

Chimia 51 (1997) 768–770
© Neue Schweizerische Chemische Gesellschaft
ISSN 0009–4293

Chemical Sensors and Computer-Aided Analytical Chemistry

Ernö Pretsch*

Abstract. A simplified thermodynamic model of potentiometric and optical ion sensor membranes allows to improve their properties and the measurement of complex formation constants in membrane phases. The simultaneous optical and potentiometric investigation of sensing films revealed diffusion-related long-term drifts. The lower detection limit of ion-selective electrodes was shifted from the micromolar to the picomolar range, thus allowing many new applications especially in environmental and biological trace metal analysis. Also, various prediction methods of spectroscopic and other physical data from chemical structures have been created which allow a fast compatibility check between structures and molecular spectra. Furthermore, programs are being developed for automatic spectra interpretation.

1. Introduction

Research related to chemical sensors and computer-aided analytical chemistry has a long-lasting tradition at the ETH-Zürich. Pioneering work on ionophore-based ion-selective electrodes (ISEs) in the group of Prof. W. Simon [1] led not only to a worldwide acceptance but also to a real breakthrough of sensor applications in clinical chemistry [2] so that well over 10^6 assays per year are performed with ISEs [3]. Similarly, the theoretical framework developed by Morf is widely approved, his book published in 1981 still being considered a standard reference [4]. The vigorous initial development of optical sensors based on coupled equilibria (bulk optodes) was also due to the same group [5]. As to computer-aided analytical chemistry, pioneering work on spectroscopic databases and computer-aided spectra interpretation was done by Prof. J.T. Clerc and collaborators [6], originally at the ETH and later at the University of Berne.

2. Ion-Selective Electrodes and Optical Sensors

Since their introduction in the late 60ies, ionophore-based ISEs have been described for over 60 analytes [7]. On the other hand, bulk optodes for over 30 analytes [7] have been developed within a few years after discovering that the basis of their response

is closely related to that of the corresponding ISEs [5]. Meanwhile, ISEs are in widespread routine use but a real breakthrough of bulk optodes for practical applications has not yet been accomplished. Actually, both fields are in continuous rapid expansion. In the following, various recent achievements are summarized.

2.1. Membrane Response Mechanisms

The theoretical basis of the response and selectivity behavior of ISEs [4] and optodes [5] has been simplified mainly by Prof. E. Bakker [8–10]. Based on thermodynamic considerations, he succeeded in establishing corresponding response mechanisms for both sensor types, thus showing that various characteristics such as selectivities and theoretical detection limits are closely related [11]. A very important achievement in these lines was the development of a new formalism [9] replacing the traditional *Nikolskii-Eisenman* equation [12] long known to be incorrect if two ions of different valences simultaneously affect the ISE response [13].

The selectivity of both types of sensors is, in particular, influenced by the interaction of ions with the ionophore. Experiments with optodes allowed to determine formal complex formation constants in the order of 10^8 – 10^{10} l mol⁻¹ for 1:1 complexes of well established ionophores in the membrane phase [14]. Very recently, potentiometric studies on ISE membranes with two ionophores have also been shown to allow the determination of such thermo-

dynamic parameters [15]. The values obtained with the two different methods are in excellent agreement and, hence, support the validity of the underlying model assumptions.

2.2. Fine-Tuning of Selectivities

The above-mentioned simple thermodynamic approach is also helpful for optimizing the composition of sensor membranes [9]. Thus, the optimal concentration ratio of ionophore/ion exchanger in polymer pH electrode membranes could be predicted [16]. It is known that membranes based on electrically neutral ionophores must contain charged sites for proper functioning [4]. It is now well established that in many cases, ionic impurities of the membrane matrix [17–19] and of other membrane components [19] served as sites. Their electrochemically relevant concentration can be determined with good precision from selectivity measurements on membranes containing different amounts of added lipophilic sites [20].

In ISE membranes based on charged ionophores, the presence of sites is not mandatory. However, it could be predicted by theory and proved in practice that sites, as assumed earlier [21], are also beneficial in the presence of a charged carrier if their charge is the same as that of the analyte, which is contrary to what is needed with an electrically neutral carrier [22]. These findings not only allowed to improve a nitrite-selective microelectrode [23] but also served as a basis of investigations on membrane response mechanisms [24][25].

At an early stage already, lipophilic salts lacking ion-exchanger properties were added to membranes to increase their conductivity but it was not recognized that they may affect the selectivity behavior [26][27]. Recently, in the case of an ISE membrane a surprising influence of such salts on the selectivity was observed that could not be explained properly [28]. A new general treatment, which also considers activity coefficients in the membrane phase, now provides a theoretical framework to explain such effects and their dependence on other membrane parameters [29].

*Correspondence: Prof. Dr. E. Pretsch
Laboratory for Organic Chemistry
ETH-Zentrum
CH-8092 Zürich
Tel.: +41 1 632 29 26
Fax: +41 1 632 11 64
E-Mail: pretsch@org.chem.ethz.ch
Internet: http://www.ceac.ethz.ch/pretsch/

2.3. Observation of Membrane Processes: Spectropotentiometry

The first optical investigations on polymeric membranes as used in ISEs was done by *Harrison* and coworkers [30]. From time-dependent concentration profiles, a detailed view of water diffusion through membranes was established [31]. Simultaneous optical and potentiometric measurements on membranes, however, were introduced only recently [32]. This spectropotentiometric monitoring of the processes during cation and anion interference in chromoionophore-based H^+ -selective membranes allowed to determine diffusion coefficients and to elucidate the origin of long-term potential drifts induced by such interferences [32][33]. By using the same experimental setup and a new lipophilic water indicator, it could be shown [34] that the water uptake of polymeric membranes was influenced by the hydrophilic indicator used [31].

