

Chapter 21

Ion-Selective Electrodes

From Glasses to Crystals and Crowns

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This paper summarizes the history of development of ion-selective electrodes from the first description of glass pH electrodes at the beginning of the century.

A Long Beginning

The history of ion-selective electrodes (ISEs) began at the beginning of this century with the discovery in 1906, by Cremer (1) of the glass electrode sensitive to hydrogen ions. This was soon followed by the detailed studies in 1909 of Haber and Klemensiewicz (2). By the late 1930s, glass membrane electrodes, as part of electronic pH meters, were seen as standard items of laboratory equipment when, along with the polarograph and photoelectric colorimeters (absorptiometers), they marked the beginning of the era of the use of physico-chemical instrumentation in chemical laboratories. Such instrumentation has evolved by advances in electronics and the phenomenal developments in computerization for experimental control and data processing. This sophistication has called for improvements in sensors and detectors. The history of ISEs shows what has been achieved in the way of an increase in the number of ions which can be selectively determined, improvements in selectivity and sensitivity, an ever-widening range of applications, and better understanding of functional mechanisms in order to promote further development.

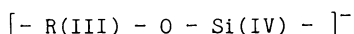
Non-glass membranes were introduced in 1935-36 by Tendeloo (3,4) who made measurements with slices of barium sulphate and calcium fluoride (fluorite). This was followed in 1937 by the use of pressed silver chloride polycrystals on platinum discs by Kolthoff and Sanders (5). Twenty years later, Tendeloo and co-workers (6-9) went on to describe membranes of calcium salts of low water solubility in low melting point paraffin.

In the late 1950s, Eisenman and co-workers exploited the

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deviation from the Nernst equation in alkaline solutions (alkaline error) observed in 1922 by Hughes (10). They showed (11-12) that glass compositions could be formulated to give metal ion function at relatively low pH. To realize this cation selectivity relative to hydrogen ions, it is necessary to introduce a structural element into the glass lattice in a coordination state higher than its oxidation state. For example, when an element R, in oxidation state -3 is introduced into glass in four-fold coordination in place of silicon(IV), the structure is



in which the replacement for Si(IV) has resulted in a site which can participate in cation exchange. When alumina is incorporated in alkali silicate glasses, cation responses are obtained. Most cation-selective glasses are alkali metal aluminosilicates and examples of useful compositions for cation selective glass electrodes are shown in Table I.

TABLE I. Some Compositions of Glasses for Cation Sensitive Glass Electrodes

Cation to be measured	Percentage glass composition			Selectivity (approximate)
	Na ₂ O	Al ₂ O ₃	SiO ₂	
Na ⁺	11	18	71	$k_{Na,K}^{pot} 3.6 \times 10^{-4}$ at pH 11
K ⁺	27	5	68	$k_{K,Na}^{pot} 0.05$
Ag ⁺	28.8	19	52.2	$k_{Ag,H}^{pot} 10^{-5}$
Ag ⁺	11	18	71	$k_{Ag,Na}^{pot} 10^{-5}$

Note: Adapted from Reference 13.

It is generally accepted that the mechanism of operation of a glass electrode depends on an ion-exchange process (14). However, although hydrogen ions undergo exchange across the solution/hydrated layer interface, these ions do not penetrate the membrane. This was demonstrated by coulometric experiments (15) involving prolonged electrolyses in glass electrode bulbs filled with tritium-labelled sample solutions when no increase in tritium was found on the non-labelled side of the membrane, even after 20 h of electrolysis. Thus, it was concluded that the charge-carrying mechanism across the membrane was based on ion-exchange at the solution/hydrated layer interface, associated with diffusion within the hydrated layer and an interstitial charge carrying mechanism (by sodium ions for sodium silicate glass) through the dry glass layer. In this middle layer, each charge carrier merely needs to move a few atomic diameters before transferring its energy to another carrier.

A Fast Awakening

The real move towards ISEs based on non-glass membranes came in 1961 when Pungor and Hollos-Rokosinyi (16) produced a membrane by incorporating silver iodide into paraffin. This led on to the development of heterogeneous membrane electrodes, especially those based on silicone rubber matrices (17-20).

