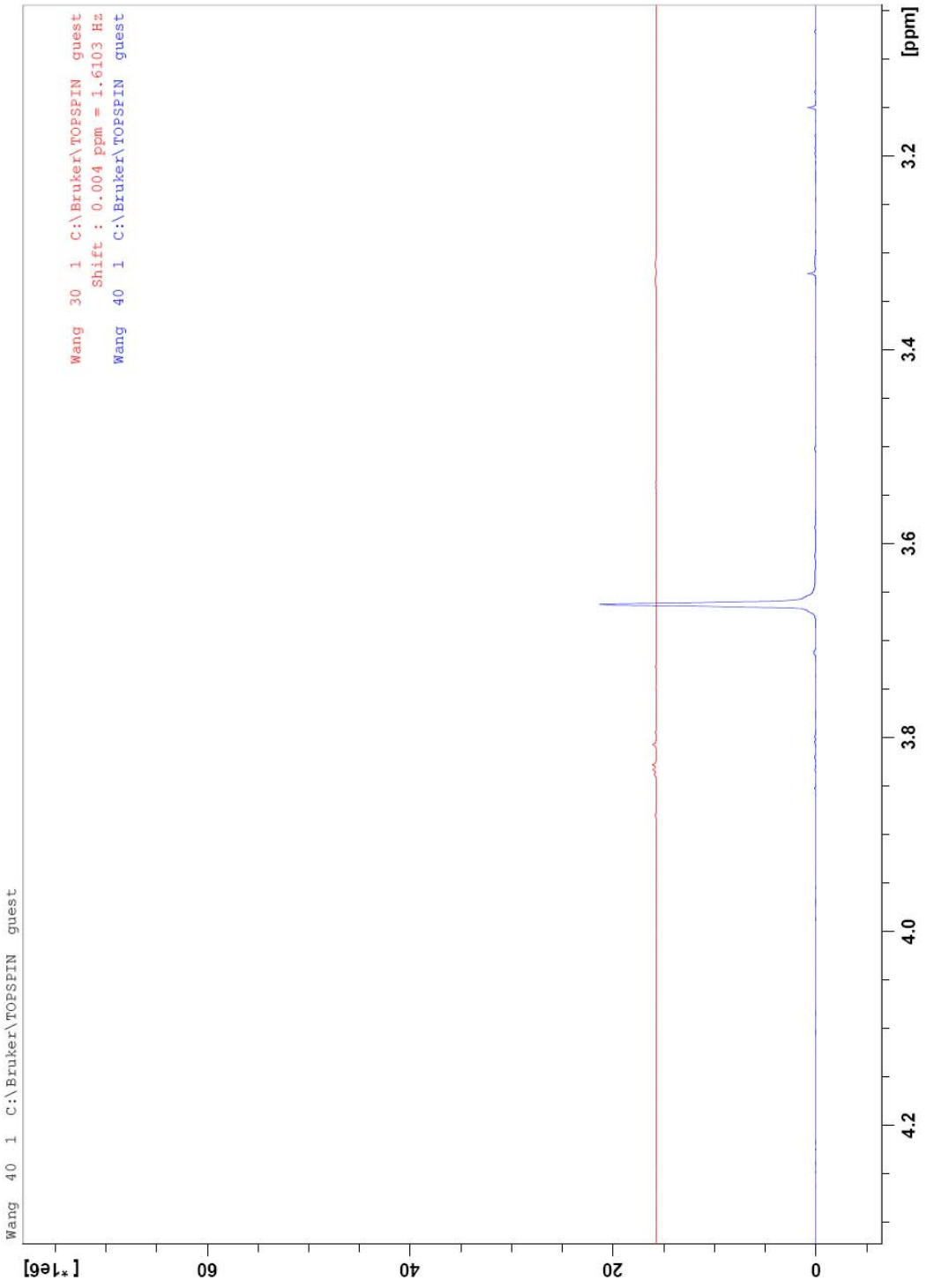
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Wang 30 1 C:\Bruker\TOPSPIN guest
