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Advanced Materials and Measuring Techniques for Chemical Sensors

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Abstract. This overview focuses on modifications of chemical compounds used in the development of chemical sensors, and on materials and chemical sensors which may be sufficiently mature to be used in the industry. Special attention is paid to gas-selective optode membranes which incorporate compounds such as cobyrinate derivatives and Ru(II)complexes that are chemically modified in view of a specific application. New materials are described, *e.g.* the magnesium-selective ionophores currently used for diagnostic applications, and a class of substituted polymethine dyes characterized by an amine donor and a bisdicyanovinylideneindandione acceptor group, where the target pK_a can be modulated by decisive substituents.

Three projects are discussed in more detail: *1*) the development of ion-selective nanoprobes on the basis of coated AFM-tips; *2*) reactands and chromoreactands which are covalently bound to acrylate-based copolymers and allow to monitor alcohols and amines continuously, and *3*) a continuous-flow module integrating a fiber-optical probe that allows to monitor variations in the absorption spectrum of chromoreactands in the transflection mode.

1. Purpose

The Center for Chemical Sensors/Biosensors and bioAnalytical Chemistry, CCS, is celebrating its 5th anniversary this year with a conference named SensLab'99 (see *information* in this issue). The CCS was founded on April 1, 1994. The activities at the CCS are focused on the modelling and synthesis of novel advanced materials for molecular recognition and their specific application in sensor development, the implementation of these materials in chemical sensors and analytical devices for continuous monitoring, and the development of appropriate measuring techniques [1][2]. The backgrounds of the specialists collaborating within the group at the CCS are, accordingly, very diverse. The CCS runs four laboratories (synthetic, electrochemical, optical, and gas-analysis) and is equipped with all the computing facilities needed for molecular modelling and calculations. Detailed information about ongoing projects can be found on our homepage.

2. Projects and Goals

Currently, the center's most challenging projects focus on the development of anion-selective peptides [1], of optical gas sensors in collaboration with *Bosch Telecom GmbH*, Germany, and of gas-permeable polymer layers that form part of an ion-mobility spectrometer by *Bruker AG*, Switzerland. The advanced materials developed at the CCS include, *e.g.*, functionalized polysiloxane copolymers with dedicated gaspermeability. For gas sensors, anion-selective metal complexes such as cobyrinate derivatives, which can be synthesized according to *R. Stepánek* and *B. Kräutler* [3], were modified in collaboration with *Pentapharm AG*, Aesch. Aquocyano[heptakis(2-phenylethyl) cobyrinato]cobalt(III) perchlorate was incorporated into solvent polymeric membranes for the selective analysis of NO_2^- by potentiometric electrodes [4] and optode membranes [5]. It was found that optode membranes incorporating these compounds, combined with a basic indicator, were sensitive to NO_2, providing a detection limit of 50–100 ppb, which is very close to the Swiss legal limit of 39 ppb. The energy consumed during the measurement was less than 30 µW, being much lower than what is needed for most fire-alarm devices on the market [6]. The interactions were reversible.

In another project, tris(4,7-diphenyl-1,10-phenanthroline)ruthenium(II) charge-transfer (CT) complexes were modified by alkylating the 4'-phenyl position (*Fig. 1*) [2]. Alkylation is necessary to solubilize these compounds in apolar polymer matrices which are crystalline up to 120° but which, nevertheless, provide a satisfying quantum yield. The metal complexes are currently being investigated with regard to their quantum yield and chemical stability. Reasons for the strong interest in these metal complexes are, *e.g.*, their favourable physico-chemical characteristics as described by *Bacon* and *Demas* [7], and the fact that Ru(II) complexes can be immobilized, *e.g.*, on 'controlled-pore glass' beads [8]. Such compounds are used in optical sensors to monitor the oxygen partial pressure in the aqueous and in the gas phase. Unlike several other competing complexes, *e.g.*, $Ru(bpy)_3$ (bpy = bipyridyl), the $Ru(II)(ph_2phen)_3$-complexes show a *Stokes* shift of > 100 nm, a relatively high quantum yield, a phospho-

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rescence lifetime of around 1 µs, a relatively good photostability, a weak pH-sensitivity and only weak solvatochromism. The latter has been referred to the high symmetry and the shielding effect of the phenyl moieties [9].

Some of the chemical transducers used in optical sensors provide a link to recent novel trends favoring the use of more and more optical components in information technology. In this field, optics are likely to play a more important role in forthcoming years [10]. Highly polarizable dyes, *e.g.*, polymethine dyes [11] based on the acceptor bis(dicyanovinylidene)indan, are being developed and investigated, and were used as chemical transducers in our optode membranes (*Fig. 1*) [12][13]. The dyes consist of an extended π-electron system, non-centrosymmetrically substituted with an electron-donor goup at one end, and an acceptor group at the other. They are characterized by an absorbance maximum at wavelengths > 630 nm. These are the properties which provide the basis for dyes to be used in second-order nonlinear optics. The pK_a of these dyes can be varied by substituting the dye molecule at an easily accessible position. The dyes are generally not immobilized onto a surface, but dissolved within a plasticized polymer layer for analytical applications. Using another approach, azo- and stilbene-chromophores can be linked to the backbone of an acrylate copolymer, albeit in low concentrations (*ca.* 0.4 weight-%). This project is discussed in more detail in section 3.2.

