

Chemically Modified ISFETs with Thin Polymer Membranes Working in a Differential Mode

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Calcium, magnesium and potassium ion-selective membranes were prepared by means of immobilization of octadecyl monophosphonate, octadecyl diphosphonate or dibenzo-18-crown-6 ionophores into cationic polymer gels. These membranes were used to produce chemically modified ion-sensitive field-effect transistors (ISFETs) working in a differential mode which showed good sensitivity and quasi-Nernstian responses. The sensitivities per decade of ion concentration for Ca^{2+} , Mg^{2+} and K^{+} were, respectively, 22.0 mV, 20.1 mV and 9.0 mV for octadecyl monophosphonate, 22.6 mV, 22.4 mV and 9.0 mV for octadecyl diphosphonate and 29.5 mV, 24.6 mV and 50.2 mV for dibenzo-18-crown-6. A small short-time drift was observed and the long-time sensitivity loss remained moderate, indicating that cross-linked polymer gels that could swell extensively in water could efficiently immobilize large amounts of small molecules for sensor membrane applications.

1. Introduction

Recently, there has been considerable interest in the development of various types of solid-state electrochemical sensors, i.e., ion sensors, gas sensors and biosensors, in which polymer membranes are cast on the solid surface of a transducer with no internal reference electrolyte solutions.⁽¹⁻⁶⁾

The membranes of ion-sensitive solid-state sensors consist of thin polymeric films into which ionophores are immobilized.⁽⁴⁻⁶⁾ Such devices are versatile because of the wide range of ionophores available and the ease with which we can select the ions of interest. Polyvinyl chloride (PVC) is the most commonly used polymer for conventional ion-selective electrode (ISE) membranes; however, this polymer is not well suited for use as a membrane of ion-sensitive field-effect transistors (ISFETs) into which neutral-carrier molecules are immobilized. One reason for this is that ion-sensing membranes based on plasticized PVC easily peel off the gate surface of FET devices.⁽⁷⁾ This poor adhesion causes deterioration of neutral-carrier-based ISFETs. Moreover, a plasticizer that can migrate into the solution, or even contribute to the electrical signal in some cases, is required.⁽⁸⁾ Room-temperature vulcanized (RTV) polysiloxane resin, so-called silicone rubber, which has been proposed as an alternative to plasticized PVC for ISE membranes,⁽⁹⁻¹¹⁾ can markedly improve the adhesion of neutral-carrier-type ion-sensing membranes to FET gates.⁽¹²⁻¹⁵⁾ This was shown by direct peel force measurements.⁽¹⁴⁾ However, there are serious problems in adopting silicone rubber as a membrane material, because few ionophores are soluble in this medium and poor dispersibility of most neutral carriers, especially highly lipophilic neutral carriers, is observed.⁽¹⁵⁾ Attempts to design polydimethylsiloxane bearing polar groups resulted in a deterioration of the long-time performance of ISFETs.⁽¹⁶⁾ In order to solve these problems, multilayered polymer membranes having a much more complex design were proposed.^(17,18)

The ISFET polymer membranes in this study were adapted from the ion-selective electrode (ISE) membranes used in earlier works. Thus, polymer membranes with good mechanical properties (tensile strength) and low polarity were required in order to reduce the transmembrane current. Such requirements are not relevant for ISFET polymer membranes since the electrostatic surface potential is measured instead of the membrane potential difference. The polymer membrane was deposited onto the ISFET gate and acted as a thin solvent medium for sensing molecules. Adhesion to the ISFET gate is an absolute requirement and the ionophores have to be soluble in the polymer membrane. Polymers that can swell in water can then be used for the immobilization of ionophores, similarly to the case of immobilization of enzymes for biosensors. The insolubility of the polymer in water can be ensured by very strong (irreversible) adsorption or by cross-linking. Adsorbed polyelectrolytes can provide an electrode surface with high affinity for ionic reactants that can be incorporated into polyelectrolyte coatings. This method was first demonstrated with poly(4-vinylpyridine).⁽¹⁹⁻²²⁾

In the present study, a cationic cross-linked polymer is investigated as a membrane material that immobilizes small ionophores. It is recognized that polymer gels that swell to a large extent in water can efficiently immobilize enzymes because of their large size;⁽²³⁾ however, this may not be the case for small molecules. A new coating material, consisting

of a cationic gel made from two random copolymers, poly(vinylbenzylchloride)-co-styrene and poly(4-vinylpyridine)-co-styrene, can be utilized to produce stable electrode coatings with properties quite comparable to those of conventional membranes. Large quantities of ionophore can be incorporated into this composite coating and are retained for a long time.