The research activity on ISEs was greatly enlivened with the development of the homogeneous crystal membrane fluoride electrode in 1966 by Frant and Ross (21) followed a year later by a liquid membrane electrode for calcium by Ross (22). Another significant development at this time was the work of Stefanac and Simon (23-24) on neutral carrier antibiotics which showed valinomycin to be very selective for potassium. After evaluating various membrane support materials, such as filter paper, polyethylene film, Thixcin and nylon mesh, they settled on membranes of low porosity and antibiotic solutions of high viscosities for obtaining high selectivity potassium ISEs from valinomycin (24). Others were active in the field, and prominent among those who contributed to wider use and appreciation of the utility of the selective properties of ISEs were Rechnitz and co-workers (13,25-27).

By the mid-1960s, the author of this paper was assembling a team for ISE researchers at UWIST (Cardiff, Wales), where the early work was based on the prospect of resacetophenone oxime as an ion-sensor for copper(II) ions, this being based on its selectivity as an ion-exchanger (28). Concurrently, recognition was given (29) to earlier membrane potential data (30) whereby membrane potentials (E_M), in a cell consisting of two compartments containing a salt (AY) solution of different activities (a' and a'' for A of valence z_A) on each side of the membrane (each containing a reference electrode) could be determined as

$$E_M = \frac{2.303RT}{z_A F} \left(\log \frac{a_A''}{a_A'} \right) \quad (1)$$

However, it was recognized (29-30) that equation (1) is an over-simplification since, in addition to the Donnan phase boundary potential, it should include a term to allow for diffusion phenomena arising from the fact that the membrane is more permeable to counter ion A than to co-ion Y:

$$E_M = \frac{2.30RT}{z_A F} \left[\log \frac{a_A''}{a_A'} - (z_Y - z_A) \int_1^2 t_Y d \log a^{\pm} \right] \quad (2)$$

where t_Y is the transport number of the co-ion in the membrane and z_Y its valence and a^{\pm} is the mean activity of the electrolyte. Essentially, the first term of equation (2) gives the thermodynamic limiting value of the concentration potential,

while the second term gives the deviation due to the co-ion flux. For a membrane ideally permselective towards the counterion, the second term vanishes ($t_y = 0$) and equation (2) reduces to the Nernst type equation (1).

In support of permselectivity, later radiotracer diffusion studies of calcium chloride through selective PVC matrix calcium ion-selective membranes based on organophosphate sensor showed calcium counterion permselectivity with negligible permeation by chloride co-ions (31). The PVC matrix membrane permeation studies also showed selective permeation of calcium ions when compared with other cations (31).

The First PVC Matrix Membrane Electrodes

Considerable interest was focussed on ISEs based on liquid ion-exchangers absorbed on an inert support. However, these early liquid membrane electrodes were affected by short life-time and poor character of the inert support needed to define the interface between the membrane and the analyte solution. These disadvantages were neatly overcome in the author's laboratories by entrapment of the liquid membrane in a PVC matrix membrane (32) by the straightforward procedure of simply dissolving PVC in a solution of liquid ion-exchanger (or neutral carrier sensor system) in tetrahydrofuran (THF) and slowly evaporating the THF at room temperature to give a master membrane sufficient for making several ISEs (32-34). This procedure is far more straightforward than an earlier proposal for a calcium ISE whereby a mixture of thenoyltrifluoroacetone calcium ion-sensor plus tributyl phosphate plasticizer and PVC was knife-coated on a woven fabric and heat-cured (35).

The PVC matrix membrane electrodes offer good mechanical resistance to stirring and pressure effects and, although several other materials have been assessed, PVC is still by far the most commonly used support matrix.

Conventional electrodes are relatively large (3-10 mm membrane diameter), and are not suitable for small samples and applications like *in vivo* measurements. This has prompted research into alternative designs and of miniature ISEs. Microelectrodes have tip sizes generally in the 0.25-5 μm range, that is, small enough to penetrate a single cell. A large number of such electrodes have been constructed using different carriers and designs (36-37) but they tend to be of high resistance and noisy due to their small size. Several designs have been developed to reduce this problem and among the newer ones in an all-solid-state construction based on a backfill of electrically conducting epoxy (38). In general, though, microelectrodes are in widespread use.