Shift : 0.004 ppm = 1.6103 Hz
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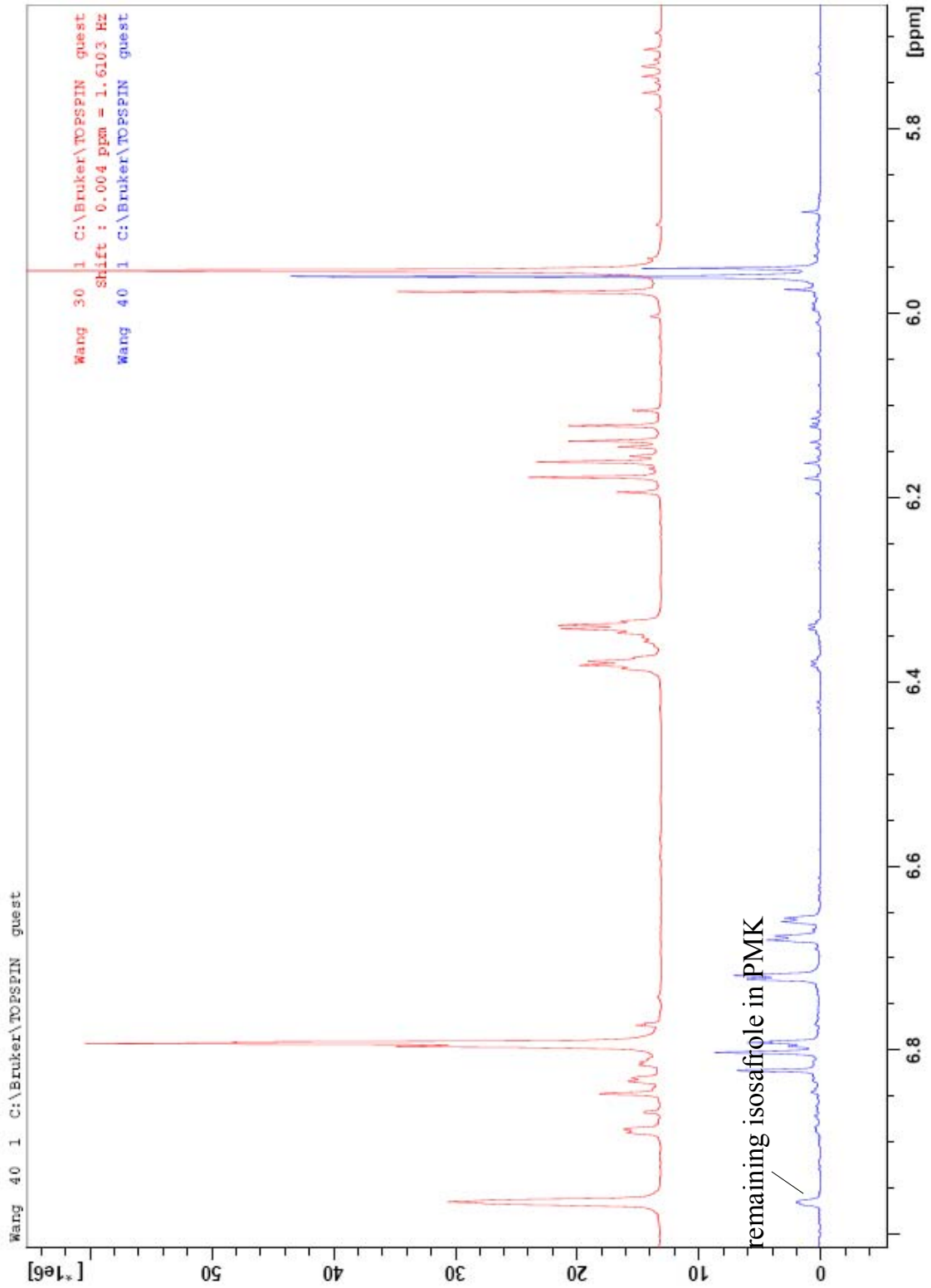
4.0
3.8
3.6
3.4
3.2
[ppm]