The detection of alkaline (K^+) and alkaline earth (Ca^{2+} , Mg^{2+}) ions was studied using cross-linked polyelectrolyte membranes doped with sensing molecules and an ISFET as a transducer. The sensing molecules (ionophores) used are shown in Fig. 1. The K^+ -sensitive molecule is dibenzo-18-crown-6 (**1**).^(24,25) For alkaline earth ion detection, two phosphonates having a hydrophobic alkyl chain that ensures poor solubility in water were used: a monophosphonate (**2**) and a gem-diphosphonate (**3**). Gem-diphosphonates are very strong chelating agents for Ca^{2+} and Mg^{2+} . Thus, the stability constant of the 1/1 complex of Ca^{2+} is $\sim 10^4$ larger for a gem-diphosphonate than for a monophosphonate, both in their fully ionized form at basic pH.⁽²⁶⁻²⁹⁾ The choice of phosphonate molecules was dictated by their very good chemical stability against hydrolysis, which is not the case of phosphates, although they are much more commonly used in ISE^(30,31) and ISFET⁽²⁾ membranes.

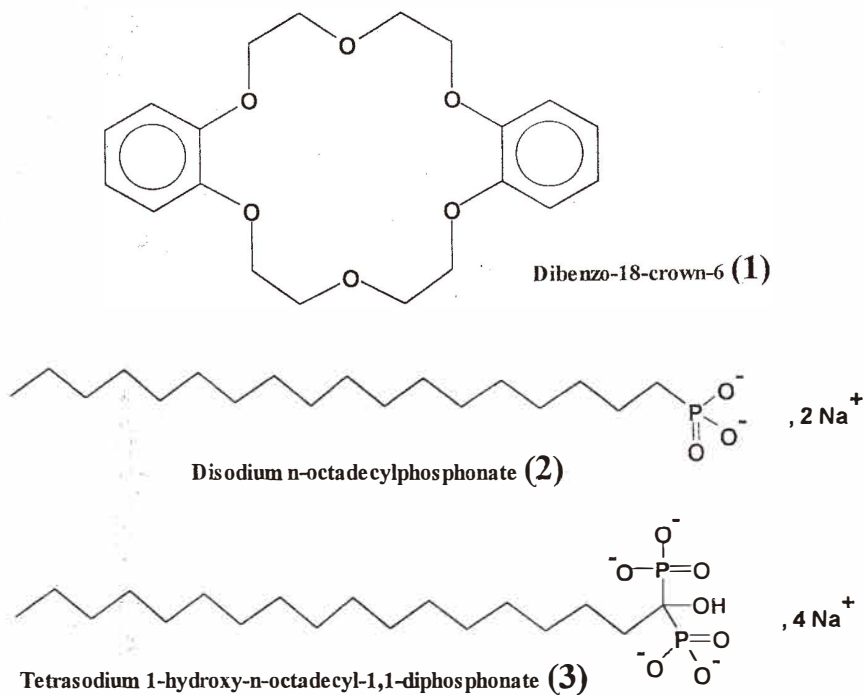


Fig. 1. Chemical formulae of sensing molecules.

2. Materials and Methods

2.1 Preparation of poly(vinylbenzylchloride)-costyrene (PVBC)

The random copolymer PVBC of vinylbenzylchloride and styrene (20 mol%) was synthesized by copolymerization of the corresponding monomers, as described by Montgomery and Anson.⁽²¹⁾ ¹H NMR and elemental analyses (C = 72.8%, H = 6.25%, Cl = 20.0%) gave the correct composition of the copolymer. The macromolecular weights as measured by size exclusion chromatography (THF as the eluent, calibrated with polystyrene standards) were $M_n = 10000$ and $M_w = 19000$. Since the reactivities of styrene and vinylbenzylchloride are nearly identical, the distribution of the monomer units in the copolymer is assumed to be random as described in the literature.⁽³²⁾

2.2 Preparation of polymer gels

Poly[(4-vinylpyridine)-co-styrene] with a styrene content of 10% (PVP, Aldrich) was used as received and dissolved in N,N-dimethylformamide (DMF) to give a 3.3% (w/v) working solution. Equal volumes of PVP and PVBC copolymer solutions were mixed and thoroughly stirred to ensure complete blending. A drop of this mixture was deposited onto an ISFET silica surface and heated at 30°C for 3 h. The reaction of the pyridine groups of PVP and the chloromethyl groups of PVBC took place during DMF evaporation (Fig. 2). The resulting material was a transparent cationic gel with pyridinium cross-links, which can swell extensively by adsorbing water. The degree of cross-linking was measured as 7% by conductimetric titration of Cl⁻ with silver nitrate. The equilibrium swelling ratio (swollen-to-dry volume ratio) by pure water is of the order of 2.

2.3 Synthesis of sensing molecules

2.3.1 Octadecyl monophosphonate

Disodium n-octadecylphosphonate was obtained by means of the following two-step procedure. Diethyloctadecylphosphonate was prepared by the Michaelis-Becker reaction using n-octadecylbromide and the sodium salt of diethylphosphite in anhydrous THF.^(33,34) The ester groups were subsequently cleaved off by the bromotrimethylsilane method.⁽³⁵⁾ The resulting octadecylphosphonic acid was filtered from the reaction medium (95% overall yield) and recrystallized twice from a water-ethanol (90:10) mixture. The structure as determined by ¹H, ¹³C NMR and elemental analyses of the acidic form was in agreement with the theoretical structure.