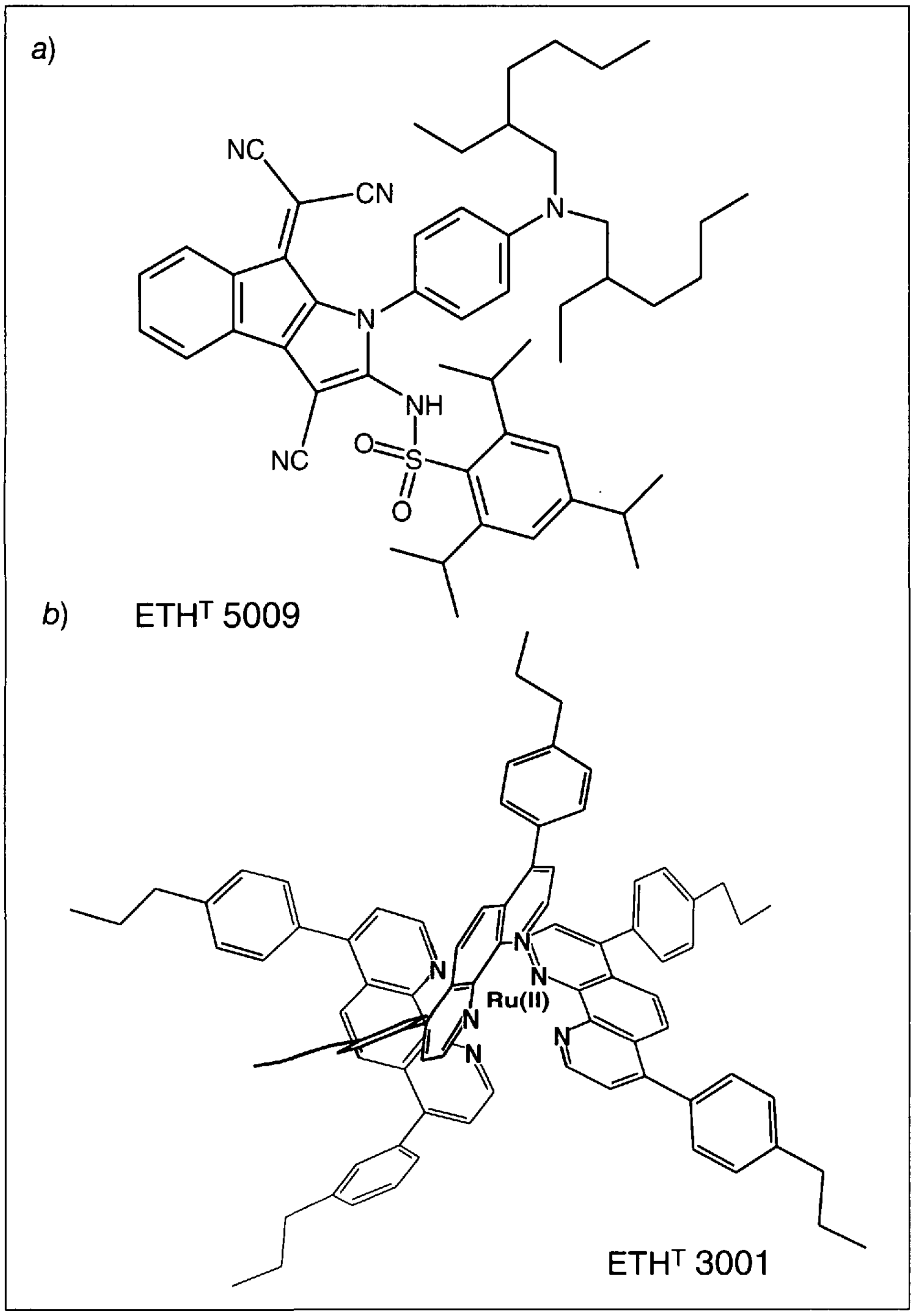


Fig. 1. *Advanced materials. a)* ETH^T 5009, 1-{4-[*N,N*-bis(2-ethylhexyl)amino]phenyl}-3-cyano-8-(dicyanomethylidene)-2-{[2,4,6-tris(1-methylethyl)phenyl]sulfonamido}-8*H*-indeno[2,1-*b*]pyrrole, apparent pK_a (PVC/DOS membrane): 7.5 ± 0.2; $\lambda_{max\ protonated}$ (MeOH): 498 nm, ε/cm^2 mol^{-1}: 2668; $\lambda_{max\ deprotonated}$ (MeOH): 638 nm, ε/cm^2 mol^{-1}: 8815 [45][13]. *b)* ETH^T 3001 to 3003: tris(4,7-diphenyl-1,10-phenanthroline)ruthenium(II) charge-transfer (CT) complexes were modified by alkylating the 4'-phenyl position by $-C_3H_7$, $-C_7H_{15}$, and $-C_8H_{17}$ substituents [2]. The structure was established by X-ray crystallographic analysis of the non-alkylated complex (*V. Gramlich*, crystallography/petrography ETH-Zürich) and confirmed by ^{1}H-NMR, ^{13}C-NMR, and elemental analysis.

