Nanostructured Sensors for Molecular Recognition

W. Gopel

| **Email alerting service** | Receive free email alerts when new articles cite this article - sign up in the box at the top right-hand corner of the article or click **here** |

Nanostructured sensors for molecular recognition

By W. Göpel

Institute of Physical and Theoretical Chemistry and Center for Interface Analysis and Sensors, Auf der Morgenstelle 8, D-72076 Tübingen, Germany

A survey is given on typical 'top-down' and 'bottom-up' approaches to design nano-structured sensors which monitor different physical and chemical quantities. Particular emphasis is put on new materials and transducers for molecular recognition by chemical sensors. These convert chemical information into electronic signals by making use of suitable 'key-lock' structures. This requires the control of surface structures of chemically sensitive materials down to the molecular scale under thermodynamically or kinetically controlled conditions. This in turn requires the molecular understanding of sensor mechanisms which is deduced from comparative microscopic, spectroscopic and sensor test studies on 'prototype materials'. Selected case studies illustrate the common mechanisms of molecular recognition with electron conductors, ion conductors, mixed conductors, molecular cages, polymers and selected biomolecular function units.

1. Introduction

New structures obtained by microstructurization ('top-down' approaches) and chemical synthesis ('bottom-up' approaches) will, in principle, lead to a new generation of physical and chemical sensors, provided that the stabilities of interfacial structures, sensitivities and selectivities of output signals can be controlled sufficiently (see schematic figure 1). The atomistic understanding of these phenomena is essential in the research and development (R+D) of these sensors (Göpel *et al.* 1991, 1992; Göpel & Ziegler 1992). This includes, in particular, the interaction mechanisms between the different particles, waves or fields with the different molecular, supramolecular or biological units. The same understanding is required to apply the different scanning tunnelling microscopy (STM) and related SXM techniques for investigating and controlling the sensor structures, or to reach the ultimate limits in the fabrication of reliable sensors for measuring physical or chemical parameters.

In the following, only chemical sensors are considered. These make use of specific 'key-lock' interactions which convert chemical information to electronic information. Three different tasks are usually fulfilled by such chemical sensors, i.e. the quantitative and selective determination of individual particles (such as molecules or ions in gases or liquids), the determination of gross parameters (such as toxicity) or the quantitative characterization of odours (such as smells monitored qualitatively by the human nose). These requirements can only be achieved with sensor systems which, in the most general case, contain ten components for analysing gases or liquids with their chemical composition given by concentrations c_i of different components i (see schematic figure 2).
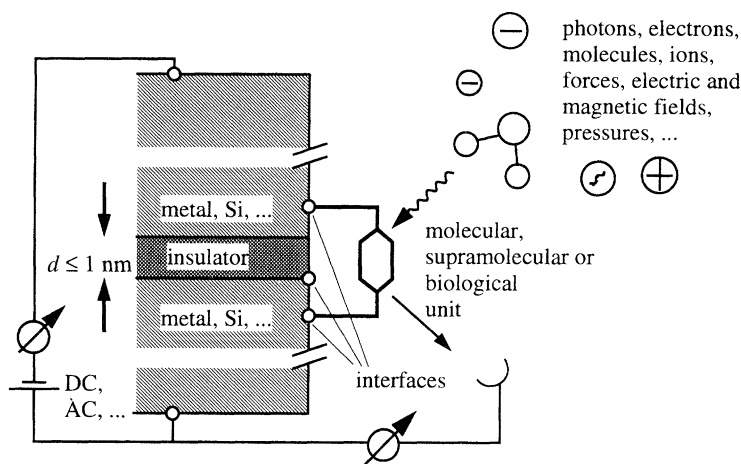
© 1995 The Royal Society

TeX Paper

Figure 1. Schematic presentation of a (bio-)molecular sensor device. The coupling is illustrated between microelectronic structures ('top-down' approach: left) and chemically synthesized or biological structures ('bottom-up' approach: right). The latter may be modified in different environments, as indicated in the upper-right part of the figure. Corresponding response signals are either collected externally (by monitoring emitted particles, waves, etc., lower-right side) or internally via signal transduction across the interfaces through the transducer device (for instance, by monitoring changes in the direct (DC) or alternating (AC) current, lower-left side) (Göpel *et al.* 1991, 1992; Göpel & Ziegler 1992).
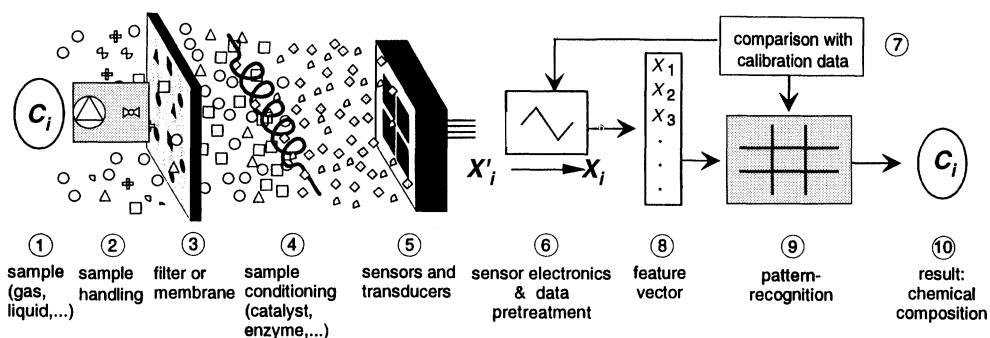
Like in a chain, the component with the weakest performance determines the overall performance of the sensor system. For most systems the weakest component is the sensor element (5). Current sensor research therefore concentrates on three approaches to reduce this bottleneck by:

(i) empirical optimization of sensor materials and of transducers in systematic tests under realistic measuring conditions;

(ii) systematic studies of elementary steps of chemical sensing under thermodynamically or kinetically controlled conditions by means of microscopies and spectroscopies; and

(iii) theoretical calculations of elementary steps of selective 'key-lock' interactions.

Commonly used transducers monitor chemical compositions by monitoring the phenomenological properties listed in table 1. Current microsystem technologies lead to new miniaturized transducers, such as interdigital structures (for complex impedance measurements), thermopiles (for temperature measurements), piezoelectric oscillators based upon bulk, surface or plate waves (for mass measurements), integrated optics components (for optical measurements), multielectrode arrays (for electrochemical measurements including recent developments for electrical connections to nerve systems), or arrays of sensor elements with integrated transducers as well as data processing (for integrated 'electronic noses') (Göpel 1995*a*, *b*).

The trends towards improved performance and lower size and price per sensor element require the systematic optimization of interface properties by means of the common tools of microscopy and spectroscopy listed in table 1. This requires, in particular, completely reversible bonding of the detectable particle to the sensor-active coating and completely irreversible chemical bonding of this sensor-active coating to the transducer.

This will be illustrated now for typical sensor materials which show characteristic

Figure 2. Different components of complete sensor systems ('electronic noses') are shown schematically with their different operation modes to determine signals in complex mixtures of molecules, odours, etc. (characterized by concentrations c_i in the gas or liquid). In simple systems, some components may be omitted (e.g. numbers 3, 4 or 9). Usually these components contain 'man-made' materials; however, all of these components may, in principle, be replaced in the future by 'natural' biomolecular components. In the far future, this may even concern the feature extraction and pattern recognition steps with neural networks. The step-by-step replacement of different 'man-made' components in this system by 'natural' biomolecular components will also make it possible to develop technologies, instruments and theories for designing and understanding also future biomolecular devices which will aim not only at electronic monitoring of molecules and odours but also at general information processing (Göpel *et al.* 1991, 1992; Göpel & Ziegler 1992; Göpel 1995*a*, *b*; Weimar *et al.* 1991).

'key–lock' interactions to detect and identify particles. Particular emphasis will be put on the discussion of ultimate limits in the miniaturization of sensor elements as a prerequisite to developing nanosensors operating at the physical limits of miniaturization.

2. Selected case studies

(a) Electron conductors: SnO_2

Electron conductors are commonly used as chemical sensors to monitor oxidizing and reducing gases such as O_2, H_2, CO, NO_2 or hydrocarbons. The operating temperature determines the predominant interaction step: with increasing temperature, physisorption, chemisorption, surface defect reactions, catalytic reactions and bulk reactions can be utilized for chemical sensing, provided that the interaction step leads to a change in the DC resistivity or, more generally, in the AC impedance (see schematic figure 3).

Particularly suitable for miniaturizing electron conducting devices is their operation in the chemisorption sensor mode. Depending on the position of the highest occupied (HOMO) or lowest unoccupied molecular orbital (LUMO) of the chemisorp-

Table 1. *Survey of typical tools of surface and interface analysis*

(These tools are commonly used in basic science studies of semiconductor and optoelectronic devices and are now also applied in studies of chemical sensors and biomolecular devices (Göpel & Ziegler 1992). Measurements of sensor signals, i.e. of their phenomenological properties are optimized in practical chemical sensors by a careful choice of the transducer and its chemically sensitive coating. The phenomenological properties measured independently include: Δm, measurements of mass differences; Q, measurements of reaction heats; σ, measurements of voltage-, temperature- and frequency-dependent conductivities, complex impedances and photoconductivities; Φ, measurements of work functions; C, measurements of capacitancies; ΔE, $I(\nu)$, measurements of electrochemical potential differences and currents as a function of frequency ν; $\varepsilon(\nu)$, optical absorption and reflection.)

geometric arrangement of atoms	elemental composititition	electronic structure	dynamic structure	coverage of adsorbed particles, sticking coefficients		
●					SEM	scanning electron microscopy
●					(SPA-)LEED	(spot-profile-analysis) low electron energy diffraction
●	●				SAM	scanning Auger microscopy
●	●				(S)SIMS	(scanning) ion mass spectrometry
●	●				(S)EDX	(scanning) energy dispersive X-ray analysis
●	●				ISS	ion scattering spectroscopy
●		●		●	STM	scanning tunnelling microscopy
●		●		●	SFM	scanning force microscopy
	●	●		●	AES	Auger electron spectroscopy
	●	●		●	XPS	X-ray photoemission spectroscopy
	●	●		●	TDS	thermal desorption spectrometry
		●			UPS	ultraviolet photoemission spectroscopy
		●			ELS	electron energy loss spectroscopy
		●			UV/VIS	optical spectroscopy
		●		●	(S)ELL	(spectral) ellipsometry
		●		●	(S)SPR	(spectral) surface plasmon resonance
		●			FS	fluorescence spectroscopy
		●	●		HREELS	high-resolution electron energy loss spectroscopy
			●		(FT)IR	(Fourier transform) infrared spectroscopy
			●		IR-ATR	infrared spectroscopy of attenuated total reflection
			●		RAM	Raman spectroscopy

tion complex relative to the Fermi level (of usually n-type conducting oxides such as SnO_2), donor or acceptor type of interaction is monitored by changes in surface conductivities $\Delta\sigma$ or work functions $\Delta\Phi$ (figure 4).