¹H NMR in CDCl₃ at 50°C (ppm from internal TMS): 0.88 (t, 3H); 1.3 (m, 30H); 1.7 (m, 4H); 6.6 (s, 2H).

¹³C NMR in CDCl₃ at 50°C (ppm from internal TMS): 14.05; 22.15 (d, ²J_{P,C} = 4.0 Hz); 22.73; 25.57 (d, ¹J_{P,C} = 145.7 Hz); 29.18; 29.42; 29.50; 29.74; 29.78; 30.52 (d, ³J_{P,C} = 16.4 Hz); 32.02.

The sodium salt was obtained by neutralization with NaOH. This salt is soluble in water above 63°C.

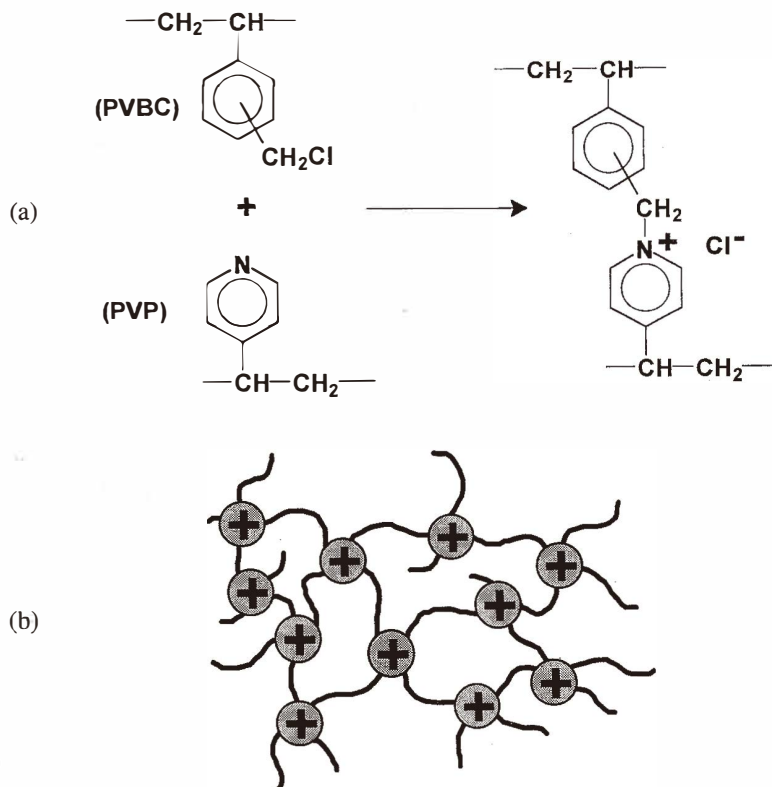


Fig. 2. Cross-linking reaction and scheme of the resulting cationic gel. (a) Cross-linking reaction, and (b) sketch of the cross-linked cationic gel.

2.3.2 Octadecyl diphosphonate

1-Hydroxyl-n-octadecyl-1,1-diphosphonic acid was prepared from the reaction of stearic acid, phosphorous acid and phosphorus trichloride according to the method described by Leroux⁽³⁶⁾ and Prentice *et al.*⁽³⁷⁾ After the reaction and the product hydrolysis with 4N HCl, a yellowish solid was obtained. For purification, a concentrated solution of this solid in THF was slowly poured into a large excess of chloroform where precipitation of white crystals occurred (75% yield). The structure as determined by ¹H, ¹³C NMR and elemental analyses was in agreement with the theoretical structure.

¹H NMR in THF-d₆ (ppm from internal TMS): 0.88 (t, 3H); 1.3 (m, 28H); 1.7 (m, 2H); 2.0 (m, 2H, ³J_{P-H} ≈ 17 Hz); 7.6 (s, 5H). No triplet at 2.2 ppm was observed, indicating complete removal of stearic acid in the purification step.

¹³C NMR in DMSO-d₆ (ppm from internal TMS): 13.72; 21.99; 22.96 (t, ²J_{P-C} = 5.7 Hz); 29.00; 29.07; 30.00; 31.23; 33.50; 72.70 (t, ¹J_{P-C} = 143.9 Hz).

2.4 Preparation of films of ion-sensitive polymer gels

Prior to use and before the thin films were cast onto the ISFET gate surface, chips were dipped into a chromic acid mixture (sodium dichromate in concentrated sulfuric acid⁽³⁸⁾) for 15 min, and then thoroughly washed with double-distilled water and dried in nitrogen flow. One drop of DMF solution containing 1 wt% PVBC, 1 wt% PVP and a small amount (1.5 wt% relative to the polymer) of either octadecyl monophosphonate, octadecyl diphosphonate, or dibenzo-18-crown-6 (from Aldrich, used as received) was deposited onto the SiO₂ gate surface using a small glass rod of 1.5 mm diameter. Membranes were allowed to form by cross-linking and solvent evaporation for 3 h at 30°C. Prior to use, the membranes were dipped in distilled water for equilibration.