Wang 40 1 C:\Bruker\TOPSPIN guest
Wang 30 1 C:\Bruker\TOPSPIN guest
Shift : 0.004 ppm = 1.6103 Hz
Wang 40 1 C:\Bruker\TOPSPIN guest
[*1e6]
50
40
30
20
10
0
6.8
6.6
6.4
6.2
6.0
5.8
[ppm]
remaining isosafrole in PMK

4.3 Measurements and Results

4.3.1 Synthesis of Molecular Imprinted Polymer

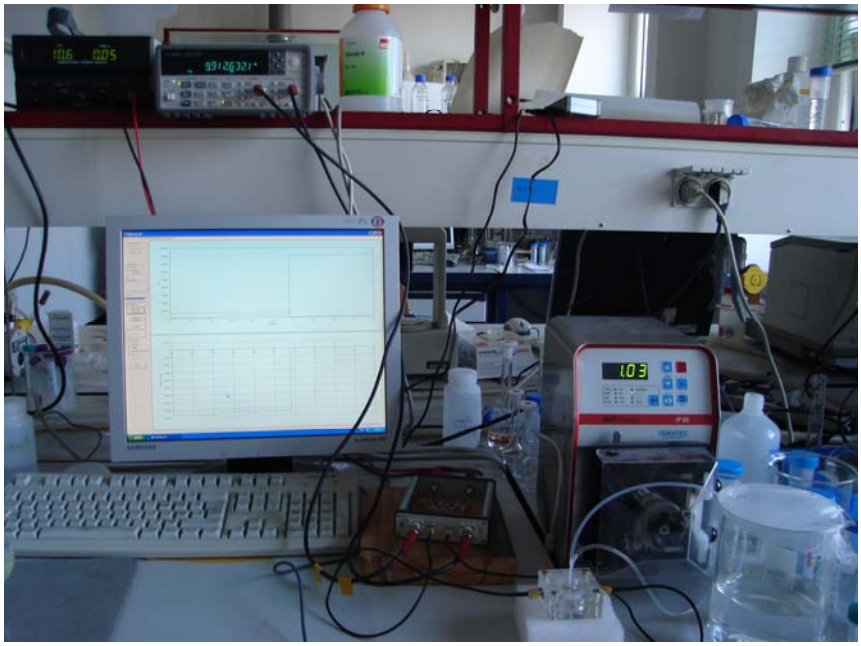
In this work, 3 analytes were measured: phenylaceteone, isosafrole and ephedrine. Among them, phenylacetone and isosafrole have the related structures. The molecular imprinted polymers, which were suitable for each analyte, were prepared as the first step for the measurement. Two kinds of polymer: Polyurethane and poly-4-vinylphenol were applied simultaneously. The amounts of monomers for the manufacture of the polymers have great variable range and could be adjusted to correspond with different analytes and different tasks. Three imprinted polyurethane and three imprinted poly-4-vinylphenol were prepared according to Tab 3.2, 3.3.

The pre-polymerized imprinted polymer was then spin-coated on one of the gold electrodes with a rate of 3000rpm for 5 minutes, which led to a homogeneous thin polymer layer. In the same way, the other electrode was coated with non-imprinted polymer and served as reference electrode. Afterwards, QCM was kept overnight at room temperature to continue the polymerization process. Finally, the template was removed from the polymer after the overnight's polymerization with different methods due to the different chemical properties of the templates. Phenylacetone and isosafrole were removed by heating in the oven at 90 °C for 45 minutes and ephedrine was removed by flushing with water due to its relative good solubility in water. After the removal of the template QCM was ready for measurements.

4.3.2 Measurments

Mass sensitive measurements[46,47] were then carried by mounting QCM in a flow cell which connected to a home-made oscillator circuit. The resonance

frequency was measured by a frequency counter (HP 53131A), then transferred by a self-made software to a PC.



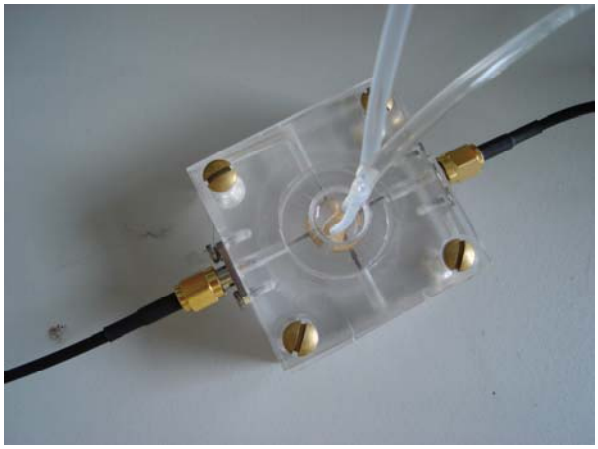


Fig 4.1 Measurement apparatus

Due to the resonance frequency drift to the measurement conditions it is necessary to ensure the defined measurement conditions. In this work, the measurements were taken by room temperature and the flow rate was controlled at 2 ml/min. The difference of the signals of the two electrodes was considered as the correspondent signal of the analyte so that the interferences of the outer conditions were balanced out.