With regard to simple miniaturization, coated-wire ISEs are an attractive approach (39-40). This involves coating the corresponding conventional polymer membrane onto a platinum or other wire. Numerous coated-wire electrodes selective to different ions have been prepared (41-42), despite the lingering controversy over the performance of these devices in terms of

stability, reproducibility and the question as to the mechanism at the interface between the metal wire and polymer film. Cattrall, Drew and Hamilton (43) proposed that, since PVC is permeable to both oxygen and water, an oxygen electrode is set up at the platinum/PVC interface. Hulanicki and Trojanowicz (44) used this model for interpreting improvements in the stability of solid-state calcium ISEs using silver or graphite contacts to the membrane compared with similar membranes contacted by silver chloride coated silver. Schindler and co-workers (45-46), also concluded that a Pt/O₂ system existed in these coated-wire type ISEs.

According to Buck (47-49) there is no basis for expecting the potentials of the membrane/metal boundary of coated wire electrodes to be stable with time. He calls this a "completely blocked system", that is, it is "blocked" for carrying both electrons and ions. Buck considers such a completely blocked interface as a condenser. Nevertheless, coated-wire electrodes are widely used, especially for potentiometric titrations (41,50-51).

Coated-wire electrodes are late entrants into the all-solid-state electrode realm, for crystal membrane electrodes of this mode were already common. The advantages of all-solid-state construction are summarized by Nikolskii and Materova (52). In general, the most important matter for all ISEs with solid internal contact is that of ensuring reversibility and equilibrium stability of the transition from ionic to electronic conductivity. Buck (47-49) as well as Nikolskii and Materova (52), have reviewed the field, covering many electrode types, including Selectrodes, where a graphite rod is covered with an ion-selective membrane of either solid crystal active substances (53-56), or liquid ion-exchanger, or chelate (53-59).

Selectivity Considerations

The name of Nikolskii is synonymous with selectivity of ISEs (60-61), through the celebrated Nikolskii equation

$$E = \text{constant} + \frac{2.303RT}{z_A F} \log (a_A + k_{A,B}^{\text{pot}} (a_B)^{z_A/z_B}) \quad (3)$$

which gives the parameters of the electrode potential, E , measured with respect to a reference electrode for Nernstian response. Thus, an ISE is taken to respond selectively to an ion, A, of activity a_A and charge z_A in the presence of an interfering ion, B, of activity a_B and charge z_B , where $k_{A,B}^{\text{pot}}$ is the selectivity coefficient. The various approaches to determining selectivity coefficients were summarized (29, 62-63), in the early heady days of ISE researches, but more recently some additional proposals have been made, such as, the matched potential method of Gadzekpo and Christian (64).

Essentially, there are two separate-solution methods with the respective solutions producing e.m.f.s., E_1 and E_2 . The

equations used depend, respectively, on equality of the primary and interferent ion activities (equation 4) or of the e.m.f.s. (equation 5):

$$\frac{E_2 - E_1}{2.303RT/z_A F} = \log k_{A,B}^{\text{pot}} + \left(\frac{z_A}{z_B} - 1 \right) \log a_A \quad (4)$$

$$a_A = k_{A,B}^{\text{pot}} (a_B)^{z_A/z_B} \quad (5)$$

A more common procedure for determining selectivity coefficients is to measure the e.m.f. in solutions containing a fixed amount of interferent, B, with varying activities of the primary ion, A, for which the electrode is designed. The general idealised pattern (65) involves the calculation of $k_{A,B}^{\text{pot}}$ by equation (5), when the values of a_A and a_B appertain to the intercept at that part of the calibration curve (of zero slope) corresponding to complete interference by the interferent with that of Nernstian or near-Nernstian slope for a more or less individual response by the primary ion. This procedure has been recommended for assessing ISEs (66-67).