2.5 ISFETs

ISFETs were fabricated at the Centre Interuniversitaire de MicroÉlectronique (CIME, Grenoble, France) using the N-MOS planar-type technology.⁽³⁹⁾ The original substrate was a p-type <100>-oriented silicon, with resistivity in the range of 0.5 to 1 Ω·cm. The dimensions of the chips were (1.2 × 0.12) cm², the channel size was (500 × 20) μm² and the gate insulator was bare thermal silica. The bonding wires were isolated from the gate insulator in order to avoid dipping them into the electrolyte solution. Inorganic encapsulation by photolithography was performed during the fabrication process.⁽³⁹⁾

2.6 Experimental conditions

All measurements were performed at room temperature and in 0.1 M acetate buffer, which ensured constant ionic strength for ion concentrations lower than this value. Double-distilled water and Merck analytical-grade reagents were employed. The pH (pH range from 2 to 8) was varied by adding suitable quantities of concentrated NaOH or HCl. K⁺, Ca²⁺ and Mg²⁺ ion concentrations were varied by the addition of KNO₃, Ca(NO₃)₂ and Mg(NO₃)₂ salts, respectively.

2.7 Individual measurements

Each ISFET was connected to a specially developed amplifier system which enabled the source voltage (V_S) to be measured at constant drain current (I_d) and drain voltage (V_d), the source and substrate being connected. V_d and I_d were respectively set to 0.5 V and 100 μA. V_S was measured against a reference calomel electrode and recorded. pH measurements were performed with a digital pH meter (Tacussel Minisis 8000).

2.8 Differential measurements

The experimental device for differential measurements has been described in previous papers.^(39,40) Two ISFETs were connected to two identical amplifiers and output signals V_S and V'_S were measured against a common platinum pseudo-reference electrode. A differential amplifier was used to obtain the difference between these two signals ($\Delta V = V_S - V'_S$). A small drop of polymer mixture containing the sensing molecules was deposited onto the gate insulator of the ISFET, and the same amount of polymer without the sensing molecules was deposited onto a reference ISFET called REFET.

When the differential output signal ΔV was measured, the responses (drift, pH, tem-

perature) of the two identical ISFETs nearly cancelled out. This result does not depend on the nature of the common reference electrode: a calomel electrode (stable potential) or platinum electrode (floating potential). It shows the feasibility of the experimental arrangement for cancelling out interferences (drift, temperature, pH) when only one of the ISFETs is ion-sensitive.

3. Results and Discussion

3.1 Ionic response in differential mode

3.1.1 Dibenzo-18-crown-6

The electrical responses ($|\Delta V|$ vs $-\log([\text{ion}]])$ to K^+ , Ca^{2+} and Mg^{2+} ions as measured in the concentration range from 10^{-3} to 10^{-1} M are fairly close to those derived from Nernst's law, with slopes of 50.2, 29.5 and 24.6 mV per decade of ion concentration, respectively (Fig. 3). The electrical signal for K^+ ions is larger than that for Ca^{2+} and Mg^{2+} ions, indicating the selectivity of this crown ether for K^+ ions.⁽⁴¹⁾ However, the slopes are slightly but significantly lower than those calculated based on Nernst's law for K^+ and Mg^{2+} ions. The dibenzo-18-crown-6 molecule is known to be a good ligand for K^+ ions, although Ca^{2+} and Mg^{2+} ions also elicit a significant response. These ions are therefore considered as interfering ions for a dibenzo-18-crown-6-based K^+ sensors.

3.1.2 Octadecyl monophosphonate

The electrical responses to ions ($|\Delta V|$ vs pX with $\text{X} = \text{K}^+$, Ca^{2+} , Mg^{2+}) as measured at $\text{pH} = 7.2$ are shown in Fig. 4. A linear response of the pX -sensitive ISFET to K^+ , Ca^{2+} and Mg^{2+}

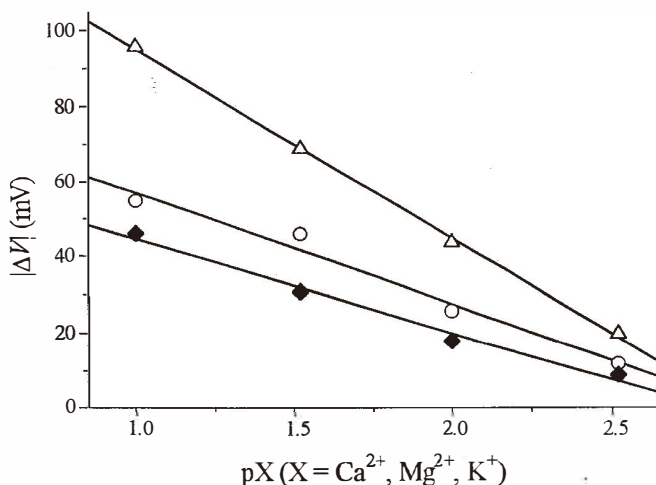


Fig. 3. Electrical response of the ISFET modified with dibenzo-18-crown-6 to different ion concentrations using the differential mode: (\triangle) K^+ , (\blacklozenge) Mg^{2+} , (\circ) Ca^{2+} .