Ephedrine yields a more significant sensor response with imprinted polyurethane compared with the result of imprinted poly-4-vinylphenol.

During the measurement with imprinted polyurethane, the molecules of ephedrine, which were present in the aqueous solution, occupied the vacant site in the polymer, which led to the decrease of the resonance frequency. After each measurement, water was applied to flush the ephedrine molecules away from the polymer to bring the resonance frequency to the initial value. The result of the measurement is shown in Fig 4.2. It could be read that the sensor response of aqueous solution of 0.25 μg/ml is about 200 Hz, and the sensor response of aqueous solution of 0.5 μg/ml is about 400 Hz, which reveals that there is a linear relation between the sensor response and the concentration of the aqueous solution of ephedrine. The signal of non-imprinted polymer layer shows only a minor response as reference. After flushing with water by each measurement, the frequency could be brought to the initial value, so the polymer had good reversibility. The second measurement of the aqueous solution of 0.25 μg/ml had almost the same sensor response as the first measurement, which reveals the relative good reproducibility of the polymer.

The thickness of the polymer layer could be estimated through the difference of the resonance frequency between before and after coating. It is know that difference of 5kHz corresponds approximately 200nm. Ephedrine imprinted polyurethane applied here had a thickness of about 2000nm.

Ephedrine imprinted poly-4-vinylphenol was also applied. In Fig 4.3 it is seen that the sensor signal is less than 40 Hz for 0,25μg/mL aqueous solution of ephedrine, which is less significant than the result of polyurethane.