The investigation of magnesium-selective ionophores, which has been one of the long-lasting research activities in the group of Prof. *W. Simon* [1][14], has resulted in a set of three useful compounds: ETH^T 3832, ETH^T 5504 and ETH^T 5506. These have been shown to fullfil the requirements of studies on Mg^2 in blood serum and plasma. The compound ETH^T 5504 can be incorporated into membrane cocktails used for microelectrodes [15], whereas ETH^T 3832 and ETH^T 5506 are preferably incorporated into plasticized polymer layers used in a continuous-flow system [2][16]. A different, promising ionophore developed in Japan [17] was compared to our own products under identical conditions [18].

In addition to synthetic chemical sensors, the sensing devices investigated in our group include antigen-antibody-based sensors and mediated enzymatic biosensors, which have been primarily studied for their use in the continuous monitoring of real specimens. Enzymatic sensors can be coupled to a bioreactor and to filtration processes *on-line* or *at-line* of the specimen flow. Continuous monitoring using a modular sensing system is being studied and improved in collaboration with the University of Applied Sciences HSW-Wädenswil and industrial partners (KTI-project Nr. 3754.1).

In this section, three projects will be presented in more detail. The first project was run within the framework of the NFP 36 on *Nanotechnology*. It involves an approach that differs fundamentally from the one used in miniaturized solid-state ion-selective electrodes and was studied in order to investigate local ion activities. The second project describes a method for the continuous monitoring of dissolved amines with optode membranes based on functionalized polyacrylate copolymers. In a third project, the diploma work of *A. Moradian* at the HSW Wädenswil, an optical reflection and transflection technique coupled to a fiber-optical probe was evaluated. The approach may be primarily of interest for industrial-process monitoring.

3. Ion-Selective Cantilevers and Continuous Monitoring of Amines

3.1. *From Ion-Selective Micro- to Nanodevices*

The technique of incorporating ionophores into solvent polymeric membranes in order to produce ion-selective sensors is well-known and used globally. The trend to miniaturize chemical sensors and to make them more convenient for use has led to the development of so-called *non-symmetrical* sensors. In these sensors, the internal electrolyte solution is replaced by a solid-phase internal electrode which contacts the analyte-selective polymer layer directly. These sensors include coated-wire electrodes (CWE), hybrid sensors, and ion-sensitive field-effect transistors (ISFET). The critical part of these sensors is the interface between the ion-selective membrane and the solid-state electrode, where the ion conductivity is converted into electron conductivity. Owing to the design and the materials used, the characteristics of this interface generally violate the rule that the membrane-specimen interface should be the only variable capacitor [19]. Very restrictive design rules should reduce the general tendency of these electrodes to show an unstable and drifting signal. However, these electrodes are increasingly implemented in single-use cartridges such as the i-STAT cartridge marketed by *Hewlett-Packard.*

An novel type of ion-selective solid-contact device was developed within the framework of the NFP 36 on Nanotechnology [20]. In atomic force microscopy (AFM), the surface of a sample is probed with a sharp tip where the apex of the tip consists of a single atom. The tip has a size close to 1 µm in length. For calculations, the tip apex is approximated by a sphere of 5 to 40 nm in diameter. The scanning-tip is mounted onto the free end of a cantilever. Forces between the tip apex and the sample surface cause the cantilever to bend, or deflect. This deflection is probed by a laser beam and displayed by a diode-array detector [21].

The interatomic forces between a specimen and the tip apex can be studied by functionalizing the cantilever tip either by attaching biomolecules such as antibodies [22][23], or by coating it with polymer layers incorporating ion-selective complexing agents such as ionophores. At the CCS, the cantilever tip was coated with a potassium-selective PVC membrane (M) based on valinomycin (L) (see *Fig. 2*, and mass balances (1) and (2)). As a substrate, a polymer layer of high viscosity, exchanging potassium ions against Na^+ in physiological NaCl solution, was prepared. Since Na^+ is discriminated by a factor of approximately 10^{-4} against K^+, the boundary potential will increase with decreasing distance from the substrate and increasing active molality of K^+ in close vicinity to the surface. Instead of measuring the boundary potential electrochemically, the electrostatic forces, induced by the charge separation and the polarized interface, were monitored relative to a muscovite substrate of the general formula $K_2Al_4[(Si_6Al_2)_8O_{20}](OH, F)_4$ (Mica) and to a blank polymer substrate [24][25]. The total interaction forces between the coated cantilever tip and the substrate were monitored by force-distance curves, and interpreted on the basis of their characteristics as well as of the error-signal image of two neighbouring substrates (see *Fig. 3*). In addition, the effect of increasing concentrations of potassium ions in the substrate and the influence of the ionic strength of the NaCl solution were traced.