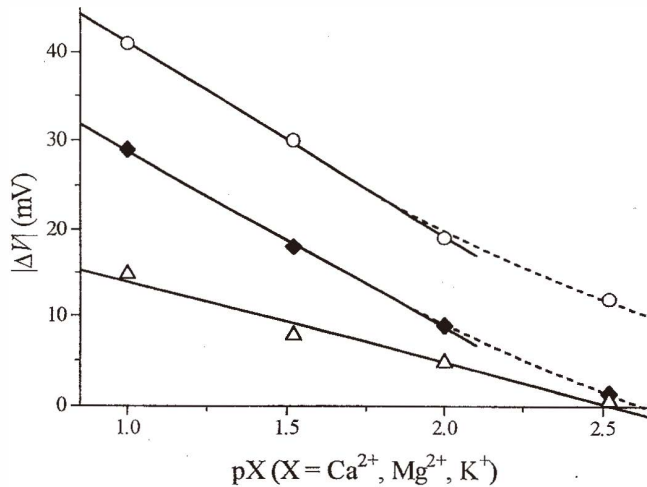


Fig. 4. Electrical response of ISFET modified with octadecyl monophosphonate to different ion concentrations using the differential mode: (\triangle) K^+ , (\blacklozenge) Mg^{2+} , (\circ) Ca^{2+} .

was observed in the high concentration range from 10^{-2} to 10^{-1} M, with slopes of 9.0, 22.0 and 20.1 mV per decade of ion concentration, respectively. A slight departure from linearity is observed for ion concentrations below 10^{-2} M. ISFETs sensitized by monophosphonate groups directly grafted onto the silica insulator surface as a monomolecular layer,⁽⁴²⁾ gave a response to Ca^{2+} ions of only 7 mV/pCa in the concentration range from 10^{-2} to 10^{-1} M, which levelled off in a similar way at lower concentrations of Ca^{2+} . In this case, the higher density of complexing sites in the polymer membranes leads to higher sensitivity; however, the response is still sub-Nernstian. There is a favorable selectivity for Ca^{2+} and Mg^{2+} ions compared to K^+ , as shown by the very weak electrical response to K^+ ions (9 mV/pK). Indeed, the phosphonate group shows poor complexing ability for alkaline ions.

3.1.3 Octadecyl diphosphonate

The $|\Delta V|$ vs pX ($X = K^+, Ca^{2+}, Mg^{2+}$) plots are linear in the entire concentration range investigated in this study (Fig. 5). The responses to K^+ , Ca^{2+} and Mg^{2+} were, respectively, 9.0, 22.6 and 22.4 mV per decade of ion concentration in the range from 10^{-3} to 10^{-1} M. The slightly higher slope obtained for the diphosphonate compared to the monophosphonate is attributed to a higher complexity constant for the diphosphonate group towards alkaline earth ions.⁽²⁶⁻²⁹⁾ The main advantage of the diphosphonate ionophore is its wide concentration range in which a linear response can be observed; however, the response is again sub-Nernstian. The increase of the slope in going from a monophosphonate to a diphosphonate is quite weak although the complexing ability is increased by several orders of magnitude. It seems that the slope observed with the diphosphonate (22 to 23 mV/pCa) is the

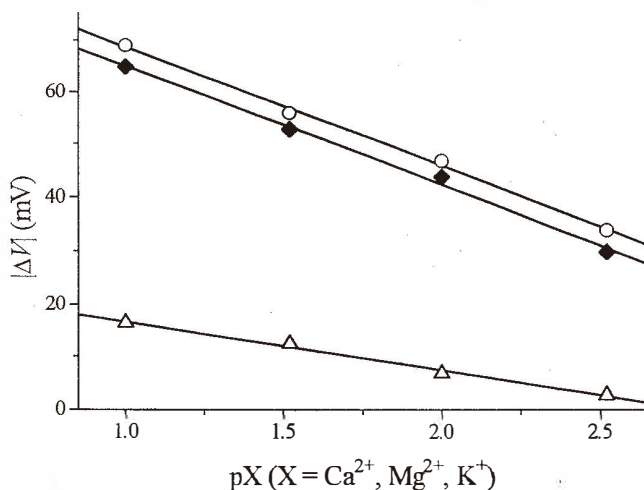


Fig. 5. Electrical response of ISFET modified with octadecyl diphosphate to different ion concentrations using the differential mode: (\triangle) K^+ , (\blacklozenge) Mg^{2+} , (\circ) Ca^{2+} .

maximum value that can be attained with this kind of membrane. As for the monophosphonate ionophore, the selectivity for alkaline earth ions is high.

3.2 pH response in the differential mode

ISFETs with three sensing molecules deposited separately were tested for pH response (Fig. 6). For octadecyl monophosphonate and octadecyl diphosphonate, the responses were, respectively, 27.4 and 27.8 mV per pH unit above pH = 5. The high sensitivity to pH is due to the acid-base properties of these ligands. Thus, with such pH-sensitive ligands, it is necessary to perform measurements in a buffered medium.