Useful parameters for both, the quantitative calibration of chemisorption sensors in applications and their theoretical atomistic understanding are:

(i) partial charges δ (determined from the ratio of transferred electrons per adsorbed surface complex in an evaluation of conductivity and thermodesorption experiments);

(ii) dipole moments μ formally attributed to the chemisorption complex (determined from electron affinity changes $\Delta\chi$, as deduced from shifts in the UPS photoemission spectra in the valence band range: see figure 4b);
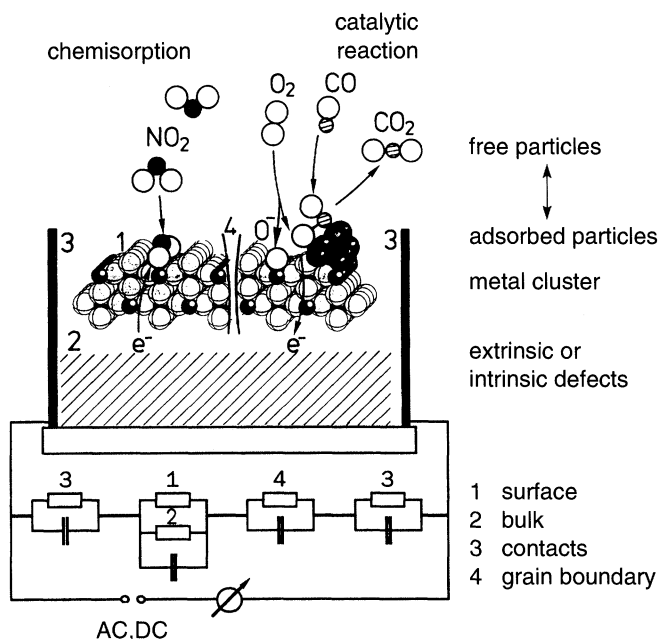
Figure 3. Schematic presentation of different sensor–gas reactions and corresponding components of equivalent circuits formally describing the frequency-dependent AC or DC behaviour which is influenced by reactions between the gas phase and an electronically conducting oxide. Indicated is the chemisorption of NO_2 (left) and the catalytic oxidation of CO to form CO_2 (right). For details, see text and Weimar (1992), Schierbaum *et al.* (1993*a*) and Weimar *et al.* (1995).

(iii) isosteric heats of adsorption q_{st} (deduced from pressure dependent coverages, i.e. adsorption isotherms at different temperatures);

(iv) activation energies of desorption E^{act} (determined from thermodesorption experiments); and

(v) sticking coefficients S_o (determined from initial rates of conductivity or work function changes upon gas exposure).

Theoretically, these parameters may be determined from quantum chemical cluster calculations by describing the atomic configurations at the adsorption site before and after formation of the chemisorption complex (Göpel 1985, 1989).

Conductivity measurements are particularly sensitive in nanocrystalline thin films if the Debye length L_D is larger than the oxide particle radius $r = \frac{1}{2}l$ (figure 5). Under these conditions, charge transfer across grain boundaries in the film, instead of charge transfer parallel to the surface of an ideal thin film, is modified during chemical sensing and equilibrium coverages of less than 10^{-5} monolayers of donor or acceptor molecules can easily be detected.

Current R+D of electron conducting sensors aims at optimizing contact geometries, film thicknesses, particle size distributions, doping, operation temperatures and operation frequencies. Usually, film thicknesses are chosen in the micrometre range with a recent trend to stabilize identical diameters of nanosized SnO_2 particles in these films. In principle, the charge transfer of individual electrons to or from the chemisorption complexes (see figure 4, but for $L_D \gg d$) should be detectable by steps in scanning tunnelling spectroscopy (STS) spectra of nanosized SnO_2 parti-
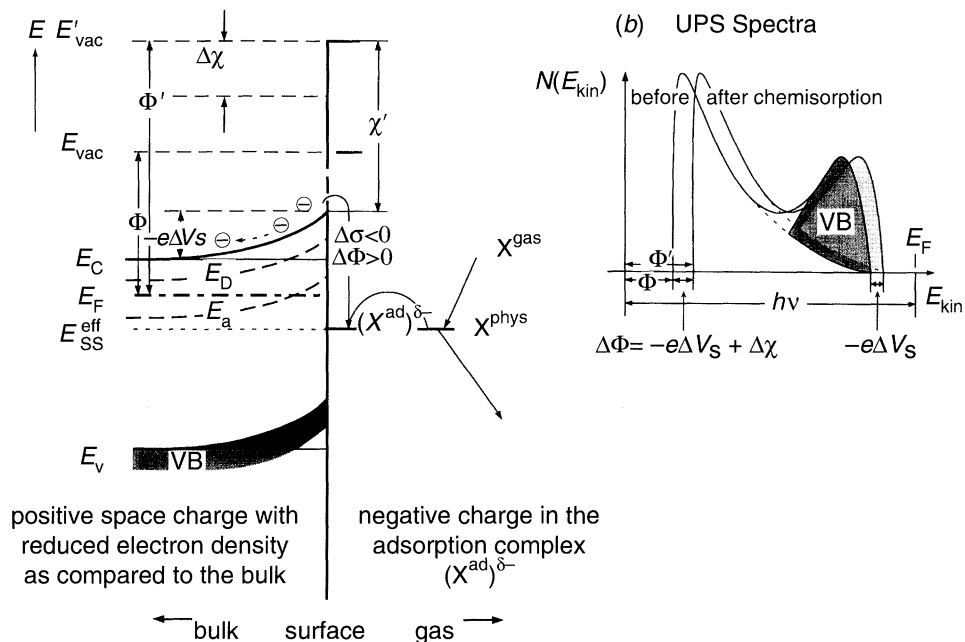
(*a*)

Figure 4. (*a*) Schematic presentation of chemisorption and charge transfer at a semiconductor surface in the electronic band scheme of the surface. The gas phase molecule X^{gas} forms the precursor physisorption state X^{phys}. Also indicated is the work function Φ, electron affinity χ and band bending $e\Delta V_s$. Chemisorption may be measured by monitoring changes in the work functions $\Delta\Phi = \Phi' - \Phi$ and changes in surface conductivities $\Delta\sigma$ upon occupation of effective surface states E_{SS}^{eff} by forming $(X^{ad})^{\delta-}$ (an example of acceptor-type of chemisorption). The band edges are denoted by E_V (valence band) and E_C (conduction band). The position of the Fermi level E_F in the bulk is determined by bulk donors E_D and acceptors E_A. (*b*) UPS spectrum (intensity N of photoemitted electrons at a given kinetic energy E_{kin}) before and after chemisorption with characteristic variations in the zero energy cut-off (determining $\Delta\Phi$) and in the valence band onset (determining $-e\Delta V_s$). The link between practical applications and theory is given by determining partial charges δ, dipole moments μ, isosteric heats of adsorption q_{st}, activation energies of desorption of chemisorbed particles E^{act} and initial sticking coefficients S_o. For further details see text and Göpel (1985, 1989).

cles in an arrangement similar to the one chosen in recent single-electron tunnelling experiments.

(*b*) *Mixed conductors: TiO₂*

Electron and ion conduction of mixed conductors is monitored at elevated temperatures ($T > 700$ K) in gas sensors based on oxides such as TiO_2. Platinum is often used to improve the selectivity of gas detection by improving the catalytic activity of the surface. The latter results from energetic shifts of the bulk Fermi level or from specific chemisorption sites at the surface. Pt is also used to electronically contact the sensor material. The Pt contacts on TiO_2 are of particular interest because recent experiments show a switching phenomenon in the current–voltage behaviour across this interface.

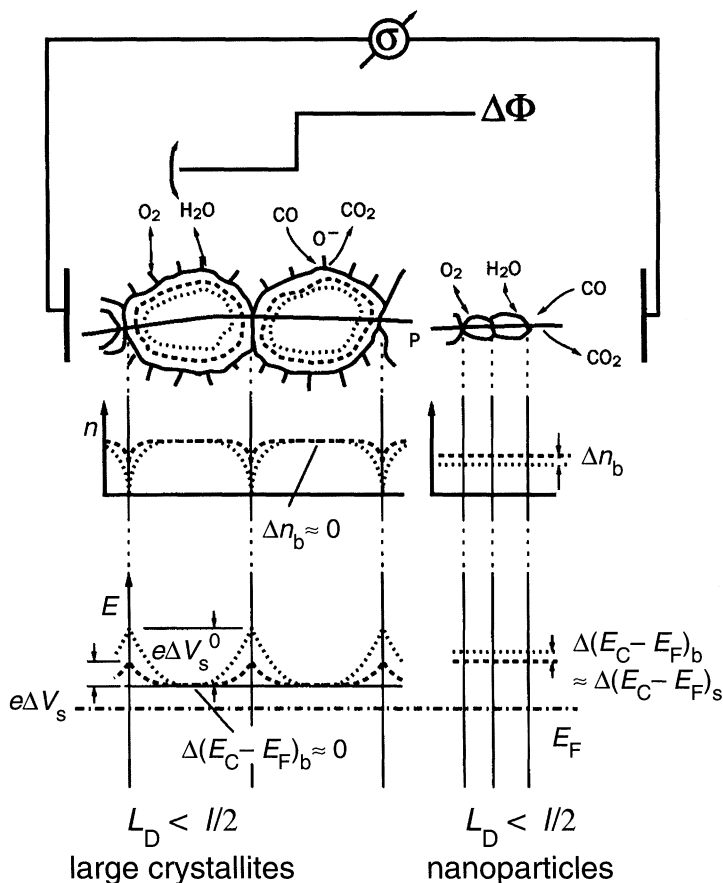(i) At low temperatures ($T < 700$ K), the electronic conductivity can be utilized in

Figure 5. Schematic presentation of an experimental setup to monitor conductivities σ and work function changes $\Delta\Phi$ (with a vibrating Kelvin probe) of nanocrystalline semiconducting particles (n-type) with Debye lengths L_D smaller (left) and larger (right) than the particle radius $r = \frac{1}{2}l$. Charge carrier concentrations of electrons (n) and electron energies (E) in the band scheme are shown in the lower part. The index 'b' denotes bulk and 's' surface values. For details, see Göpel *et al.* (1995*b*, figure 4) and text.

sensitive Schottky-barrier sensors to monitor gases like O_2 or CO (see typical results in figure 6). Under these conditions, the Pt atoms at the surface act as acceptors.