Srinivasan and Rechnitz (62) used two rather complicated equations according to whether high $k_{A,B}^{\text{pot}}$ or low $k_{A,B}^{\text{pot}}$ values were being determined. The matched-potential method of Gadzekpo and Christian (64) is an alternative mixed solution method. Here, the potential of a reference solution of the primary ion is measured and then again after addition of a further known amount of primary ion. To a second aliquot of the reference solution, a solution of the interfering ion is added to produce the same potential change as the added primary ion. The ratio of the concentrations of the primary ion and interfering ion needed to give the same potential change represents the selectivity coefficient. Among the claimed advantages (64) are the fact that the method makes no assumption about the slope of the response curve for the interfering ion, and that there is freedom of interference from drift.

Ion-Selective Field Effect Transistors (ISFETs)

An alternative approach to miniaturization of ISEs has been through ion-selective field effect transistors (ISFETs). Essentially, these integrate the ISE with the field effect transistor (FET) of the input stage of a pH/millivoltmeter, which takes the high-impedance signal of an ISE and outputs a low-impedance signal which is less sensitive to noise pick-up. In effect, ISFETs eliminate the connecting cable between the ISE and the input FET by coating the ion-selective material directly on to the gate area of the FET as innovated by Janata and co-workers (68). Important contributions have since been made as reviewed by Janata and Huber (69-70). More recently, Sibbald, Covington and Carter (71) have described a four-function ISFET

assembly for hydrogen, potassium, sodium and calcium ions, as well as certain other advances at Newcastle (72). Progress also continues at other centres, such as, in a flatpack mounted ISFET device set in a Perspex flow cell which permits flow injection analysis (FIA) and rapid substitution of one ISFET sensor for another (73) and in photopolymerisable butyl methacrylate membranes (73) which offer prospects of mass produced membranes on the FET gate (73).

Bergveld (74) was, of course, the first to report an ISFET as a chemically sensitive semiconductor device (CSSD). A broader grouping is that of chemically sensitive electronic devices (CSEDs), sub-classified by Bergveld and van der Schoot (75) into ISFETs as "active electronic components" as one member of a four-class system. Other categories are passive electronic components (resistor, capacitor, etc.), electronic and opto-electronic systems (oscillating crystal sensors, etc.), and systems with a chemical feedback (dynamic oxygen sensor, and coulometric sensors).

Exploitation of Ion-Selective Electrodes

The above is a rather condensed historical survey of the development of glass, solid and liquid membrane types of ISEs. The further developments have been modifications for actual applications of which micro electrodes are but one example. Other modifications include incorporation of ISEs into flowing systems as in the FIA mode pioneered by Ruzicka and co-workers (76-78), the use of complementary membranes, such as, gas-permeable membranes for gas sensing (79), and enzyme membranes for utilizing the additional selectivity available from enzyme reactions (80-81).

Among variations in approaches for electrolyte measurements with ISEs is the Kodak Potentiometric Dry Chemistry System, where batchwise measurements are made on disposable slides. These are manufactured by coating an appropriate polymeric membrane over an internal reference gel layer on a conductive substrate. Slides for potassium, sodium, chloride and carbon dioxide are available. A drop of sample is placed on one half of the slide and a drop of reference solution on the other half. The drops are connected by an electrolyte bridge and the e.m.f. measured via metallic contacts.

Liquid Membrane Type Sensors

Without in any way negating the wide-ranging utility of glass membrane electrodes for pH, pNa and pNH_4 measurements and the good solid-state membrane electrodes for fluoride, sulphide and other ions, the main focus of development work of the last twenty years has been in the search for better liquid membrane systems. This has been stimulated by the convenience of PVC matrices for trapping and supporting liquid membranes (32-34,83).