In contrast, the response is only 6 mV per pH unit for dibenzo-18-crown-6. Neutral molecules cause this membrane to have low pH sensitivity.

3.3 Time drift

Adhesion of polymer membranes to the sensor surface is one of the factors determining sensor lifetime, and it has been one of the limiting factors in most miniaturized solid-state sensors reported to date. It is believed that poor membrane adhesion can cause potential drift at the membrane/solid interface due to osmotic transport of water into this ill-defined layer.⁽⁴³⁾

A short-time drift, using individual measurements on ISFETs modified with the polymer membrane, is recorded for the three sensing molecules in an acetate buffer at pH = 7.4. This short-time drift is 0.2 mV/h for dibenzo-18-crown-6, octadecyl diphosphonate and octadecyl monophosphonate after continuous measurement in electrolyte solution for 15 h. The short-time drift increases by about 4% of its initial value after two months of storage in water at 4°C, which is not a significant variation. The short-time drift is quite

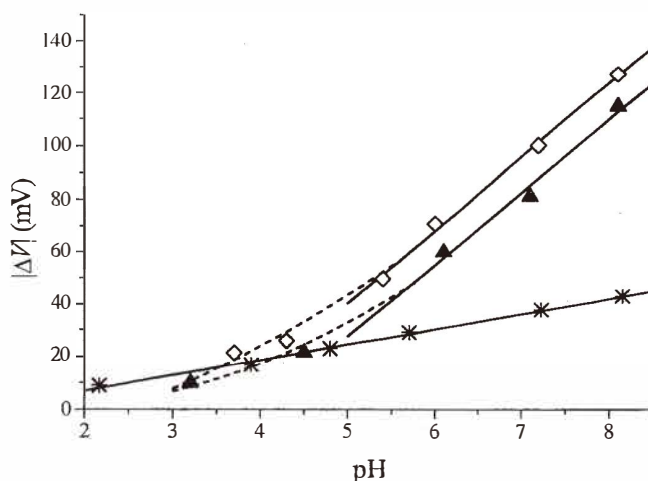


Fig. 6. pH response of ISFETs using the differential mode: (◇) Octadecyl monophosphate, (◆) Octadecyl diphosphate, (*) Dibenzo-18-crown-6.

low for an ISFET with a silica insulator, which can be ascribed to the slow rearrangement of the membrane in the presence of ions or to the slow diffusion of ions into the silica gate.

3.4 Variation of sensitivity with storage

Membrane adhesion was evaluated by measurement of the long-time drift of ISFETs sensors after two months of storage in water at 4°C. After storage, the membranes containing sensing molecules (monophosphate, diphosphate, dibenzo-18-crown-6) lost, respectively, 47%, 26%, and 39% of their sensitivity (the slope of the ΔV vs- $\log[\text{ion}]$ curves). This is attributed to the slow leaching-out process of the sensing molecules from the membrane. These sensitivity losses are significant but the ISFETs retained some sensitivity after two months of storage in water. Complete solubilization of the sensing molecules in water was prevented by the polymer membrane, in spite of its extensive swelling in water. Because of this, periodic calibration of the sensors is necessary.

3.5 Discussion

A polymer membrane with eliciting performance could be designed from a cationic cross-linked polymer gel that can extensively swell in water. This gel, which is unsuitable for use as an ion-selective electrode membrane, is efficient in retaining ionophores at the ISFET gate surface. It offers the obvious advantage that ions can diffuse rapidly from the water-swollen membrane to the silica insulator where an ion concentration-dependent surface potential is expected. The cationic polymer membrane was chosen so as to ensure good adhesion to the silica gate of the ISFETs. Although no direct adhesion measurements were carried out, the measured long-time drifts were very low. This was expected, since a

cationic polymer strongly adheres to an anionic silica surface via electrostatic interaction.

The use of an ionic membrane did not interfere very much with the electrical response of the sensors. Thus, although the positive electrical charge of the polymer membrane repelled K^+ , Ca^{2+} and Mg^{2+} ions, a quasi-Nernstian response was observed for all ionophores studied. However, the large electrical charge of the membrane may be the origin of the slight but significant departure from the plot derived from Nernst's law, since the observed slopes are lower by a factor of 0.8 than the theoretical ones. Electrical responses to K^+ and Ca^{2+} ions were found to be very close to those derived from Nernst's law in the case of plasticized PVC membranes, as described in the literature.⁽¹⁻³⁾ Comparison with the present work is not straightforward however, since the ionophores used in Janata's work were different (valinomycin for K^+ and octylphenyl phosphate or dodecyl phosphonate for Ca^{2+}). In spite of the slight variation of the slopes with the theory, the electrical responses of the ISFETs are satisfactory for analytical purposes. This is because of the electrostatic screening effect due to the high ionic strength conditions of the present measurements. Since the detection was conducted in the differential mode, the effects of specific anion attraction to the cationic polymer membrane were not observed. The high and constant ionic strength conditions also decreased electrostatic effects of the co-ions (anions) that might be observed in cases of imperfect compensation in the differential mode.