The main effect observed was a decrease in elastic behaviour (indentation) of the cantilever in the retraction phase with increasing concentration of K^+ in the substrate, and an increase in ionic strength of the solution (see *Tables 1* and *2*). The latter result was explained by a decrease in the *Debye* radius, and an increase in the local charge density or electric field strength of contributing ions. The minimum distance between tip and substrate, when the motion of the cantilever changes from the adhesion to the retraction phase, is presented in *Table 1* (column 3) for 50 repetitions in 0.15M NaCl pH 6.5. In column 2, the measured net forces in units of 10^{-9} N are shown for three substrates containing different K^+-concentrations. The second row shows the results for the polymer blank substrate. The net force was calculated from the mean total adhesion force during the retraction phase, and was referred to the mean adhesion force between the coated tip apex and the blank polymer substrate. In the calculations, the spring constant of the cantilever was taken into account [26]. The pattern of the variation in the net adhesion force evaluated from the nanoindentation in 10^6 Pa was compared to the *Young*'s elastic modulus

Substrate:

$$R^-(s) + K^+(s) + Cl^-(aq) + Na^+(aq) \rightarrow R^-(s) + Na^+(s) + Cl^-(aq) + K^+(aq) \qquad (1)$$

Tip membrane:

$$L(m) + K^+(aq) + Cl^-(aq) \rightarrow KL^+(m) + Cl^-(aq) \qquad (2)$$

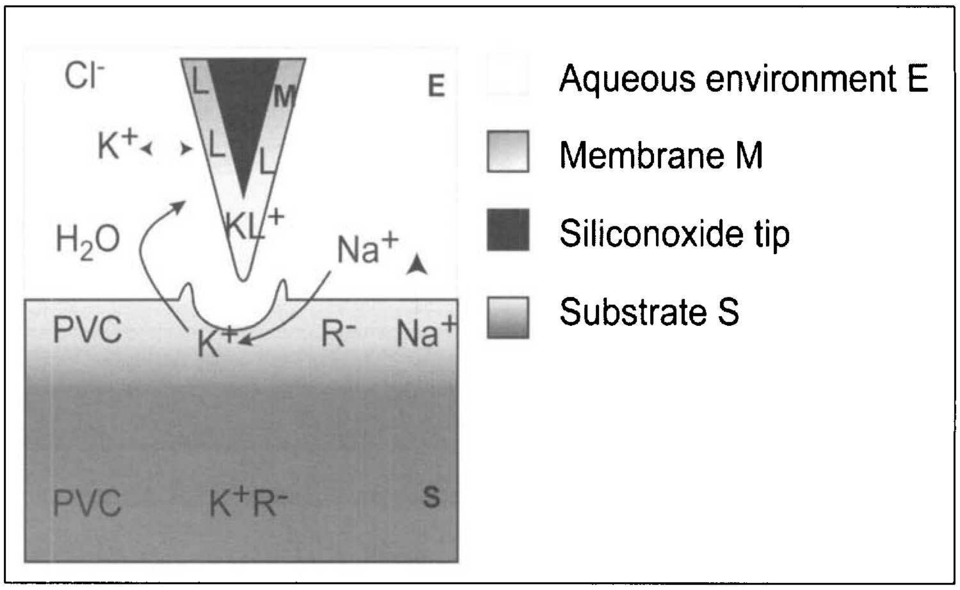


Fig. 2. *K⁺-selective AFM probe and principle of the ion exchange.* Scheme of the ion exchange as shown by the mass balances in *Eqns. (1)* and *(2)* between the aqueous medium (E), the K^+-selective membrane coated onto the tip apex (M), and the K^+-releasing substrate (S). The AFM experiments were performed in 0.15M NaCl solution at pH 6.5. The substrate contains an organic lipophilic potassium salt ($K^+ \cdot R^-$), the tip membrane contains varying amounts of valinomycin (L).