The original calcium bis didecylphosphate used with dioctyl-phenyl phosphonate (22) as a liquid ion-exchanger for

calcium ion-sensing was improved by incorporating a phenyl group between the alkyl and phosphate oxygen of the ion-selective component (84). Attention to purification of the ionophore yielded a conveniently synthesized (85) long-ranging calcium ion sensor (86). The calcium ion-selectivity function is dependent on the synergism of dioctylphenyl phosphonate as plasticizing solvent mediator (22,87), while decan-1-ol when used in place of the phosphonate reduces selectivity to yield a divalent electrode (87-89). Under appropriate conditions, such as low calcium ion levels, the divalent electrode can be used as a magnesium ISE. This has been nicely shown for physiological and intracellular model systems for speciation using chemometrics approaches (90-93). The use of ligands for ion-buffer systems (84) is also nicely demonstrated for extending the calibration range of calcium ISEs down to 10^{-8}M , that is, to well within the intracellular range (87,90-94). Of considerable interest in this respect is a single pH buffered multi-ligand system based on HEDTA, EGTA and NTA for setting up $[\text{Ca}^{2+}]$ standards between 10^{-4} and 10^{-8}M by mere spiking with 0.02M calcium chloride (90,91,93).

Liquid membrane anion ion-exchanger type sensors are best illustrated by the nitrate ISE (95-96). This has seen a role in the environmental screening of waters and effluents (97) for nitrate, but such use has been somewhat diminished by the high sensitivity and facility for multi-ion analysis of the newer approach of ion-chromatography.

The ion-exchanger type ISEs can be readily converted to other forms, as illustrated by conversion of a nitrate ion-exchanger to the chlorate form, and assembly into a chlorate ISE (98). Much work continues to be done on anion liquid ion-exchangers for anion ISEs (see Recent Titles in each Volume of Ion-Selective Electrode Reviews). For these tetraalkylammonium and -phosphonium, tetraphenyl-arsonium and -phosphonium, and dye salts are a popular basis (99).

Cation liquid ion-exchanger sensors are much more varied in type (99). Some examples are: dialkyl- and di(alkylphenyl) phosphates for calcium and divalent ions (as discussed above); tetraphenylborates for onium ions and for drug type cations either by directly or by potentiometric titration; lead diethyldithiocarbamate in trichloroethane for lead(II) (100); and mercury(II) PAN chelate in trichloromethane for mercury (101).

Crown Ether and Neutral Carrier Sensors

Considerable work has been directed to the search for better neutral carriers, motivated by the very successful valinomycin sensor for potassium (23-24). Impetus was given to the development of this electrode by the observation of Moore and Pressman (102) that the antibiotic is capable of actively transporting potassium across rat mitochondria membranes. There are numerous synthetic macrocyclic polyethers capable of forming complexes with monovalent cations. Some of the earliest ISE studies were by Rechnitz and Eyal (103) on dicyclohexyl- and dibenzo-18-crown-6 ligands synthesized by Pedersen (104). Soon

afterwards, Petranek and Ryba (105-106) assessed various types of crown-6 and larger crown compounds for potassium ion-sensing and promoted dimethyldibenzo-30-crown-10 with dipentyl phthalate in PVC as the best of the series. Generally, these and later studies on crown ether sensors have indicated that the selectivity for potassium does not exceed that of valinomycin.

Researches on crown ether derivatives are now much more widespread. Thus, Pungor and co-workers (107) have studied the synthesis and application of different mono- and bis-crown ether derivatives with urethane and urea linkages. Moody, Owusu and Thomas (108-110) have studied dibenzo-30-crown-10 and its derivatives as ISE sensors for diquat (DQT) and paraquat (PQT), the best being based on dibenzo-18-crown-10 with DQT.2TPB and 2-nitrophenyl phenyl ether in PVC. These studies integrate the molecular receptor researches of Stoddart at Sheffield and structural work of Williams at Imperial College, London, with the ISE work at UWIST (111). On the fundamental side, the researches showed (111-112), that DB30C10 changes its shape dramatically to accommodate the guest molecules, while bis para-phenylene-34 crown-10 (BP34C10) hardly modifies its shape when it engulfs PQT. However, this feature is not carried through to improving the PQT²⁺ electrodes which are best based on PQT.2TPB without crown ether, and activated by a charge transfer interaction (113) between PQT²⁺ and TPB⁻. There is no advantage gained in replacing TPB by an alternative anion (109).