The origin of the long-time drifts is thought to be the slow leaching out of sensing molecules into water. Although the two phosphonates were anionic, the cationic polymer membrane was inefficient in completely retaining them at the ISFET gate surface. This process is slow, however, and may be caused by the weak degree of cross-linking of the polymer. Thus, according to the degree of cross-linking, the mean polymer chain length separating two cross-links corresponds to 14 monomer units, or a mean distance of 36 Å, assuming that the polymer chains are extended. This is much larger than the size of the ionophores. The distribution of cross-linking points is actually not random in most polymer gels. The present cross-linking process involves a chemical reaction between two different polymers initially present as a mixture. Based on a Friedel and Crafts cross-linking reaction of polystyrene which is quite similar in principle to the present one, Davankov *et al.*^(44,45) found a non-random distribution of cross-links in the polymer gel. Moreover, a large increase in scattered light intensity at low angles, which is often (if not always) observed in light scattering or in small-angle X-ray and neutron scattering experiments on swollen gels,⁽⁴⁶⁻⁴⁹⁾ shows that large-scale inhomogeneities are present in such materials, even if they are transparent. The structure of swollen gels thus consists of dense domains of highly cross-linked polymers separated by highly swollen parts with low cross-linking density. It is likely that ionophores located in the low cross-linking density domains cannot be efficiently retained in the membrane and are the origin of the observed drift. On the other hand, the ionophores entrapped in the high cross-linking density domains ensure the long-time response of the ISFETs. The problem is then quite complex since the control of the membrane material cannot be reduced to the choice of an optimal mean degree of cross-linking; the distribution of the cross-linking points and the structure of the polymer gel in its swollen state also contribute to the electrical response and the drifts. The present results show that ISFET polymer membranes can be prepared with ionic hydrogels but the optimization of membrane properties will require systematic studies on

the relationships between ISFET characteristics and both the polymer chemical nature and the structure of the swollen membrane.

4. Conclusions

Chemically modified ISFETs based on a cationic cross-linked polymer thin film in which dibenzo-18-crown-6 or phosphonate amphiphilic molecules were immobilized, were realized.

A quasi-Nernstian response to K^+ was observed for dibenzo-18-crown-6 ionophores having very low pH sensitivity, but some sensitivity to alkaline earth ions was observed.

Mono- and diphosphonate ionophores gave a quasi-Nernstian response to Ca^{2+} and Mg^{2+} and a weak response to K^+ ; both ionophores exhibited acid-basic properties which resulted in high pH sensitivity. The larger complexing ability of the diphosphonate ionophore extends the range of linearity towards lower ion concentrations.

The advantages of using the presently described cationic polymer gel as an ISFET membrane are its ability to retain ionophores, Nernstian electrical response, and low drift because of good surface adhesion to silica. However, the slow leaching out process of the sensing molecules to water remains a problem. This can be avoided by chemically grafting the ionophores to the polymer membrane.

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References

- 1 S. D. Moss, J. Janata and C. C. Johnson: *Anal. Chem.* **47** (1975) 2238.
- 2 P. T. McBride, J. Janata, P. A. Comte, S. D. Moss and C. C. Johnson: *Anal. Chim. Acta* **101** (1978) 239.
- 3 S. D. Moss, C. C. Johnson and J. Janata: *IEEE Trans. BioMed. Eng.* **BME-25** (1978) 49.
- 4 B. A. McKinley, B. A. Houtehem and J. Janata: *Ion-Selective Electrode Rev.* **6** (1984) 173.
- 5 J. Janata and A. Bezegh: *Anal. Chem.* **60** (1988) 62R.
- 6 P. Cléchet, N. Jaffrezic-Renault and C. Martelet: in *Chemical Sensor Technology*, ed. S. Yamauchi, Vol. 4, p. 205 (1992).
- 7 K. Tsukada, M. Sebata, Y. Miyahara and H. Miyagi: *Sensors and Actuators* **18** (1989) 329.
- 8 W. P. R. V. Stauthamer, J. F. J. Engbersen, W. Verboom and D. N. Reinhoudt: *Sensors and Actuators* **B17** (1994) 197.
- 9 J. Pick, K. T'ht, E. Pungor, M. Vasàk and W. Simon: *Anal. Chim. Acta* **64** (1973) 477.
- 10 W. Crowe, A. Mayevsky and L. Mela: *Am. J. Physiol.* **233** (1977) C56.
- 11 M. Mascini and G. Marrazza: *Anal. Chim. Acta* **231** (1990) 125.
- 12 K. Kimura, Y. Tsujimura and M. Yokoyama: *Pure Appl. Chem.* **67** (1995) 1085.
- 13 B. K. Oh, C. Y. Kim, H. J. Lee, K. L. Rho, G. S. Cha and H. Nam: *Anal. Chem.* **68** (1996) 503.