(ii) At higher temperatures and higher oxygen partial pressures, Pt^{2+} ions are formed at the surface, which subsequently move to subsurface positions at which they are stabilized as Pt^{4+} ions. The Pt^{4+} ions are significantly smaller than the Pt^0 atoms and act as subsurface ('bulk') donors between the first and second TiO_2 layer (figure 7*a*). As a result, a drastic change occurs in the conductivity across the Pt–TiO_2 interface from Schottky barrier to Ohmic contact behaviour (see figure 6). Under the latter conditions, the point defect thermodynamics of oxygen vacancies in the TiO_2 bulk can be utilized to monitor oxygen over a large pressure range by the mixed (electron and oxygen vacancy V_O^{2+} (or alternatively oxygen ion O^{2-})) conduction mode. The two different operation conditions of Pt–TiO_2 interfaces and their charge generating steps as surface state controlled chemisorption and bulk controlled defect formation both depending on p_{O_2} and T, may be illustrated schematically in a band scheme (figure 7*b*).
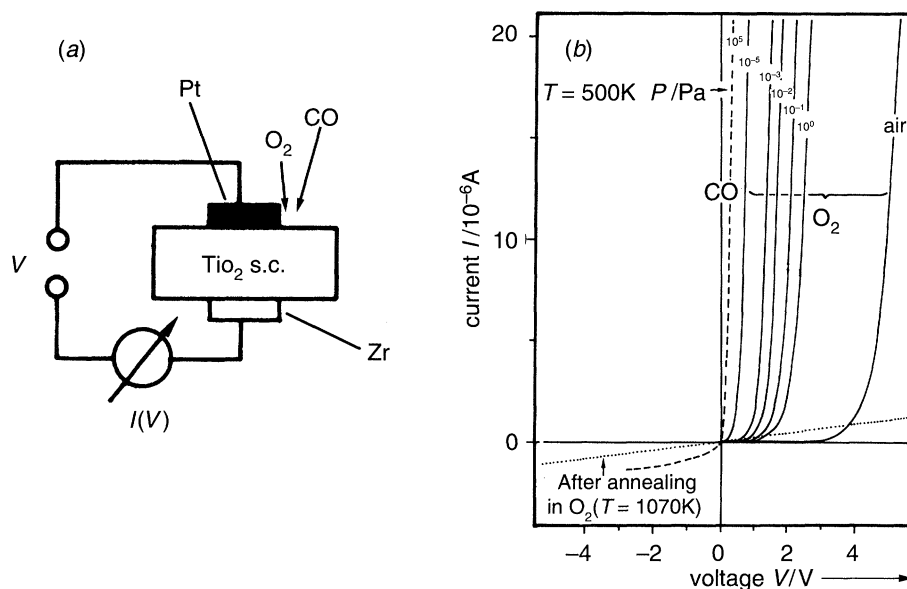
Figure 6. Current–voltage (I–V)-characteristics for Schottky-barrier and Ohmic-contact sensors based upon Pt–TiO$_2$ in an arrangement as illustrated in (a). The Zr–TiO$_2$ interface always shows Ohmic contact behaviour at the backside. (b) Typical (I–V) results are shown here. Similar changes in the sensor response are observed for single crystal (s.c.) or thin film samples of TiO$_2$. For details, see text, Schierbaum *et al.* (1992), Schierbaum & Göpel (1994), Göpel (1990) and Wiemhöfer & Göpel (1991).

Recent investigations aim at miniaturizing these devices down to the atomic scale. The two different sensor operation modes may be adjusted intentionally at medium temperatures by externally applying a positive or negative DC voltage to the Pt electrode and by thereby switching the effective platinum charge of neutral Pt^0 to ionic Pt^{2+} or Pt^{4+} species and vice versa with the tip of an STM. This also switches the sensor as well as the catalytic properties of the Pt–TiO$_2$ interface. The next step is to perform this switching with individual Pt atoms in an STS setup and to modify the current–voltage curves taken at individual surface or subsurface Pt sites by charge transfer reactions as they occur during chemical sensing of donor- or acceptor-type molecules.

(c) *Ion conductors: ZrO$_2$*

ZrO$_2$ is widely used as a chemical sensor to monitor O$_2$ by utilizing its high-temperature ion (O^{2-}) conduction in the bulk. In potentiometric devices, the cell voltage is determined by the pressure difference between two Pt contacts of ZrO$_2$ samples. In amperometric devices, the current is monitored at a given voltage. Of key importance for both applications is the stability of the three-phase boundary at which oxygen molecules from the gas phase are converted to ions in the solid (figure 8). A detailed understanding of potentiometric devices is deduced from an experimental determination of the energetic position of the Fermi level E_F under various operation conditions (figure 9).

By externally applying a voltage, the value of E_F at the electrode and thereby the concentrations and chemical reactivities of different oxygen species at the surface may be shifted intentionally with reference to a constant electrochemical potential
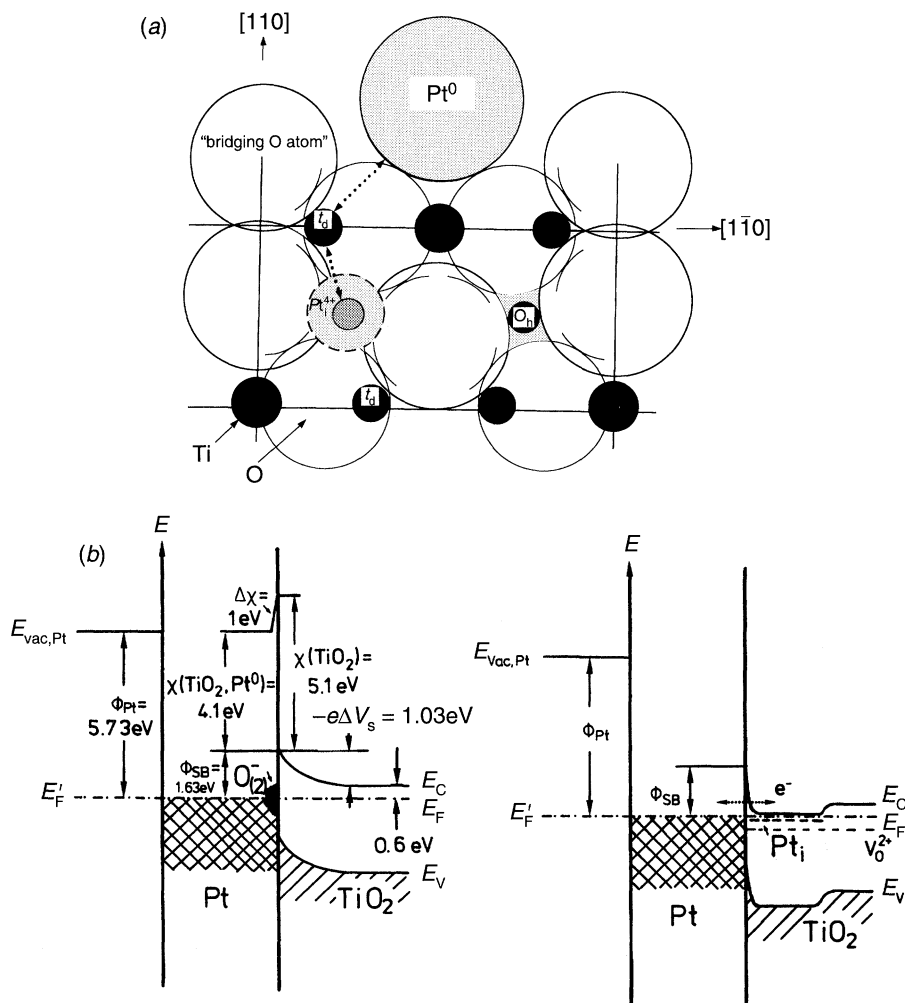
Figure 7. (*a*) Surface and subsurface geometry of metallic Pt^0 atoms, ionic Pt^{4+} ions, tetrahedronal interstitial sites t_d, octahedral interstitial sites O_h at $TiO_2(110)$ surfaces and the diffusion path of Pt between the surface and the subsurface site (dotted line); (*b*) energy diagram and characteristic reactions leading to changes in the Schottky-barrier and Ohmic-contact behaviour, respectively, of Pt–$TiO_2(110)$. E_F is the Fermi level, Φ_{SB} the Schottky-barrier height, $e\Delta V_s$ the band bending, $\Delta\chi$ the change in electron affinity upon evaporation of Pt atoms onto TiO_2, E_{vac} the vacuum level, E_V and E_C the valence and conduction band edge, respectively. For further details, see text, Schierbaum *et al.* (1992), Schierbaum & Göpel (1994) and Fischer *et al.* (1995).