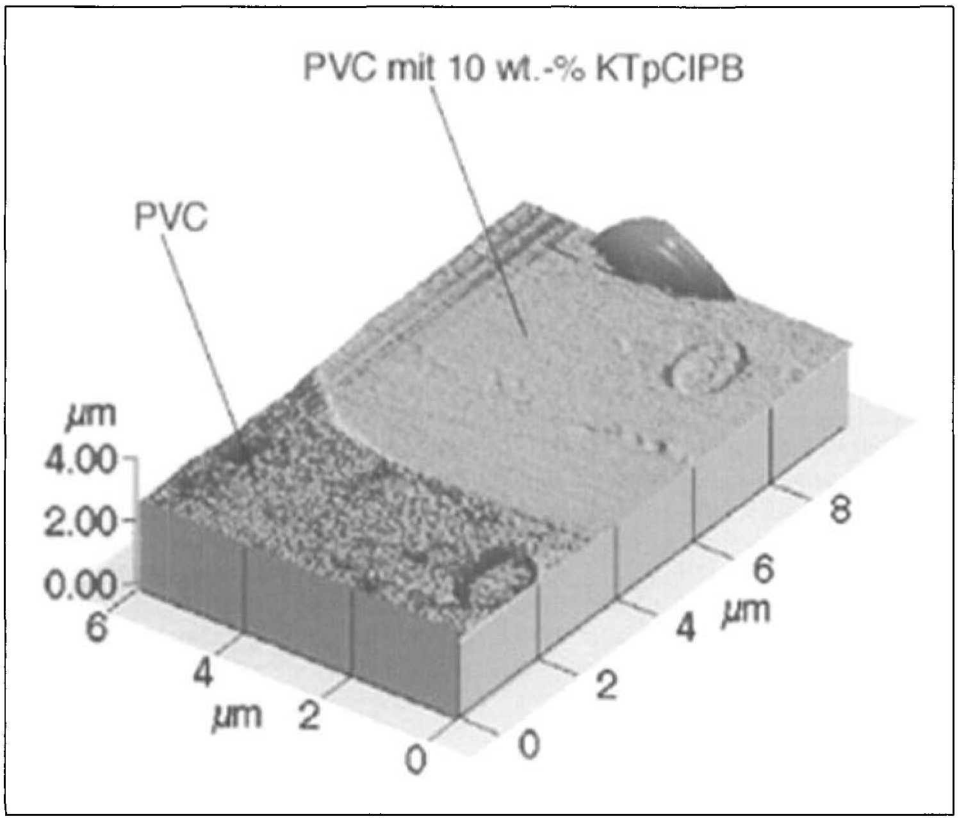


Fig. 3. *Error-signal image, which results from the motion of the cantilever, coated with a solvent polymeric membrane containing 55 mol kg^{-1} valinomycin, on two neighbouring substrates.* The substrate is scanned in contact mode. Left side: a substrate without lipophilic potassium salt; right side: substrate containing 10 weight-% KTpClPB. The small capillary forces, which induce the apparent roughness of the surface, are smoothened as a consequence of the interaction forces arising from the boundary potential.

Table 1. *Net Forces (*mean ± 2SD*) Calculated from Total Measured Forces* (see text). Mean minimum distance between cantilever and surface of the substrate in the same experiments for two different concentration of the ion exchanger in the substrate, and a concentration of 55 mmol kg^{-1} valinomycin in the tip coating; lifetime of the tip coating: 92.5% decay of the adhesion forces within 8 days in solution.

K⁺-concentration, substrate	Tot. measured net forces/nN, *n* = 50	Mean distance measured/nN, *n* = 50
Reference, PVC-layer	–	76 ± 15
2 weight-% KTpClPB	90.65 ± 33.5	150 ± 25
10 weight-% KTpClPB	330.15 ± 113.0	409 ± 74

Table 2. *Adhesion Force (mean ± 2SD) Calculated from the n-Repetitions of Force* vs. *Distance Curves, Accounting for the Spring Constant of the Cantilever.* The tip coatings contained 55 mmol kg^{-1} valinomycin. The E-modulus, evaluated from nanoindentation using AFM, refers to *A. Vinkier* and *G. Semenza* [44]. The E-modulus of the conditioned wet membranes was determined by strain-force analysis (*Mecsin M 1000E*, mean ± 2SD).

K⁺-concentration, substrate	Tot. adhesion force/nN, *n* = 50	E-modulus, nanoindentation/MPa	E-modulus, wet /MPa
Reference, PVC-layer	9.826 ± 3.275	0.6066 ± 0.1213	4.08 ± 0.64
2 weight-% KTpClPB	100.855 ± 33.615	59.5 ± 8.9	5.07 ± 0.15
10 weight-% KTpClPB	340.110 ± 113.37	65.4 ± 13.1	6.84 ± 0.77

(E-modulus) of the same wet substrate measured by strain-force analysis (see *Table 2*). The E-modulus (column 3) increases significantly which means that the elasticity decreases with increasing concentration of KTpClPB (potassium tetrakis(4-chlorophenyl)borate) in the substrate and increasing active molality of K⁺ at the substrate-electrolyte boundary. The variations in the elastic behavior of the cantilever motion showed the same pattern, but could not be explained by the *Young*'s modulus (*Table 1*, column 4).

The extraction and complexation of K⁺ to valinomycin is reversible, so that the experiments can be repeated several times (thickness of the tip polymer layer: 7.5 ± 2.5 nm, TEM experiments [27]).

The reversibility of the ion-exchange gives rise to a model similar to an artificial sodium-potassium pump. At the tip apex, K⁺ is subjected to a forced extraction into the tip polymer layer by valinomycin. The energy is provided by the cantilever moving into contact with the substrate against repulsive forces. The minimum distance to the substrate corresponds to the *Coulomb* interactions involving in the polarisation of the gap between tip apex and substrate. In the retraction phase, the polarisation is reduced and K⁺ is released from the tip apex layer with increasing distance from the substrate and with decreasing molality of K⁺ relative to the Na⁺-molality (mol · kg$^{-1}_{H_2O}$).

Further investigations will focus on:

1) developing a theoretical model to describe the force-distance curves accounting for the selectivity coefficients.
2) studying the ion-exchange kinetics where covalent attachment of valinomycin may be necessary;
3) imaging the density of specific ions on surfaces;
4) the application of ion-selective AFM techniques for the study of biological membranes.