- 14 G. S. Cha, D. Liu, M. E. Meyerhoff, H. C. Cantor, A. R. Midgley, H. D. Goldberg and R. B. Brown: *Anal. Chem.* **63** (1991) 1666.
- 15 Y. Tsujimura, M. Yokoyama and K. Kimura: *Sensors and Actuators* **B22** (1994) 195.
- 16 D. N. Reinhoudt, J. F. J. Engbersen, Z. Brzózka, H. H. van den Vlekkert, G. W. N. Honig, H. A. J. Holterman and U. H. Verkerk: *Anal. Chem.* **66** (1994) 3618.
- 17 D. N. Reinhoudt: *Sensors and Actuators* **B6** (1992) 179.
- 18 J. A. J. Brunink, J. G. Bomer, J. F. J. Engbersen, W. Verboom and D. N. Reinhoudt: *Sensors and Actuators* **B15-16** (1993) 195.
- 19 N. Oyama and F. C. Anson: *J. Electrochem. Soc.* **127** (1980) 247.
- 20 M. Majda and L. R. Faulkner: *J. Electroanal. Chem.* **169** (1984) 77.
- 21 D. D. Montgomery and F. C. Anson: *J. Am. Chem. Soc.* **107** (1985) 3431.
- 22 C. E. D. Chidsey and R. W. Murray: *J. Phys. Chem.* **90** (1986) 1479.
- 23 P. Gatenholm, J. Michálek and J. Vacik: *Macromol. Symp.* **109** (1996) 127.
- 24 C. J. Pedersen: *J. Am. Chem. Soc.* **89** (1967) 7017.
- 25 C. J. Pedersen: *Angew. Chem. Int. Ed. Engl.* **27** (1988) 1021.
- 26 J. D. Curry, D. A. Nicholson and O. T. Quimby: *Top. Phosphorus Chem.* **7** (1972) 37.
- 27 R. L. Carroll and R. R. Irani: *J. Inorg. Nucl. Chem.* **30** (1968) 2971.
- 28 H. Wada and Q. Fernando: *Anal. Chem.* **44** (1972) 1640.
- 29 M. Wozniak and G. Nowogrocki: *Talanta* **26** (1979) 381.
- 30 J. W. Ross: *Science* **156** (1967) 1378.
- 31 H. M. Brown, J. P. Pemberton and J. D. Owen: *Anal. Chim. Acta* **85** (1976) 261.
- 32 M. Nègre, M. Bartholin and A. Guyot: *Angew. Makromol. Chem.* **80** (1979) 19.
- 33 G. M. Kosolapoff: *J. Am. Chem. Soc.* **67** (1945) 1180.
- 34 R. Engel: *Synthesis of Carbon-Phosphorus Bonds* (CRC Press, Boca Raton, 1988).
- 35 C. E. McKenna, M. T. Higa, N. H. Cheung and M. C. McKenna: *Tetrahedron Lett.* (1977) 155.
- 36 Y. Leroux: *Int. Appl. Patent* WO 8400,966 (1984).
- 37 J. B. Prentice, O. T. Quimby, R. J. Grabenstetter and D. A. Nicholson: *J. Am. Chem. Soc.* **94** (1972) 6119.
- 38 A. I. Vogel: *Vogel's Textbook of Practical Organic Chemistry*, 4th ed. (Longman, London, 1978) p. 3.
- 39 V. Rocher, J. M. Chovelon, N. Jaffrezic-Renault, Y. Cros and D. Birot: *J. Electrochem. Soc.* **141** (1994) 535.
- 40 H. Perrot, N. Jaffrezic-Renault, N. F. De Rooij and H. H. Van den Vlekkert: *Sensors and Actuators* **20** (1989) 293.
- 41 R. M. Izatt, K. Pawlak, J. S. Bradshaw and R. L. Bruening: *Chem. Rev.* **95** (1995) 2529.
- 42 N. Jaffrezic-Renault, J. M. Chovelon, H. Perrot, P. Le Perchec and Y. Chevalier: *Sensors and Actuators* **B5** (1991) 67.
- 43 U. Oesch, S. Caras and J. Janata: *Anal. Chem.* **53** (1981) 1983.
- 44 V. A. Davankov, S. V. Rogozhin and M. P. Tsyurupa: *Angew. Makromol. Chem.* **32** (1973) 145.
- 45 V. A. Davankov, S. V. Rogozhin and M. P. Tsyurupa: *J. Polym. Sci.: Symp.* **47** (1974) 95.
- 46 A.-M. Hecht, R. Duplessix and E. Geissler: *Macromolecules* **18** (1985) 2167.
- 47 C. Picot: *Progr. Colloid Polym. Sci.* **75** (1987) 83.
- 48 A. Moussaid, J.-P. Munch, F. Schosseler and S. J. Candau: *J. Phys. II* **1** (1991) 637.
- 49 F. Mallamace, N. Micali, C. Vasi, R. Bansil, S. Pajevic and F. Sciortino: *Macromol. Symp.* **79** (1994) 179.