of an oxygen reference electrode (i.e. a suitable metal–metal oxide system such as Ni–NiO or Pd–PdO). This leads to variations in the kinetics of different electrocatalytic reactions, some of which are illustrated in figure 10. As a result, different educts from the gas phase react predominantly at different voltages. The charge transfer rate monitored in this amperometric operation mode at constant voltage is then determined by the concentration of educts in the gas phase which compete with O_2 to form a mixed potential at the surface. Recent developments of new electrode materials (mostly perowskites) make possible the amperometric detection of CO or NO_2 and lead to very efficient catalytic reactions of fuel cells or of electro-catalysts.
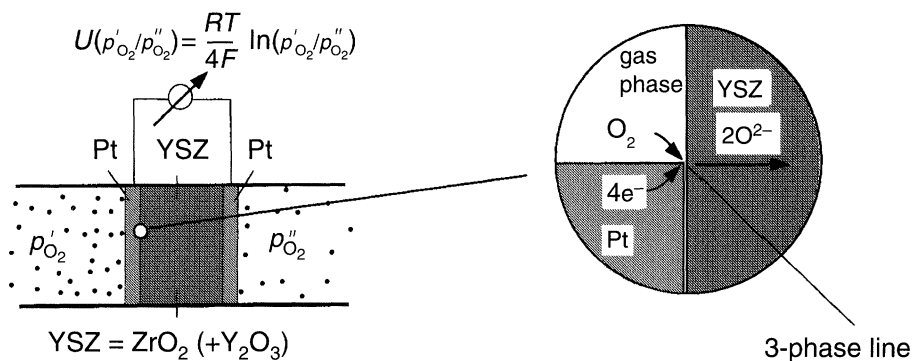
Figure 8. Schematic presentation of the three-phase boundary in Y-stabilized ZrO_2 (YSZ) sensors to monitor differences of oxygen partial pressures in the gas phase. The Nernst equation in the upper part describes the potentiometric sensor response (voltage U) upon differences in partial pressures p_{O_2} with F as the Faraday constant and the number 4 representing the number of electrons transferred per O_2 molecule to form O^{2-} ions in the bulk of ZrO_2.

The miniaturization of such devices is limited by several fundamental aspects of physical chemistry concerning the required properties of the bulk and electrode materials. The first aspect concerns the electron conducting electrodes. Large differences in the surface free energies between metallic Pt and oxidic ZrO_2 cause adhesion problems. Relatively large three-dimensional Pt clusters are required to form a spatially coherent net of an electron conducting contact which allows the O_2 to access the three-phase boundary gas–electrode–solid electrolyte (left part of figure 8). For lower cluster concentrations, percolation effects become crucial. Miniaturization of such contacts is therefore more promising if mixed conducting perowskites with surface free energies similar to ZrO_2 are used, which form continuous overlayers (right part of figure 10). The ultimate limit to reduce the thickness of such mixed conducting layers and of ion-conducting ZrO_2 thin films (which have to be impermeable for neutral O_2 molecules) in these sandwich devices cannot be estimated yet because corresponding epitaxial thin film structures have not been prepared and, as a result, conductivity phenomena in monolayer thin films have not yet been investigated. Evidently, the commonly used scaling laws in the size reduction of microelectronic devices cannot be applied under these conditions and local bonding, as well as quantum size effects, must be taken into account when adjusting the chemical and electronic properties of ultrathin films.

Typical surface and interface properties to be controlled in such devices are summarized below in figure 11, a few typical geometric arrangements of thin film devices are also shown below in figure 15.

Because of the experimental problems in preparing ideal epitaxial thin films with a structural control in the monolayer range, the different transport phenomena of charged or neutral particles in these films and across their interfaces are not yet understood on the atomic scale. Consequently, ultimate limits for the miniaturization of these chemical sensors cannot be estimated precisely. Particular problems arise from the fact that the long term stability and reversibility are the most important properties for any application of future 'nanosensors'.
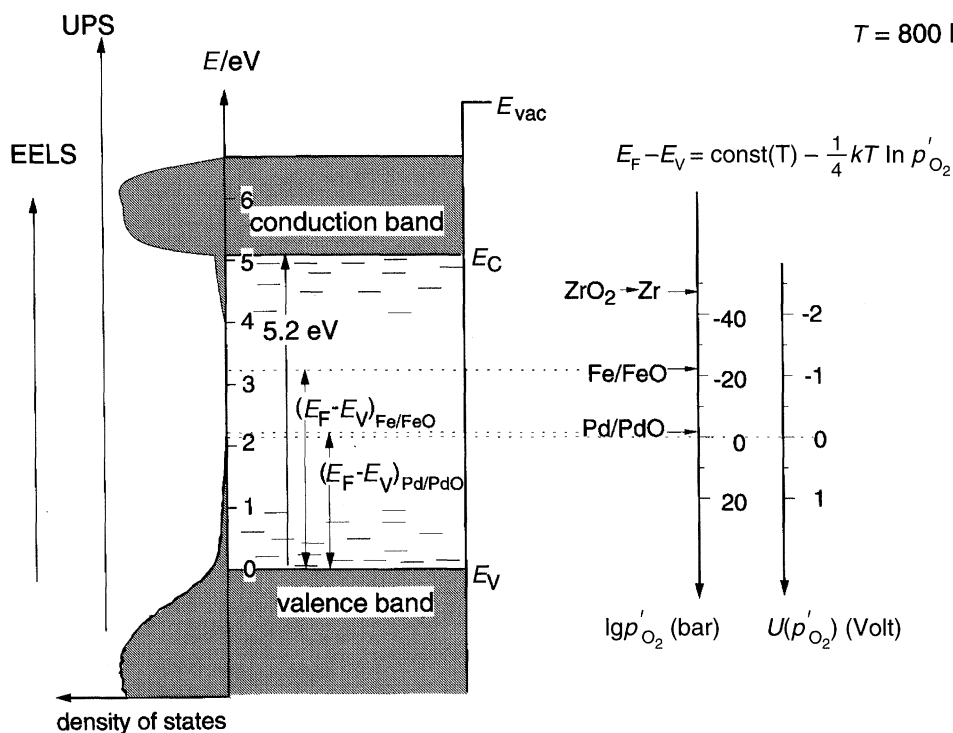
Figure 9. Electron energies in a band scheme of YSZ (compare notation in figure 4). These experimental data, from *in situ* electron energy loss (EELS) and ultraviolet photoemission (UPS) spectroscopic results, were obtained for different partial pressures of oxygen in measurements using reference contacts based on metal–metal oxide systems. At constant temperature ($T = 800$ K was chosen here), the reference contacts (Fe–FeO and Pd–PdO) determine the chemical potential of oxygen at the energetic positions as indicated in this figure. The YSZ sample decomposes for E_F positions above the ZrO_2–Zr equilibrium. Voltages are referred to an oxygen partial pressure of 1 bar (with the reference voltage $U = 0$ V). Applied voltages shift the Fermi level relative to the reference contacts chosen in the experiment. This leads to the nominal drastic variations in the oxygen partial pressures also indicated in this figure. For details, see figure 10, Göpel (1992), Wiemhöfer *et al.* (1991) and Wiemhöfer (1993).

(d) Molecular cages: calixarenes and resorcinarenes

A completely different optimization is required for chemical sensors which make use of supramolecular recognition structures. Typical molecules for utilizing the geometric 'key-lock' principle are calixarenes, which incorporate small molecules (figure 12). Signal transduction of these sensors is possible by monitoring changes in mass, capacitance or temperature upon incorporation of organic molecules. The geometry of these calixarenes may be modified by substituting atoms in the ring or by using different numbers of repeat units in the ring. The molecule–ring interaction energies can be calculated with sufficient accuracy by force-field approaches (figure 12).

To achieve a controlled key–lock geometry, the covalent coupling of cage compounds to Au(111) via sulphur bridge bonds may be used to advantage in chemical sensors. An example is the structure shown in figure 13, which shows a two-dimensional layer of resorcinarenes on Au(111) as the coating of a mass-sensitive transducer (Schierbaum *et al.* 1994).

The ultimate step towards miniaturization of these sensors is to manipulate indi-
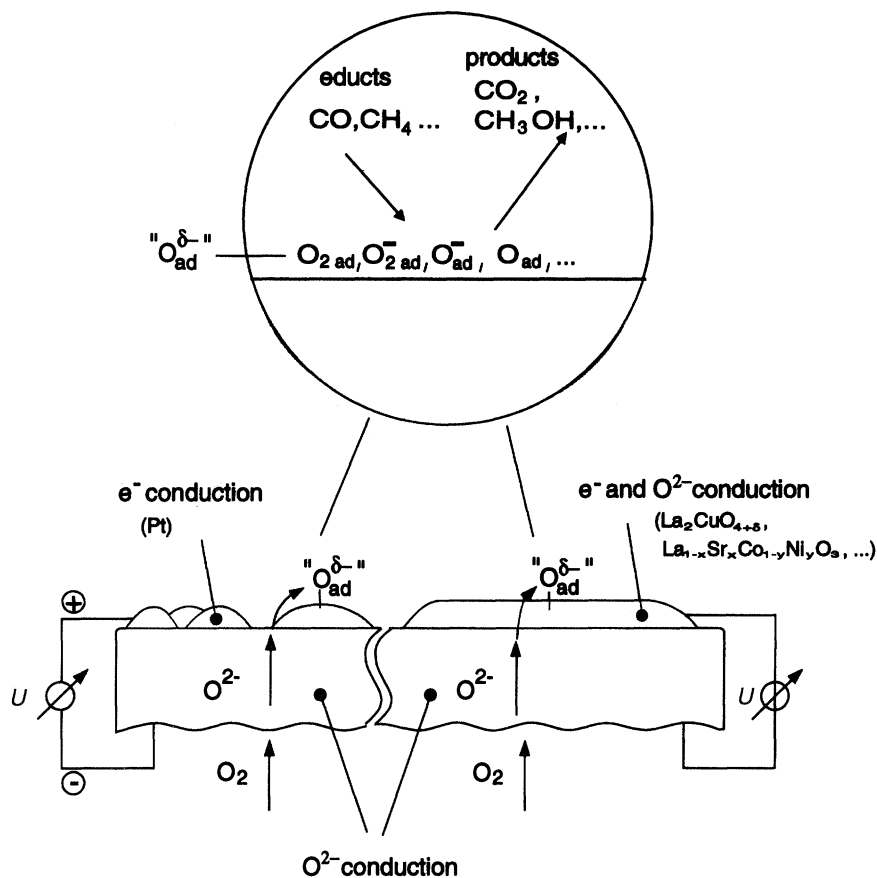
Figure 10. Schematic illustrations of typical oxygen surface species, electrocatalyst reactions, sensor parameters and fuel cell properties of ion conductors which change by applying an external voltage. The electrode forms either a three-phase boundary (e.g. Pt–YSZ–gas, left part) or a two-phase boundary (perowskite–gas, right part). For details, see text, Göpel (1992), Wiemhöfer et al. (1991) and Wiemhöfer (1993).

vidual molecules with a cage-modified STM tip. This approach is particularly promising if the tip voltage causes sufficient changes in the interaction energies.