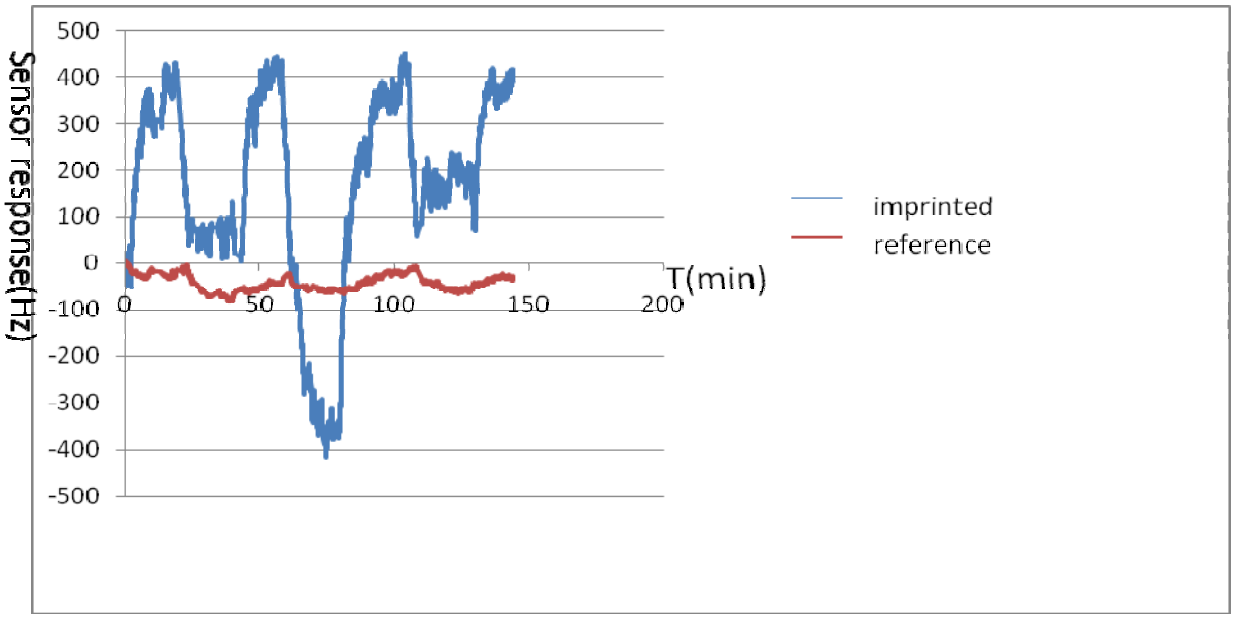


Fig 4.2 Sensor response of ephedrine imprinted polyurethane to aqueous solution of ephedrine with different concentrations at 25 °C. Response of the non-imprinted polymer is also shown as a reference. Thickness of the ephedrine imprinted and non-imprinted polymer was approximately 200nm

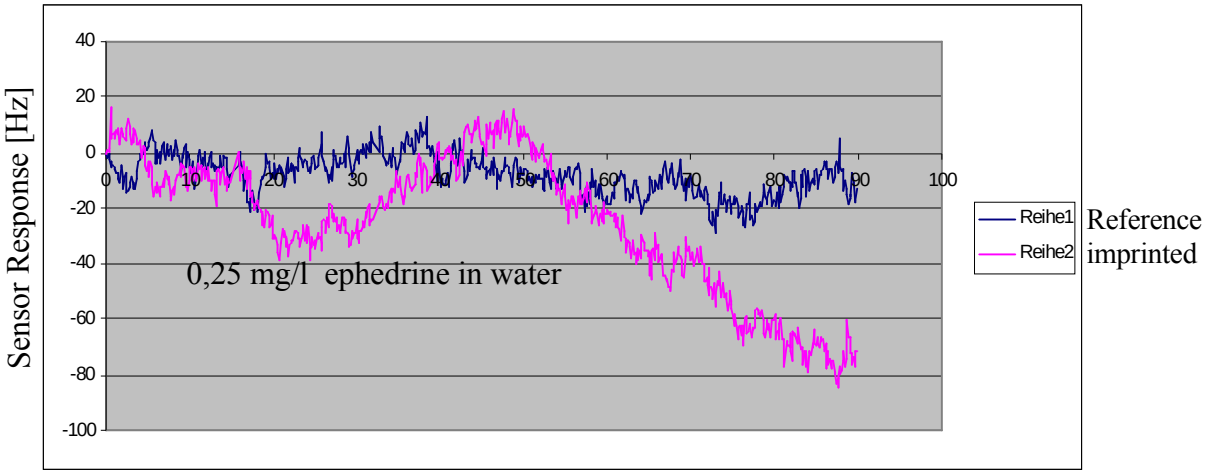


Fig 4.3 Sensor response of ephedrine imprinted poly-4-vinylphenol to 0,25 µg/mL aqueous solution of ephedrine at 25 °C. Thickness of the ephedrine imprinted and non-imprinted polymer was approximately 200nm.

Phenylacetone, isosafrole were measured separately with imprinted polyurethane. Since phenylacetone and isosafrole do not have good solubility in water (solubility of phenylacetone in water is 5.2g/L, solubility of isosafrole in water is 45mg/L), standard solutions were prepared firstly.

A defined amount of the analyte was given in water and this solution was kept in water bath by sonication for 30 minutes. The standard solution was subsequently diluted to the solutions with desired lower concentrations.

After each measurement with aqueous solution of analyte, distilled water flowed through the cell till the sensor response was again relatively constant. The flow rate was controlled at 5 ml/min. The measurement results are shown below in Fig 4.4,4.6,4,7