Apart from Pungor and co-workers (107), others have prospected in the area of bis crown ethers, e.g., Shono and co-workers have shown good potassium ion-selectivity for some bis (15-crown-5) derivatives (114-115) where one containing a dodecyl group in the link exhibits good lipophilicity and longer lifetime for the resulting ISEs (115).

Passing onto smaller crowns, Shono and co-workers (116) have studied a very useful dodecylmethyl-14-crown-4 which shows good ISE selectivity towards lithium over sodium. Lithium ISEs have to function over a small range around 1 mM [Li⁺] in the rather stringent conditions of blood electrolyte levels: only relatively few sensors approach the required selectivity specifications (117). Among other sensors that have received recent attention, and having reasonable prospects of meeting the requirements in respect of lithium selectivity over sodium, and of being functional for use with blood serum, are a barium propoxylate complex which functions by its affinity for lithium (118-119), and some sensors based on non-crown diamide carriers studied by Simon and co-workers (120-122) and by Christian and co-workers (123-124).

The function of neutral carriers, such as the crown ether compounds discussed above, is to bind ions reversibly and to transport them across the aqueous/organic interface. The neutral carrier forms a solvation shell around a cation of appropriate charge and size, thereby solubilizing it in the organic phase. Some influencing factors are important, such as, steric interaction and the effect of the solvent on the metal cations (125). Ideally, these induce a selective permeation of one type

of ion into the membrane, although the detailed mechanism for a particular ion appears not to be fully resolved (126). However, despite mechanistic permselectivity controversies, a large number of neutral ligands have been shown to be good ionophores for use in ISEs. An early, tremendously successful, case of the synthetic systems is that of ETH 1001 for calcium (127) which has been widely adopted in commercial calcium ISEs instead of the earlier organophosphate calcium ion-sensors. Simon and co-workers (128) have reviewed neutral carrier ISEs, while some more recent reviews have taken on more specialized aspects, e.g., for lithium (117).

More recent work has pressed towards even more selective sensors for calcium, stimulated by a 2:1 ligand:calcium stoichiometry found by Petranek and Ryba (129) for a calcium crown ether which exhibited high calcium ion selectivity over magnesium. Thus, Shono and co-workers (130) have studied a bicyclic polyether amide derivative with enhanced selectivity for calcium, while Simon and co-workers (131) have reported a non-crown neutral carrier for calcium which forms a 3:1 ligand:calcium complex with very high selectivity for calcium over sodium and potassium, that is, by factors of $10^{7.4}$ and 10^8 , respectively. This indicates that macrocyclic systems are not a prerequisite for high selectivity.

A further prospecting area for neutral carrier ligands is in the field of anion binding, where Simon and co-workers are making some significant inroads (132-133).

Conclusion

The numerous studies on developing ion-selective electrodes far exceed those which can be covered in this short historical review. The full extent of researches are reflected in a huge volume of references given in more comprehensive reviews, such as, an earlier article by Moody and Thomas (134), the various articles in Ion-Selective Electrodes Reviews (135), and in many published reviews. The recent Database on Electrochemical Sensors (136), with bibliography covering 1983-86 emphasizes the continuing additions to the literature; here, there are more than 2500 individual entries from more than 3500 authors. Not quite all are on ISEs, but four of the five most active electrochemical sensor groups cited are of the ISE fraternity, namely, Pungor (Budapest), Simon (Zürich), Rechnitz (Delaware, USA) and Thomas (Cardiff, Wales, UK); the fifth group is that of Karube (Tokyo, Japan) who are mainly engaged on non-potentiometric biosensors.

Finally, it has not been a prime aim of this review to discuss applications. Detailed information on specific application areas can be obtained from reviews cited in this article and elsewhere. Nevertheless, the widest application area concerns the clinical chemical use of ISEs for blood electrolyte analyses where Working Group on Ion-Selective Electrodes, affiliated to the International Federation of Clinical Chemistry, have devoted their energies to promoting the use of ISEs in this way and to equating that data obtained so that interpretation can

be based on the procedures used for flame spectrometric data. The published Proceedings of the Annual Meetings are an invaluable record of deliberations in this area (137).

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