(e) Monomers, polymers and oligomers

Lead phthalocyanine (PbPc) is the best known *monomeric* organic compound which, in a thin film device, may be used to monitor NO_2 by conductivity changes. PbPc had also been investigated in view of its potential application for molecular computers (Göpel et al. 1991, 1992; Göpel & Ziegler 1992; Göpel 1995a, b, 1992; Mockert et al. 1989). Switching effects observed in Au–PbPc–Au sandwich structures had been described by transitions of Pb ions in the non-planar ring from one side to the other for linearly aligned PbPc molecules in a monoclinic crystal structure. These experimental findings, however, turned out to be unreproducible and based upon irreversible electromigration of Au atoms which short-circuit the Au contacts on both sides of the thin PbPc layer along the grain boundaries (Ottenbacher et al. 1991).
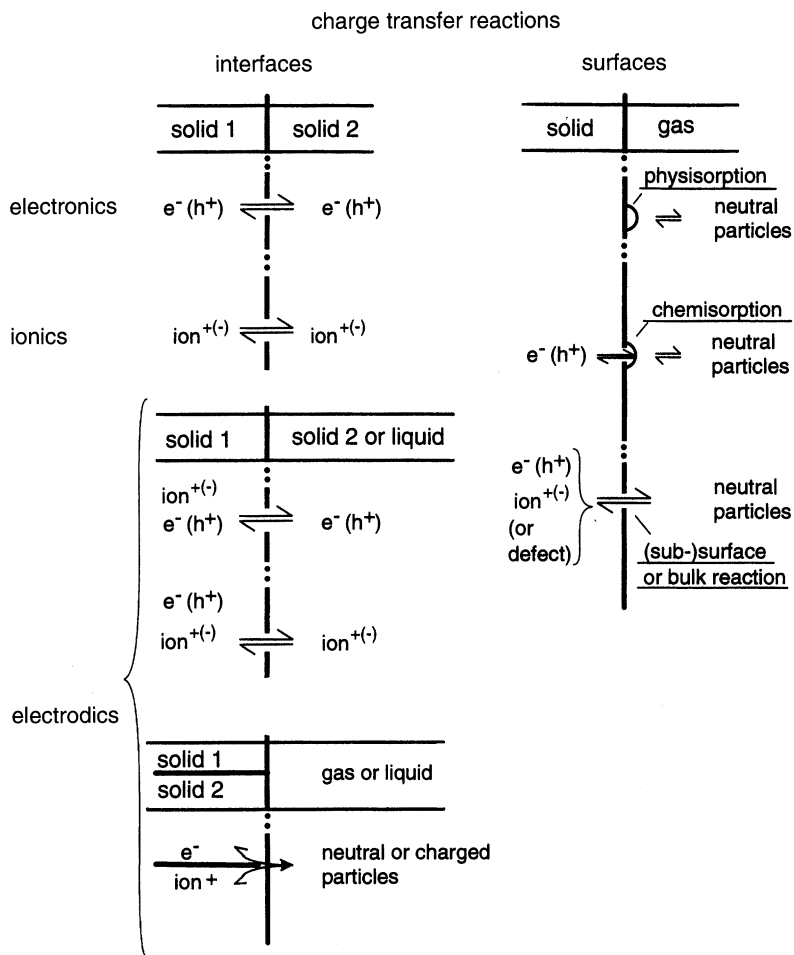
Figure 11. Survey on interfaces and surfaces of electronic or ionic devices including chemical sensors. For details, see text.

Unfortunately, such degradation effects are a common phenomenon in molecular systems: because of the increasing electrical fields and high diffusion coefficients in organic sandwich devices with decreasing size (but constant operation voltage), electromigration of their metallic contacts often limits the miniaturization for future sensor or molecular electronics components.

In contrast to monomers with their limited use as sensor materials, *polymers* have been widely used as very reliable chemical sensor materials. A huge variety of different polymers is available and shows reversible interactions with a variety of organic and inorganic molecules. Typical transducers monitor changes in the *mass*, *complex impedance* or *temperature* (see typical examples for polymer–gas partition coefficients $f_{p/g}^0$ determined from mass changes in figure 14). Because of the statistical local order in polymers, miniaturization of such sensors is, in principle, limited.

Recent developments therefore aim at the preparation of well-ordered *oligomers* with a controlled chain length. Examples include α-oligothiophenes with their potential use in thin film transistors. Different contact geometries, which could be used
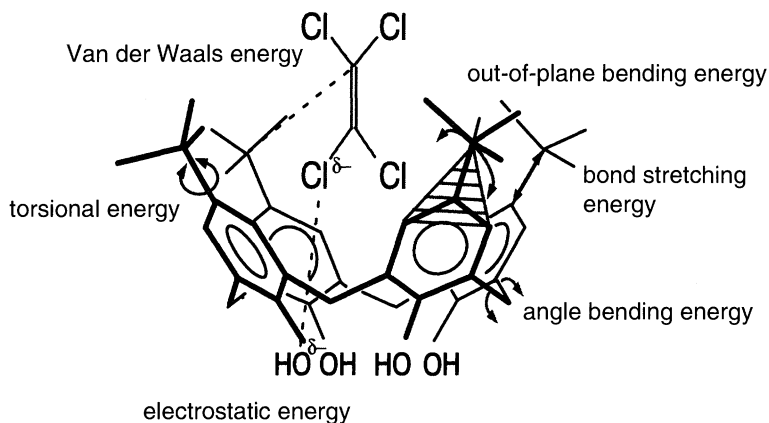
Figure 12. Schematic presentation of 'key-lock' interactions between C_2Cl_4 as a typical organic molecule and calix(4)arene with different contributions to the overall interaction energy E_{tot} as determined from force field calculations: $E_{tot} = \sum E_{vdw} + \sum E_{tors} + \sum E_{elec} + \sum E_{oop} + \sum E_{str} + \sum E_{bend}$. For details, see Göpel (1991), Schierbaum *et al.* (1992, 1993*b,c*), Schierbaum & Göpel (1993) and Dominik *et al.* 1994.

for molecular sensors based on monomers or oligomers, are shown in figure 15. Systematic experiments, however, are missing, which concern the stability of electrical contacts of oligomers with thicknesses in the monolayer range.

(*f*) *Biomolecular function units*

Hybrid structures with inorganic, organic and biological function units that make use of biospecific recognition may be divided into four categories, with an increasing complexity of structures and functions.

(i) *Systems based on bioaffinity*

A variety of receptor-based interactions may be used for highly selective biomolecular recognition. The controlled preparation of thin films with embedded receptor structures of high molecular weight is a difficult task. One approach is therefore to mimic the biological function by fully synthesizing structures of lower molecular weight, which represent a copy of the recognition site of the biological function unit. This 'biomimetic' approach was chosen in a typical example illustrated in figure 16. Layers of synthetic peptide epitopes with two different alkane thiols are covalently coupled to gold substrates by using a mixed composition of small (unmodified) and large (epitope modified) molecules. Low surface coverages of the latter are required for thin film devices to selectively monitor large biomolecules. In this case, the antibodies of the foot-and-mouth disease virus have been detected, after their attachment to the epitopes, by monitoring capacity variations of the sandwich structure. The signal transduction across the interface determines the sensitivity in these devices and limits their minimum lateral dimensions.

(ii) *Systems based on catalytic activity*

Enzymes are particularly suitable for biomolecular recognition. The catalytic activity of their active sites may be sensitively monitored by changed electrochemical behaviour at the electrode. This, however, requires a 'molecular wiring' which makes an ionic or electronic charge transfer possible. A few different concepts are indicated
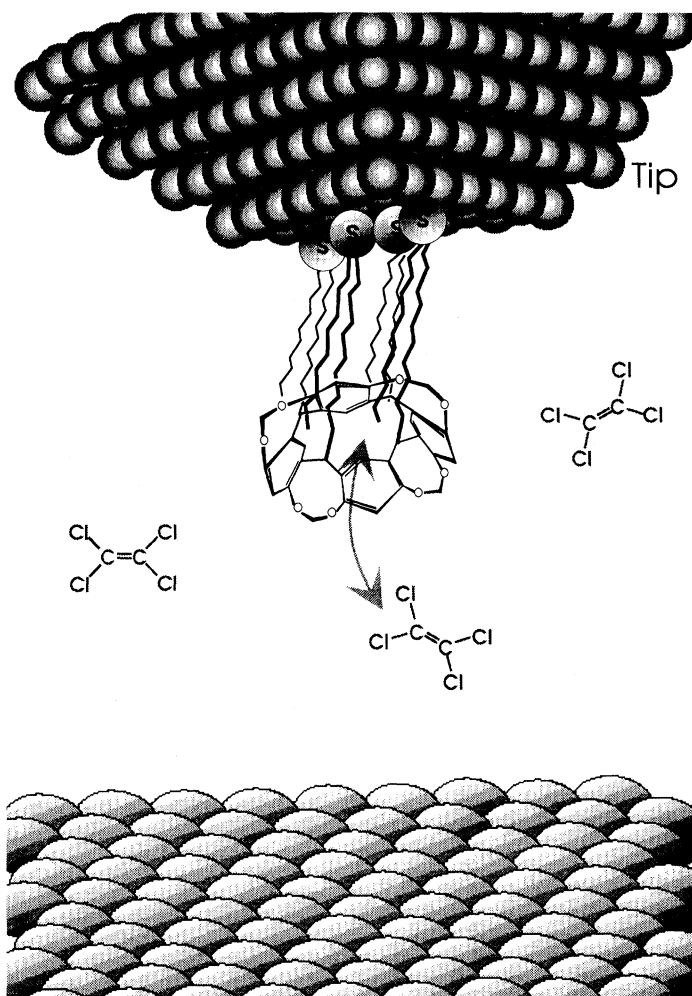
Figure 13. Schematic representation of thiol-coupled resorcinarenes on Au(111) surfaces, which, as a thin film device, are known to selectively incorporate the organic molecule perchloroethylene (Schierbaum *et al.* 1994): in this presentation a suggestion is made to use the modified tip for depositing organic molecules at controlled sites of an underlying substrate by, e.g. modifying the tip voltage.

in figure 17. None of these molecular wiring concepts, however, is understood yet on the molecular scale, even for the best understood enzyme glucose oxidase with its molecular weight of 186.000 atomic mass units.