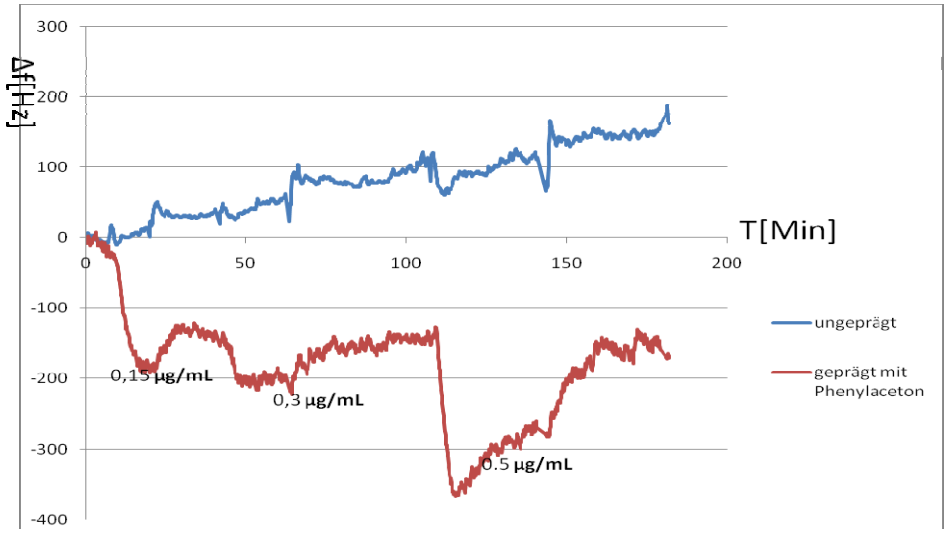


Fig 4.4 Sensor response of phenylacetone imprinted polyurethane to aqueous solution of phenylacetone with different concentrations at 25 °C. Response of the non-imprinted polymer is also shown as a reference. Thickness of the phenylacetone imprinted and non-imprinted polymer was approximately 200nm.

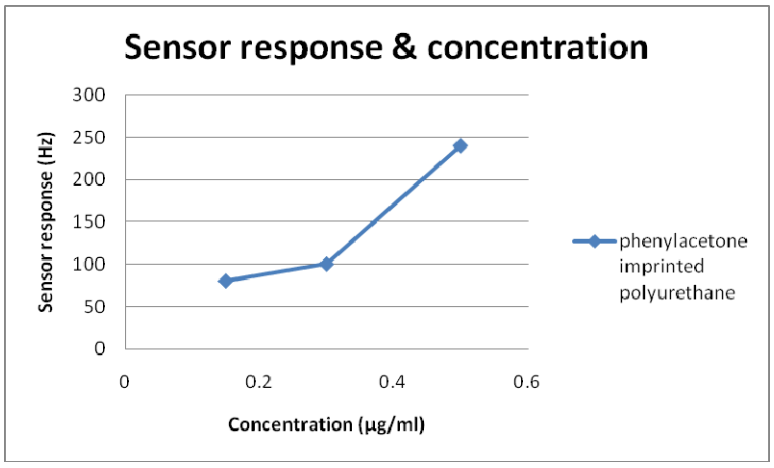


Fig 4.5 Relation between sensor responses and concentrations of phenylacetone solution

In Fig 4.4 the response of reference electrode increased during the measurement. It may be due to the falling of the non-imprinted layer off the reference electrode. It can be read from the curve of the measuring electrode that the frequency came to a relative stable end point by every measurement after flushing with water. It represents the reversibility of the polymer. The frequency difference of the concentration 0,15µg/ml is about 80 Hz and the difference of the concentration 0,5µg/ml is about 240 Hz. The relation between sensor responses and concentrations of phenylacetone solution is shown in Fig 4.5.

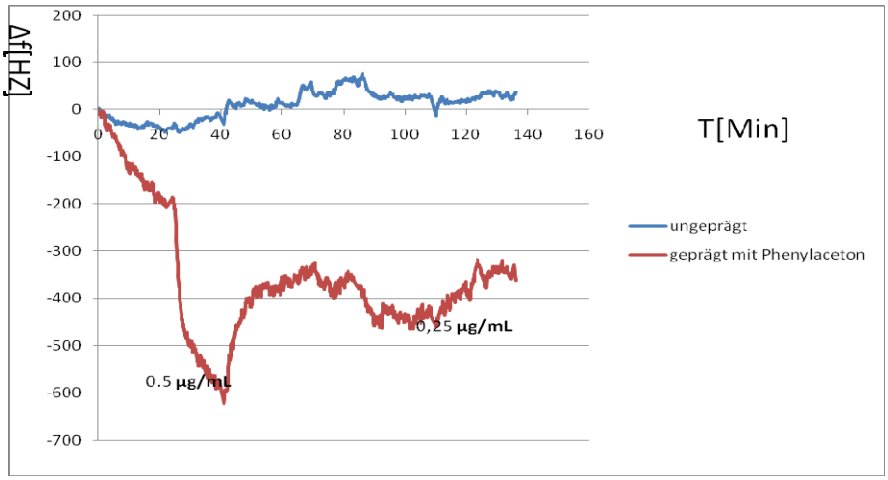


Fig 4.6 Sensor response of phenylacetone imprinted polyurethane to aqueous solution of phenylacetone with different concentrations at 25 °C. Response of the non-imprinted polymer is also shown as a reference. Thickness of the phenylacetone imprinted and non-imprinted polymer was approximately 200nm.