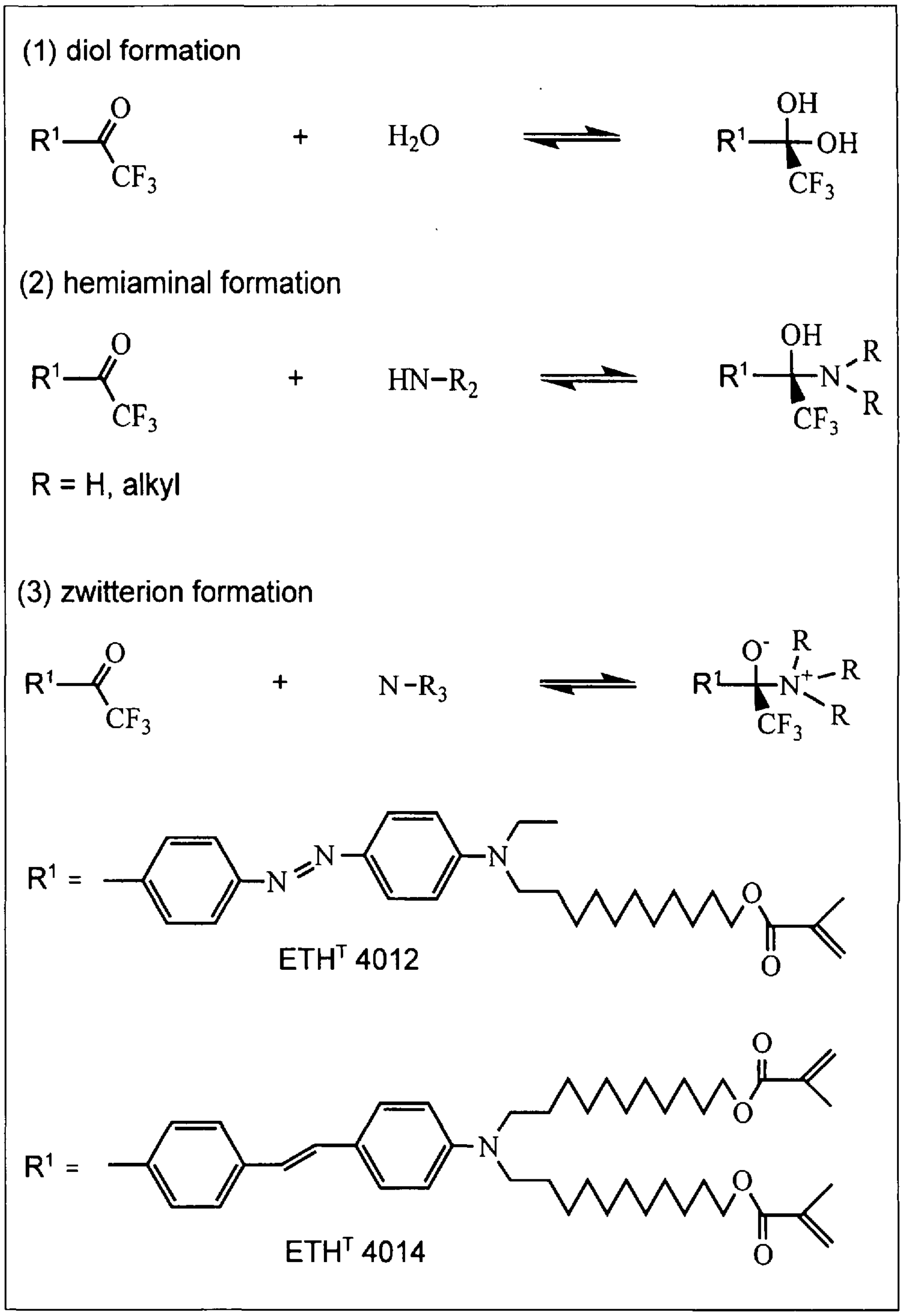
3.2. *Reactands for the Continuous Monitoring of Amines*

In the past, ion-selective complexing agents were studied preferentially, and a large variety of selective ligands and ionophores are now available [28]. Similar to a biological cell membrane, the ionophores were incorporated into a 'membrane' which consisted of a plasticized polymer [29]. This approach results in a two-phase system which allows the analyte to be extracted into an organic phase and the site of the recognition process to be separated from the aqueous specimen. Only a few projects have looked at neutral analytes such as glucose [30–32], creatinine [33], and ethanol [34]. In analogy to ligands, *reactands* and *chromoreactands* allow neutral analytes, such as alcohols and amines, to be addressed by means of a reversible chemical reaction. Aminal formation between primary and secondary amines and the *reactand*, an aromatic trifluoroacetyl derivative, is reversible within the environment of solvent polymeric membranes [35]. If a reactand is coupled to a chromophore, the compound is called a *chromoreactand.* The nucleophilic attack at the carbonyl group causes a hypsochromic shift of the absorption band of interest in the visible range of the spectrum (see *Fig. 4*).

The inter-class selectivity of trifluoroacetophenone reactands to, *e.g.*, ammonia, alcohols and water, and the intra-class selectivity to various amines were investigated. Ammonia is discriminated from, *e.g.*, hexylamine, by a factor of > 10^3, but only by a factor of *ca.* 7 from methylamine. The detection limit for, *e.g.*, butylamine in aqueous solution, is *ca.* 0.3 mM and 0.5 mM for propylamine [35]. Both the solubilisation and the recognition process of a target compound exert a joint influence on the selectivity. If a lipophilic membrane bulk is used, lipophilic organic compounds are preferred over inorganic ions. The possibility of detecting organic ions and compounds selectively has scarcely been investigated systematically.