(iii) *Transmembrane channels, carriers and pumps*

Because of their great importance in the living cell, a variety of such biomolecular function units has been identified and may in the next step be utilized as components of future 'intelligent' biomolecular devices, provided that they can be contacted or interfaced to appropriate transducers. To achieve stability, they must be incorporated in natural or synthetic bilayers. A recent example is the cotransporter molecule lactose permease (LP) which shows a 1:1 active transport of protons and lactose molecules (figure 18). In an ion-sensitive field effective transistor (ISFET) arrangement, this proton makes it possible to monitor variations in the lactose con-
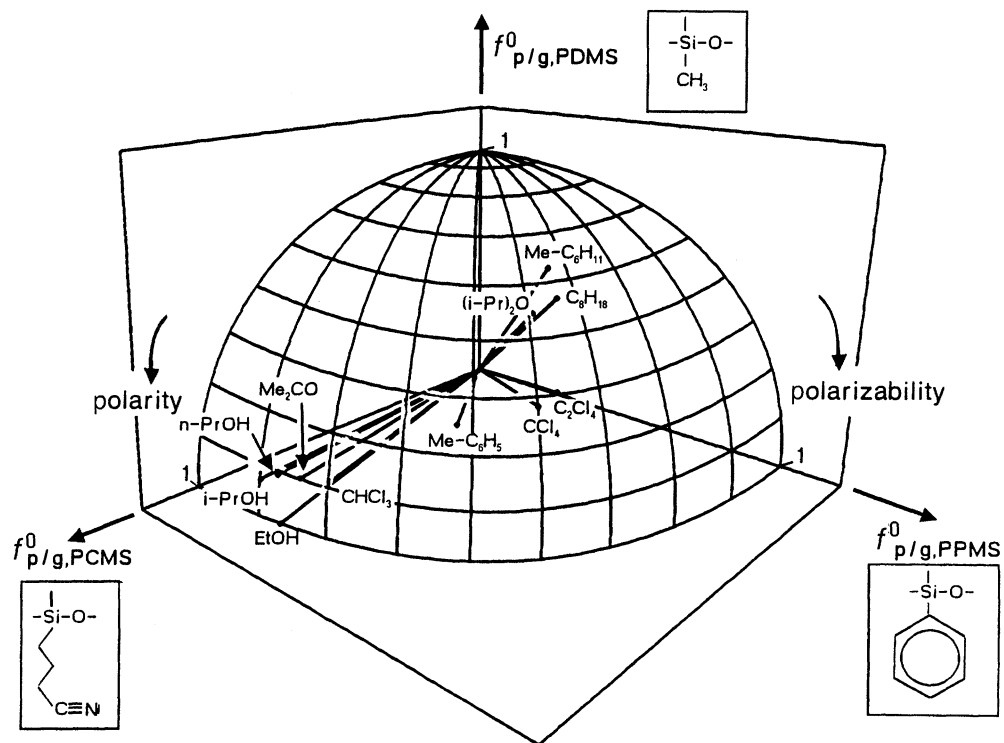
Figure 14. Typical sensor results of different polymers which monitor different organic volatiles by different selectivities in their response behaviour. Changes in the mass of three thin film devices have been recorded by quartz crystal oscillators as transducers coated with polydimethyl-siloxane (PDMS), polycyanopropylmethlysiloxane (PCMS) and polyphenylmethylsiloxane (PPMS). The three-dimensional plot of normalized response vectors ($f_{p/g}^0$ (PCMS), $f_{p/g}^0$ (PDMS), $f_{p/g}^0$ (PPMS)) describes their contribution to the sensor signals expressed by the partition coefficients of different gases in PCMS, PPMS and PDMS. The end points of each vector are positioned at a spherical surface which is represented here by azimuthal and longitudinal lines. The small figures indicate monomeric units of the different polysiloxanes with the polar cyano groups in PCMS, the polarizable aromatic ring in PPMS, and the methyl group in PDMS. C_8H_{18} = n-octane; Me–C_6H_{11} = methylcyclohexane; C_2Cl_4 = perchloroethylene; $CHCl_3$ = chloroform; CCl_4 = tetrachloromethane; Me–C_6H_5 = toluene; i–Pr_2O = isopropylether; Me_2CO = acetone; EtOH = ethanol; n–PrOH = n-propanol; i–PrOH = iso-propanol; n–$BuNH_2$ = n-butylamine;

$$f_{p/g,PCMS}^0 = f_{p/g,PCMS}/[f_{p/g,PCMS}^2 + f_{p/g,PDMS}^2 + f_{p/g,PPMS}^2]^{1/2};$$
$$f_{p/g,PPMS}^0 = f_{p/g,PPMS}/[f_{p/g,PCMS}^2 + f_{p/g,PDMS}^2 + f_{p/g,PPMS}^2]^{1/2};$$
$$f_{p/g,PDMS}^0 = f_{p/g,PCMS}/[f_{p/g,PCMS}^2 + f_{p/g,PDMS}^2 + f_{p/g,PPMS}^2]^{1/2}.$$

Further explanations are given in the text and in Göpel (1991), Schierbaum *et al.* (1992, 1993*b*, *c*), Schierbaum & Göpel (1993) and Göpel (1995*a*).

centrations in the outer compartment by monitoring pH changes in the inner ISFET compartment. Perfect spriting of the modified bilayer and stabilizing the thickness of the inner compartment between the bilayer and the transducer are the main issues of current R+D in this field, which limit their miniaturization and perfection.

(iv) *Membrane receptors, cells and tissues*

These systems perform sophisticated tasks related to information transfer in life organisms and, hence, are of principal interest for future bioelectronic or hybrid ('biological–man made') devices. Any practical utilization of such systems, however,
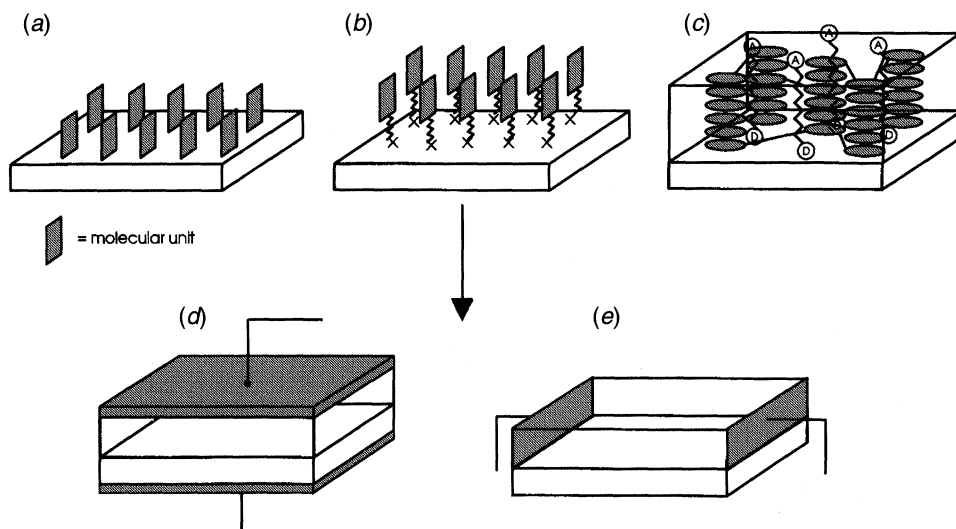
Figure 15. Schematic presentation of different ways of controlled deposition of organic monolayers for their subsequent application in electron conducting or capacitive devices. Systematic studies have been performed, for instance, for α- and end-capped oligothiophenes (αnT, $ECnT$) with different chain lengths $n = 4$–8 (Oeter *et al.* 1993*a,b*, 1994). (*a*) physisorbed; (*b*) chemisorbed; (*c*) the oriented arrangement of a donor (D)/spacer/acceptor (A) molecule for optical switching in a matrix of inactive molecules is illustrated schematically; (*d*) and (*e*) two different contact geometries are indicated. For spatial distances of contacts in the nanometre range, quantum effects may on principle be detected. A variety of different contact geometries may be chosen to optimize specific requirements of electrical measurements in chemical sensing.

has to take into consideration their very complex supramolecular structures. The controlled immobilization, e.g. in thin film devices, requires careful fine-tuning of stabilities and only model systems with reconstituted activities of neuro-receptors could be realized so far.

A variety of different concepts have been developed to deduce electrical signals from membrane receptors or from even more complex biological systems such as whole cells or tissues. Some typical setups are characterized schematically in figure 19. High spatial resolution of outer point contacts to monitor ionic or electronic currents is desired to, for example, understand the function of individual trans-membrane proteins. Using metallically conducting substrates, electrical extracellular signals may be monitored. Although details about the signal transduction in this arrangement are still not understood, the signals may formally be described by electrical equivalent circuits. They may be correlated with the metabolism in the cell, and may hence be used to investigate the influence of drugs on the cell metabolism. Evaluation of signals from an array of many cells improves the statistics and, hence, empirical correlations. Arrays may also be used to investigate cell–cell interactions, learning processes in neural networks, etc. In all of these applications, however, comparative patch-clamp and extra-cellular signals obtained in controlled geometric arrangements of the electrodes are highly desired but still missing.