In Fig 4.6 the sensor effect of the phenylacetone solution with the concentration of 0,5 µg/ml was about 250 Hz, which proved the reproducibility of the sensor.

From Fig 4.7 it is read that the isosafrole imprinted polyurethane had sensor response to the aqueous solution of isosafrole. But after flushing with water by each measurement, the frequency did not arrive the initial point, which reveals the bad reversibility of isosafrole imprinted polyurethane. The

relation between sensor responses and concentrations of isosafrole solution is shown in Fig 4.8.

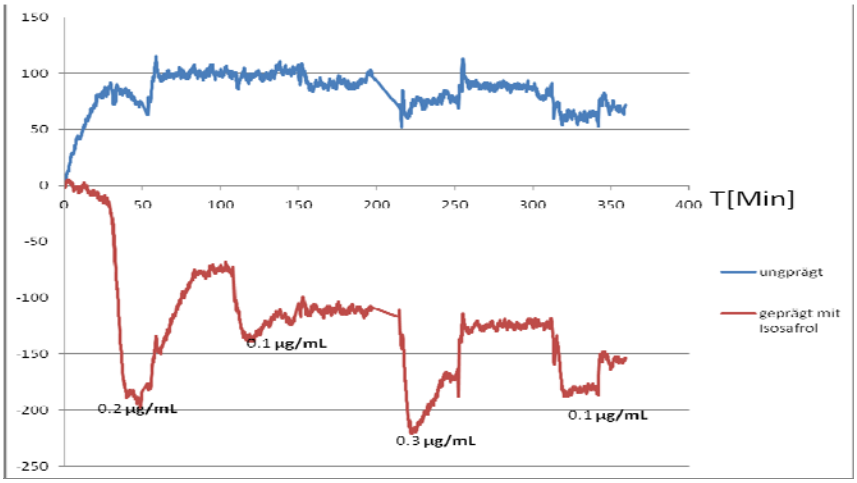


Fig 4.7 Sensor response of isosafrole imprinted polyurethane to aqueous solution of isosafrole with different concentrations at 25 °C. Response of the non-imprinted polymer is also shown as a reference. Thickness of the isosafrole imprinted and non-imprinted polymer was approximately 200nm.

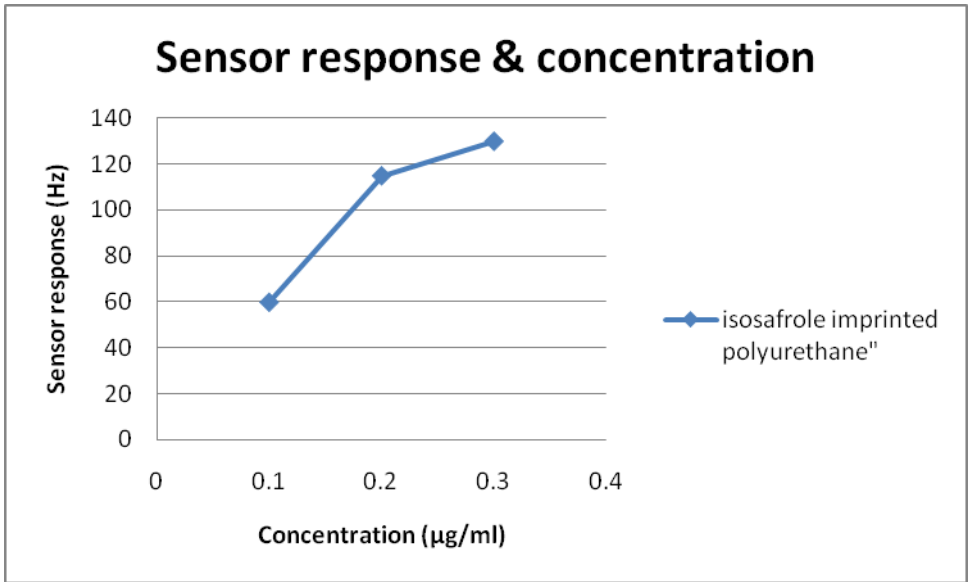


Fig 4.8 Relation between sensor responses and concentrations of isosafrole solution