In general, the membrane's components are dissolved in the membrane bulk but not immobilized. This allows a diffusion-limited response within both the organic membrane-bulk phase and the aqueous boundary phase of the specimen. For bulk sensors, such as optodes, a $t_{95\%}$ response time of < 5 min is usually achieved for a one-decade change in molality with a total membrane thickness of < 10 µm. Leaching is prevented by using highly lipophilic compounds (log P 7–18) [36]. Nevertheless, for industrial applications, the response velocity may be less important than an extended lifetime. Thus, members of a new class of chromogenic copolymers based on substituted trifluoroacetophenones were synthesized. These copolymers still interact reversibly with dissolved aliphatic amines, which leads to a change in absorbance [37]. The copolymers are composed of methyl methacrylate (MB 10) and butyl acrylate (MB23 & MB32) at different ratios with a constant amount of the monomeric dye 11-[*N*-ethyl-*N*-(4-{[4-(2,2,2-trifluoroacetyl)phenyl]diazenyl}phenyl)amino]undecyl 2-methylprop-2-enoate (ETH^T 4012) linked to the polymer backbone (see *Scheme*). Upon exposure to aqueous amine solutions buffered to pH 13, thin layers of the copolymer (thickness < 1 µm) usually show a decrease in absorbance at a wavelength around 490 nm and an increase in absorbance at approximately 430 nm. The low dielectric constant of these copolymers, which is similar to that of diethylether, makes them attractive candidates to be tested for their second-order nonlinear properties [10][38]. So far, however, very low mass ratios of the chromoreactand relative to the copolymer (< 1 weight-%) have been used.

Scheme. *The monomer of the chromophoric reactand ETH^T 4012* (11-[*N*-ethyl-*N*-(4-{[4-(2,2,2-trifluoroacetyl)phenyl]diazenyl}phenyl)amino]undecyl 2-methylprop-2-enoate) *and ETH^T 4014* (11-[*N*-[(2-methylprop-2-enoyl)oxy]undecyl-*N*-(4-{(*E*)-2-[4-(2,2,2-trifluoroacetyl)phenyl]ethenyl}phenyl)amino]undecyl 2-methylprop-2-enoate), *and the aminal reaction involving water and amines*



The response time, $t_{95\%}$, of the membranes is extended to 10–15 min for increasing concentrations, and 20–30 min (reverse response) for a one-decade change in concentration. In an analogous approach, using a stilbene-based reactand 11-[*N*-[(2-methylprop-2-enoyl)oxy]undecyl-*N*-(4-{(*E*)-2-[4-(2,2,2-trifluoroacetyl)phenyl]ethenyl}phenyl)amino]undecyl 2-methylprop-2-enoate (ETH^T 4014) [39] (see *Scheme*) and fluorescence-emission detection, the thickness of the polymer layers on the glass plate was measured using a surface profiler with an accuracy of 0.05

µm. This allowed the change in the overall diffusion coefficient to be estimated. Taking the reduced thickness of the polymer layers (*ca.* 0.4 µm) into account, the overall diffusion coefficient must be reduced by a factor of *ca.* 6.10^{-3} due to immobilization of the reactand. The reproducibility of the concentration measurements running continuously over a period of 2 weeks (*n* = 20) was found to be 1.57% (%cv = coefficient of variation) at 12.1 mM propylamine. No leaching was observed. The shelf-life of membranes stored in the dark was > 6 months.