3. Summary and outlook

The few case studies discussed in this paper illustrate the importance of a controlled signal transduction across interfaces of carefully chosen sandwich systems for today's or future chemical or biochemical sensors.
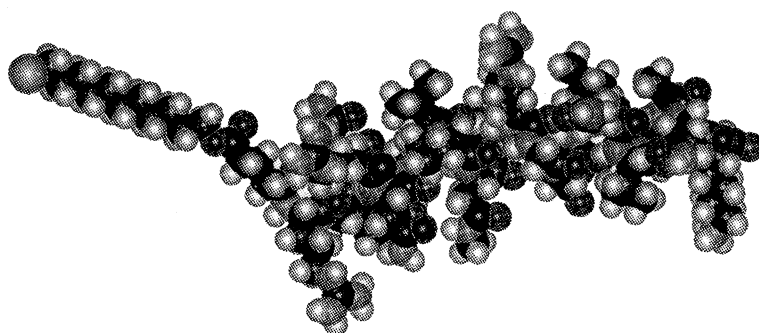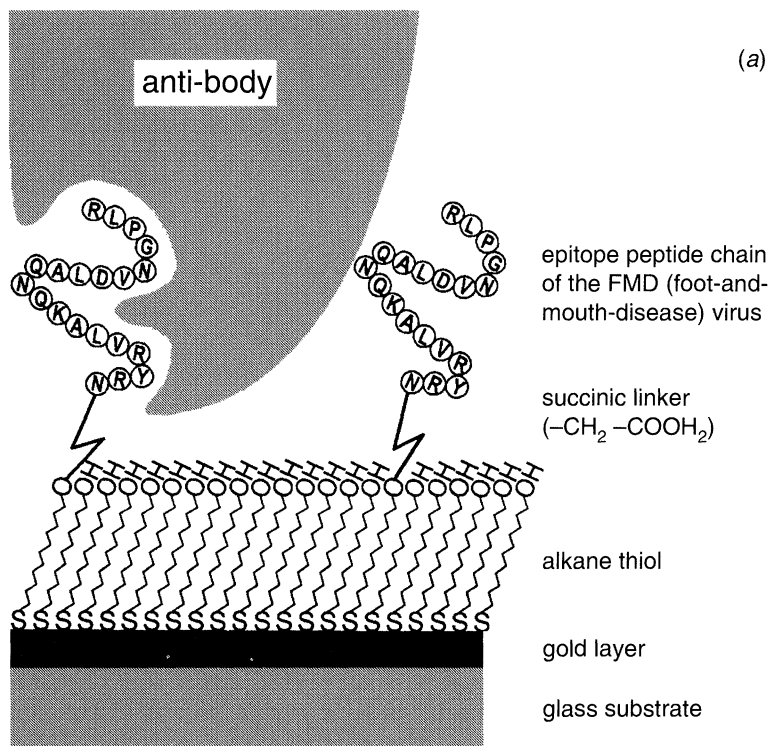
Figure 16. (a) Schematic presentation of the covalent coupling of two different alkanthiol units to Au(111). The longer component contains an epitope which selectively interacts with an antibody (foot-and-mouth disease virus). (b) Space fill representation of the thiol-modified epitope peptide chain with thiols on the left and peptides on the right-hand side (Heiduschka *et al.* 1994; Knichel *et al.* 1995).

The molecular understanding of chemical sensing *ipso facto* requires to understand 'key-lock' structures on the nanometre scale. One might therefore consider all chemical sensors as nanosensors. The geometric arrangement of chemically sensitive structures may be achieved in the form of an organized monolayer, which shows nanometre dimensions only in the direction of the film normal, but macroscopic dimensions in the two other directions perpendicular to the film normal. The next step
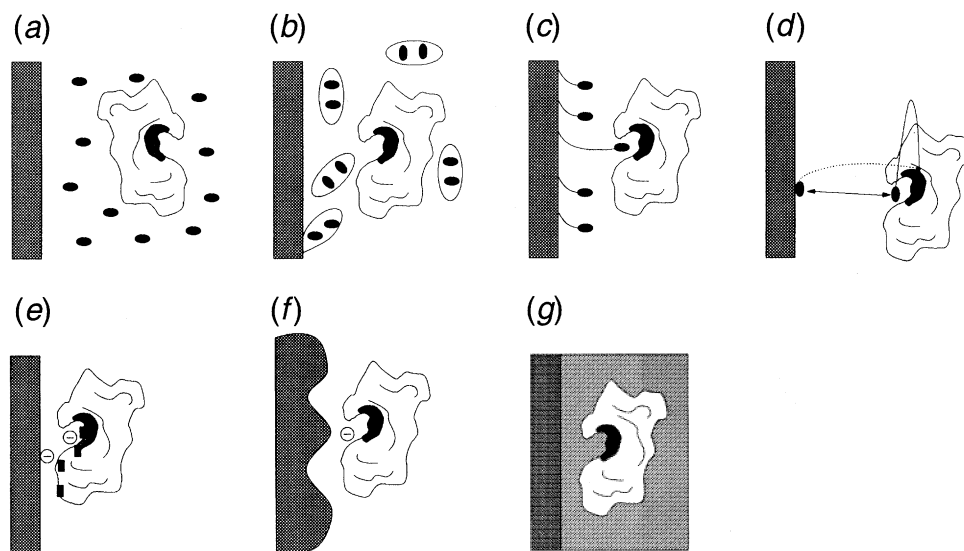
Figure 17. Different concepts for mediators linking the information about the electrochemical status at the catalytically active centre of the enzyme with the electrode (Schuhmann *et al.* 1990; Löffler *et al.* 1991).
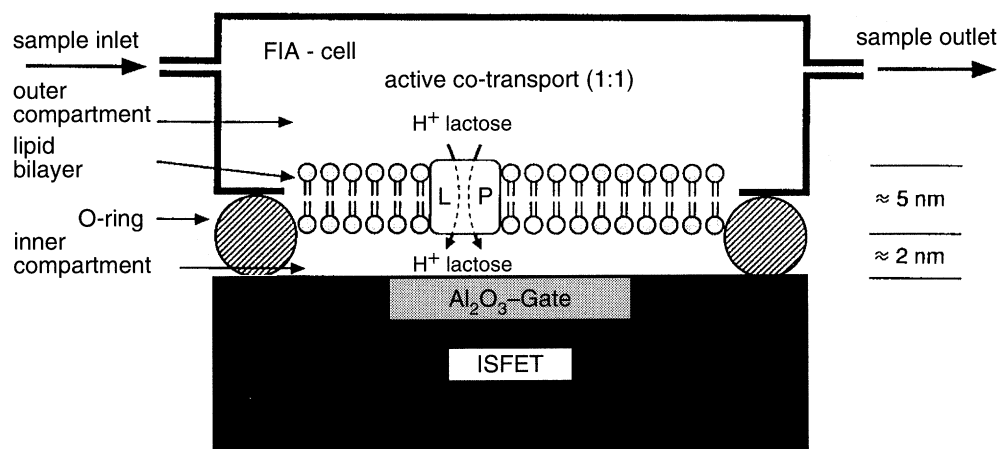

Figure 18. Schematic presentation of a biosensor based upon an active cotransport using lactose permease (LP) which transports protons and lactose in a strictly 1:1 ratio in a flow injection analysis (FIA-cell) arrangement. Lactose may be monitored by monitoring pH changes with an ion-sensitive field effect transistor (ISFET) (Ottenbacher *et al.* 1993; Göpel *et al.* 1989).

is to arrange chemically sensitive structures with nanometre sizes in two dimensions, or even three dimensions, with an increasingly difficult task to address individual chemically active sites with controlled signal transduction.

The 'man-made' inorganic materials and, in particular, the electron conducting sensor materials will make it possible to develop 'bottom-up' concepts in which individual active sites of chemical sensors are addressed and controlled. Of particular interest in this context is scanning tunnelling spectroscopy (STS) combined with STM and AFM imaging in different contact modes.
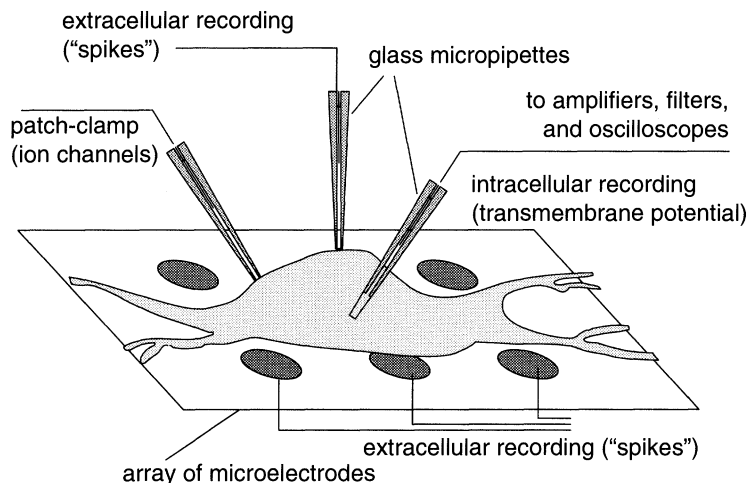
Figure 19. Schematic presentation of different electro-physiological recording techniques to investigate cells or neurons in a network (Hämmerle 1995). For further details, see Göpel (1994) and Göpel & Heiduschka (1994).

The use of 'natural' biological materials is particularly promising if a combination of biological and synthetic structures, i.e. a hybrid approach, is chosen to build chemical sensor systems. Again the controlled signal transduction across interfaces plays the central role in current research.

By systematically replacing, adapting or exchanging step by step the different components of sensor systems (cf. figure 2) in the two different worlds (i.e. the 'electronic nose' and the 'human nose'), a systematic improvement in the understanding of recognition and signal generation, signal processing and data storage is obtained. This will finally lead to experiments in which individual reversible reactions are controlled on the molecular level.

References

Dominik, A., Roth, H. J., Schierbaum, K. & Göpel, W. 1994 Supramolecular complexes based on calixarenes: force field calculations and applications for chemical sensors. *Supramol. Sci.* **1**, 11.