Conclusion

Quartz crystal microbalance, abbreviated as QCM, is a well-known and widely used mass sensing device with the ability to measure minor mass changes by a quartz crystal resonator in real-time. Due to the high sensitivity of QCM it is capable of measuring mass change as small as a single layer of atoms. The adsorbed mass on the QCM surface can be detected down to a few ng/cm^2. The high sensitivity and the real-time monitoring of mass changes on the sensor crystal make QCM an attractive tool for a large range of applications. With the development of QCM applied in liquid system interests towards this technique increase dramatically. Label-free detection of molecules is the major advantage of the QCM technique used for liquid system compared with other analytical methods.

In this work, three analytes were analysed with QCM: phenylacetone, isosafrole and ephedrine. The task was to develop the right artificial antibodies as sensitive and selective layer on QCMs to detect each analyte in aqueous solution. Molecular imprinted polyurethane and poly-4-vinylphenol were applied here. It was proven that polyurethane was working better than poly-4-vinylphenol for the three analytes and it was possible to detect analytes in 'ng/L' range. The sensor responses of ephedrine and phenylacetone imprinted polyurethanes have relative good reversibility and reproducibility due to the fine non-covalent interactions between the imprinted polyurethanes and aqueous solutions of analytes. There have considered van der Waals interactions and hydrogen bonding. Compared with ephedrine and phenylacetone, the sensor responses of isosafrole imprinted polymer are sluggish, which may be due to the interaction between the polymer and isosafrole.

The work in hand has investigated the possibility to analyse the precursors of drugs amphetamine with QCM. The critical point is molecular imprinted polymer. So the work in the future is to modify the structure of the molecular imprinted polymer to improve further the sensitive layer to enhance the quality of sensors.

Zusammenfassung

QCM (quartz crystal microbalance) ist ein bekannter und häufig angewandter massensensitiver Sensor. Dank der hohen Sensitivität ist der QCM in der Lage, Massenänderung von einer Atomlage zu detektieren. Mit der Entwicklung von QCM in flüssiger Phase steigt das Interesse an dieser Technik beträchtlich an.

Im Zuge dieser Arbeit wurden drei Analyte: Phenylaceton, Isosafrol und Ephedrin mittels QCM in flüssiger Phase analysiert. Die Aufgabe war MIPs (molecular imprinted polymer) für die angesprochenen Analyten zu entwickeln. Die MIPs wurden als sensitive und selektive Schichte auf die QCMs aufgebracht. Dabei wurden folgende Polymere herangezogen: Polyurethan und Poly-4-vinylphenol angesetzt. Die Messungen zeigten, dass Polyurethane für die drei Analyte besser geeignet sind als Poly-4-vinylphenol. Die Analyte konnten im 'ng/mL' Bereich detektieret werden. Aufgrund der nicht-kovalenten Wechselwirkungen zwischen der sensitiven Schicht und dem Analyt zeigten die Signale von Ephedrin und Phenylaceton relativ gute Reversibilität und gute Reproduzierbarkeit. Van der Waals Wechselwirkungen und Wasserstoffbrückenbindungen waren hierfür verantwortlich. Signale von Isosafrol lieferten ein träges Ansprechverhalten und geringere Reproduzierbarkeit. Es liegt vermutlich an den Wechselwirkungen zwischen Isosafrol und dem Polymer.

Diese Arbeit zeigte die Möglichkeiten auf, die Vorstufen von Amphetaminen mittels QCM zu analysieren. Der kritische Punkt ist die Entwicklung des MIP. Zukünftige Arbeiten werden zur Modifizierung dieser Polymere führen, damit die Sensitivität und Selektivität der Erkennungsschichten erhöht wird und generell die Anwendbarkeit des Sensors sich erhöht.

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