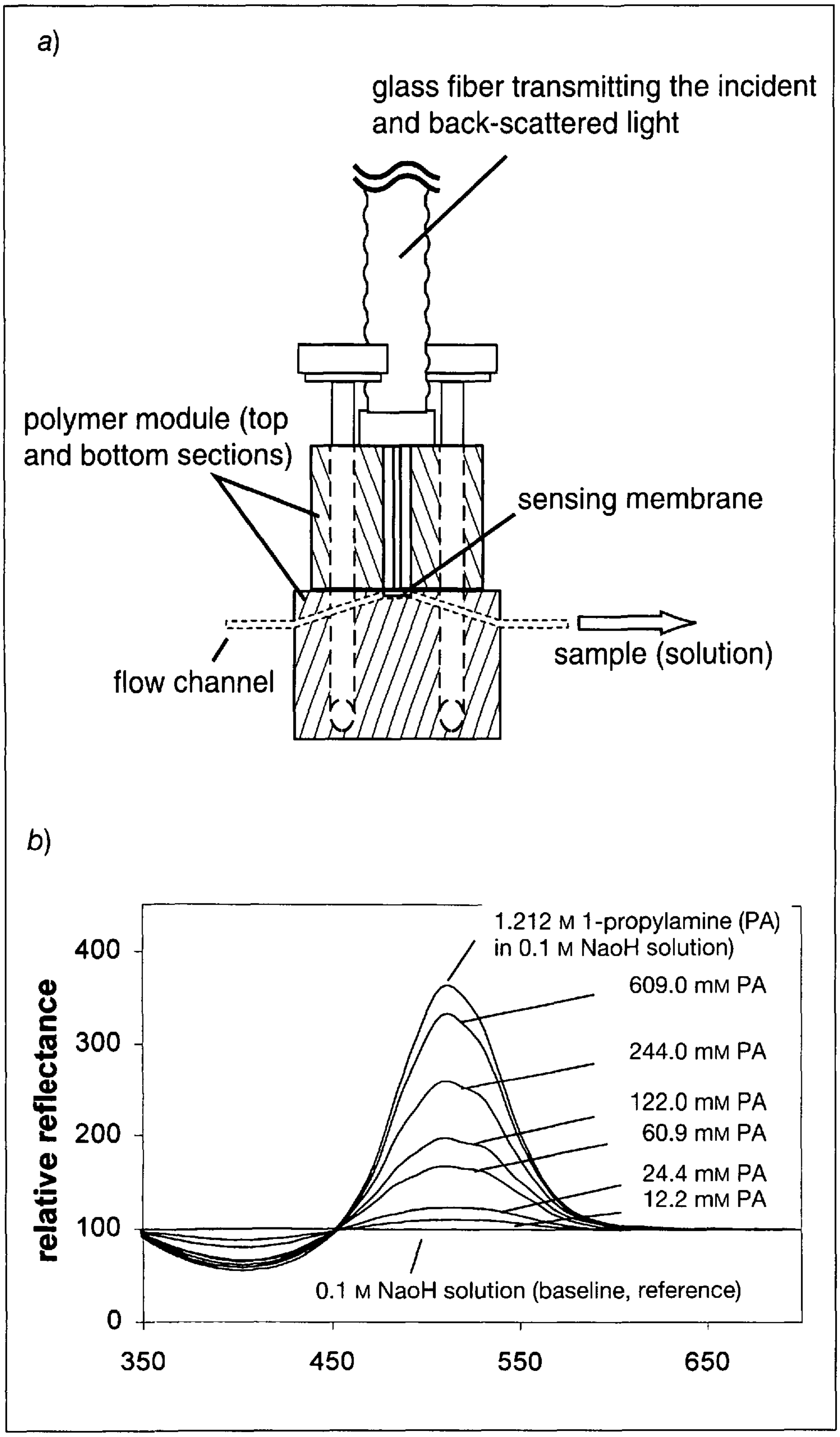


Fig. 4. *a*) The transflection probe, a fiber-optical Y-probe (*Zeiss Jena GmbH, MCV 520* photometer) in contact with the optode membrane within the continuous-flow module (flux: 3.4–41 cm min^{-1}). *b*) Transflection spectrum of a *Teflon*-coated PVC-membrane incorporating 1.7 weight-% of the reactand ETH^T 4001 (1-(4-{[4-(*N,N*-dioctylamino)phenyl]diazenyl}phenyl)-2,2,2-trifluoroethanon); plasticizer: DOS (dioctylsebacate) 60 weight-%; pH 13 (0.1 M NaOH); resolution (3SD in % of mean): 0.65% (609 mM) to 5.9% (24.4 mM), *n* = 4 repetitions.

3.3. *Continuous Optical Monitoring in Internal Reflection and Transflection Mode*

Simultaneously with the development of these reactand-based copolymer membranes, an optical measuring technique in transflection mode has been studied. Unlike potentiometric and amperometric sensors, which respond to surface activities, optode membranes equilibrate homogenously with the analyte, which means that a bulk property is measured. Therefore, variations in the electromagnetic characteristics of a membrane may be detected along the side of the incident light in the reflection, transflection [40], or internal reflection mode [41][42]. These techniques complement the range of spectroscopical methods used in sensor technology, such as luminescence emission, total internal reflection, and interferometry [43]. They are extremely useful in dealing with turbid and heterogenous specimens such as waste water, effluents from production plants, and can also be used in specific applications, *e.g.*, tablet-dissolution tests.

In his diploma work at the HSW Wädenswil, *A. Moradian* investigated the reflection and transflection technique using a *Zeiss MCS 521* spectrometer equipped with a fiber-optical Y-probe [40]. The Y-probe was inserted into the head part of a sensor module made of a polysulfone polymer (*Fig. 4*) and was in direct contact with the inner boundary of the membrane support. Two different set-ups were studied using a membrane based on ETH^T 4001 (1-(4-{[4-(*N,N*-dioctylamino)phenyl]diazenyl}phenyl)-2,2,2-trifluoroethanon [35]) under continuous-flow conditions. In the first experiment, a *Teflon* film was stretched over the amine-selective polymer layer along the side of the contact with the specimen. In a second experiment, colloidal titanium dioxide was incorporated into the polymer layer. Unlike the absorbance measurements, the transflection at, *e.g.*, 511 nm increases with an increase in concentration of the amines (propylamine, butylamine). Since the initial results were very promising, further investigations are being made in which the parameters of the analytical approach, such as sensitivity, resolution and long-time stability, will be evaluated. So far, the response time, the sensitivity, and the dynamic range of the amine sensor were comparable to measurements in the transmission mode. Neither applying a *Teflon* layer, nor using the transflection technique changed the favourable characteristics of the chemical sensor.

Additional information on current projects can be found at www.chemsens.ethz.ch.

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