Fischer, S., Munz, A., Schierbaum, K. D. & Göpel, W. 1995 The geometric structure of intrinsic defects at TiO_2 (110) surfaces: an STM study. *Surf. Sci.* **337**, 17.

Göpel, W. 1985 Chemisorption and charge transfer at ionic semiconductor surfaces: implications in designing gas sensors. *Progr. Surf. Science* **20**, 9.

Göpel, W. 1989 Solid state chemical sensors: atomistic models and research trends. *Sensors and Actuators* **16**, 167.

Göpel, W. 1990 Atomistic understanding of sensor mechanisms: spectroscopic studies at prototype electronic and ionic conductors. In *Conf. Proc. Solid State Ionics '89 (Hakone)*; *Solid St. Ionics* **40/41**, 1009.

Göpel, W. 1991 Chemical sensing, molecular electronics, and nanotechnology: interface technologies down to the molecular scale. In *Conf. Proc. Eurosensors IV (Karlsruhe)*; *Sensors and Actuators* B **4**, 7.

Göpel, W. 1992 Future trends in the development of gas sensors. In *Gas sensors* (ed. G. Sberveglieri), pp. 365ff. Dordrecht: Kluwer. ISBN: 07923-2004-2.

Göpel, W. 1994 New materials and transducers for chemical sensors. In *Conf. Proc. Eurosensors V (Budapest)*; *Sensors and Actuators* **18–19**, 1.

Göpel, W. 1995*a* Supramolecular and polymeric structures for gas sensors. In *Conf. Proc. 5th Int. Meeting on Chemical Sensors (Rome)*; *Sensors and Actuators* B **24**–**25**, 17.

Göpel, W. 1995*b* Controlled signal transduction across interfaces of intelligent molecular systems. In *Proc. 2nd. CEC-Workshop on Bioelectronics (Frankfurt)*; *Biosensors Bioelectronics* **10**, 35.

Göpel, W. & Heiduschka, P. 1994 Introduction to bioelectronics: interfacing biology with electronics. In *Conf. Proc. 2nd European Workshop on Bioelectronics (Frankfurt, 11/1993)*; *Biosensors Bioelectronics* **9**, iii.

Göpel, W. & Heiduschka, P. 1995 Interface analysis in biosensor design. In *Invited Talk 3rd. World Cong. on Biosensors (New Orleans)*; *Biosensors Bioelectronics* (in the press).

Göpel, W. & Schierbaum, K. 1994 SnO_2 sensors: current status and future prospects. In *Conf. Proc. Eurosensors VIII (Toulouse)*; *Sensors and Actuators* B **26**, 1.

Göpel, W. & Ziegler, Ch. (eds) 1992 *Nanostructures Based on Molecular Materials.* Weinheim: VCH. ISBN 3-527-28416-8.

Göpel, W., Hesse, J. & Zemel, J. N. (eds) 1991 and 1992 *Sensors: a comprehensive survey* vol. 1– 8. Weinheim: VCH. In particular see vols 2 and 3: *Chemical and biochemical sensors* ISBN 3-527-26768-9 and ISBN 3-527-26769-7.

Göpel, W., Gauglitz, G., Jung, G. & Jähnig, F. 1989 Biosensor systems based upon receptor functions. In *Proc. Int. Workshop 'Biosensors' (Braunschweig)*; 1990 *GBF Monographs* vol. 13, pp. 165–177. Weinheim: VCH.

Heiduschka, P. *et al.* 1995 Utilisation of a mixed self-assembled monolayer in an impedimetric immunosensor. In *Conf. Proc. 3rd. World Cong. on Biosensors (New Orleans)*; *Sensors and Actuators* **28**, 85–94.

Knichel, M., Heiduschka, P., Beck, W., Jung, G. & Göpel, W 1995 Utilisation of a self-assembled peptide monolayer for an impedimetric immunosensor. *Sensors and Actuators* B **28**, 85.

Löffler, U., Wiemhöfer, H.-D. & Göpel, W. 1991 Amperometric biosensors: characterisation of dispersed mediator systems. In *Conf. Proc. Biosensors '90 (Singapore)*; *Biosensors Bioelectronics* **6**, 343–352.

Mockert, H., Schmeisser, D. & Göpel, W. 1989 Leadphthalocyanine (PbPc) as a prototype organic material for gas sensors: comparative electrical and spectroscopic studies to optimize O_2 and NO_2 sensing. *Sensors and Actuators* **19**, 159.

Oeter, D., Ziegler, Ch., Naarmann, H. & Göpel, W. 1993a Undoped and doped oligothiophenes: an in-situ XPS-, UPS, and HREELS-study. In *Conf. Proc. 'In-Situ Investigations of Physico-chemical Processes at Interfaces, Bunsen Discussion Meeting (Lahnstein, 10/1992)*; *Ber. BunsenGes. Phys. Chem.* **97**, 448–451.

Oeter, D., Ziegler, Ch. & Göpel, W. 1993b Doping and stability of ultrapure α-oligothiophene thin films. In *Conf. Proc. E-MRS Spring Meeting (1993, Strassburg)*; *Synth. Met.* **61**, 147–150.

Oeter, D., Egelhaaf, H.J., Ziegler, Ch., Oelkrug, D. & Göpel, W. 1994 Electronic transitions in α-oligothiophene thin films: comparison of UV/VIS and HREELS investigations. *J. Chem. Phys.* **101**, 6344.

Ottenbacher, D., Jähnig, F. & Göpel, W. 1993 A prototype biosensor based on transport proteins: electrical transducers applied to lactose permease. In *Conf. Proc. 4th Int. Meeting on Chemical Sensors (Tokyo, 9/1992)*; 1993 *Sensors and Actuators* B **13**–**14** 173–175.

Ottenbacher, D., Schierbaum, K.-D. & Göpel, W. 1991 Switching effects in metal phthalocyanine metal sandwich structures. *J. Molec. Electron.* **7**, 79.

Schierbaum, K.-D. & Göpel, W. 1993 Functional polymers and supramolecular compounds for chemical sensors. In *Proc. European Materials Research Society Meeting (5/93, Strassburg)*; *Synth. Met.* **61**, 37.

Schierbaum, K. D. & Göpel, W. 1994 Schottky barriers and Ohmic contacts with Pt–TiO_2: implications to control gas sensor properties. In *Adsorption on ordered surfaces of ionic solids and thin films* (ed. H.-J. Freund & E. Umbach), p. 268. Berlin: Springer.

Schierbaum, K.-D., Geiger, J., Weimar, U. & Göpel, W. 1993a Specific palladium and platinum doping for SnO_2-based thin film sensor arrays. In *Conf. Proc. 4th Int. Meeting on Chemical Sensors (Tokyo, 9/1992)*; *Sensors and Actuators* B **13**–**14**, 143.

Schierbaum, K. D., Gerlach, A., Haug, M. & Göpel, W. 1992 Selective detection of organic

molecules with polymers and supramolecular compounds: application of capacitance, quartz microbalance, and calorimetric transducers. *Sensors and Actuators* A **31**, 130.

Schierbaum, K. D., Haug, M., Nahm, W., Gauglitz, G. & Göpel, W. 1993*b* Chemical sensors based upon polysiloxanes: comparison between optical, quartz microbalance, calorimetric, and capacitance sensors. In *Conf. Proc. 1st Europ. Conf. Opt. Chem. Sensors and Biosensors (Graz, 4/1992)*; *Sensors and Actuators* B **11**, 383.

Schierbaum, K.-D., Weiss, T., van Velzen, U. Th., Reinhoudt, B. N. & Göpel, W. 1994 Molecular recognition with self-assembled monolayers of supramolecular compounds. *Science* **265**, 1413.

Schierbaum, K. D., Wei-Xing, X. & Göpel, W. 1992 Solid–gas interactions on surface-doped oxides: C-V, I-V, XPS, UPS, and ELS studies on Pt–TiO$_2$ and Pd–SnO$_2$(110). In *Conf. Prof. 'In-Situ Investigations of Physico-chemical Processes at Interfaces', Bunsen Discussion Meeting (Lahnstein, 10/1992)*; 1993 *Ber. BunsenGes. Phys. Chem.* **97**, 363.

Schuhmann, W., Wohlschläger, H., Lammert, R., Schmidt, H.-L., Löffler, U., Wiemhöfer, H.-D. & Göpel, W. 1990 Leaching of dimethylferrocene, a redox mediator in amperometric enzyme electrodes. In *Conf. Proc. Eurosensors III (Montreux)*; *Sensors and Actuators* B **1**, 571–575.

Weimar, U. & Göpel, W. 1995 AC measurements on tin oxide sensors to improve selectivities and sensitivities. *Sensors and Actuators* B **26**, 13.

Weimar, U., Vaihinger, S., Schierbaum, K.-D. & Göpel, W. 1991 Multicomponent analysis in chemical sensing. In *Chemical Sensor Technology* (ed. N. Yamazoe), vol. III, p. 51. Tokyo: Kodansha.

Wiemhöfer, H.-D. 1993 Processes at interfaces between solid electronic, ionic, and mixed conductors — characterization by voltage and frequency dependent measurements. *Ber. BunsenGes. Phys. Chem.* **97**, 461.

Wiemhöfer, H.-D. & Göpel, W. 1991 Interface analysis for solid state electrochemical devices and chemical sensors. In *Conf. Proc. Angew. Oberflächenanalytik (Kaiserslautern)*; *Z. Analyt. Chem.* **341**, 106.

Wiemhöfer, H.-D., Vohrer, U. & Göpel, W. 1991 Interface analysis for solid state electrochemistry. In *Systems with fast ionic transport (Materials Science Forum 76)* (ed. G. Schuster, K. Künstler & H. Ullmann), pp. 265–268. Zurich: Trans. Tech. Publications.

Zheng, J. G., Pan, X., Schweizer-Berberich, M., Zhou, F., Weimar, U. & Göpel, W. 1995 Growth twins in nanocrystalline SnO$_2$ thin films. *Phil. Mag. Lett.* (submitted).