2.4. Lowering of the Detection Limit of ISEs from Micromolar to Picomolar Concentrations

The lower detection limit of polymer-based ISEs usually is around 10^{-6} M. Theoretical response below this concentration was only found in buffered sample solutions [35]. It was assumed that ions leaching from the membrane [36] bias the analyte concentration at the sensor surface and impede the assessment of true detection limits. The selectivities were biased as well and could only be determined by using special measuring procedures [37]. Till now, no analytical use of true detection limits and selectivity values was possible. Very recently, however, the lower detection limit of ISEs has been improved by a factor of $\geq 10^6$ so that measurements down to the picomolar concentration range are now feasible (*Fig.*) [38]. Also, true selectivities towards strongly discriminated ions are now directly accessible. These achievements open up new dimensions in ISE applications, especially for trace metal analyses in environmental and biological samples.

2.5. New Sensors

In recent years, our main focus has been placed on developing optical sensors with measuring ranges required for environmental analyses [39–42]. Further work is in progress to realize inexpensive test strips for heavy metal pollutants such as Pb^{2+}/Cd^{2+} , Ag^+ , and Hg^{2+} . The extension of the ISE response range (see *Sect.* 2.4) will allow the development of corresponding potentiometric sensors as well.

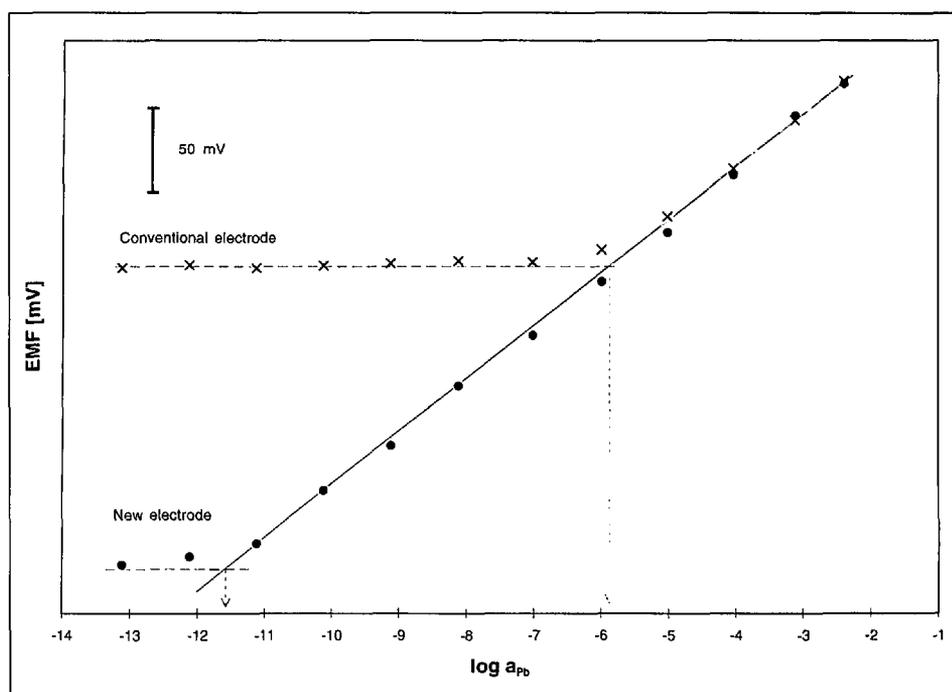


Figure. Response of two Pb^{2+} ISEs with the same membrane but different internal electrolytes: a) 1:1 mixture of 10^{-3} M $PbCl_2$ and 0.1 M $MgCl_2$ (conventional), b) 1 ml of 0.1 M $Pb(NO_3)_2$ in 100 ml of 0.05 M EDTA- Na_2 ; measured pH: 4.34.

3. Computer-Aided Analytical Chemistry

Owing to the ever increasing amount of stored and newly generated data, their automatic reduction to relevant information is a problem of high actuality. Most of the activities described below are, therefore, focused on this problem domain.

3.1. Hypermedia – The Electronic Book Concept

The undiminished popularity of a printed collection of spectroscopic reference data [43] prompted us to develop a corresponding electronic book [44–47]. Based on hypermedia technology [48], it integrates reference data, spectra, and computer tools required for the interpretation of 1H -NMR, ^{13}C -NMR, IR, and mass spectra.

A fast and reliable estimation of properties from chemical constitutions is required both for the design of drugs and agrochemicals and in environmental chemistry. Therefore, the hypermedia concept has also been used to generate a prototype of an electronic book for chemical properties [49]. In addition, a new method has been developed for estimating distribution coefficients in the octanol/water system [50]: From a reference database, clusters of related compounds are found and used to build individual local models. Since the process is fully automatic, it can be implemented as a self-learning system.

So far, the bottleneck of the development of electronic books was the fact that

data had to be entered manually. Therefore, the concept of automatic hypermedia generation was introduced [49].

3.2. NMR Spectra Prediction

Programs have been developed for the prediction of ^{13}C -NMR [51–54] and 1H -NMR [55][56] chemical shifts of organic compounds. Various automatic extrapolation techniques are used so that shifts of over 90% of C- and H-atoms in *ca.* 150 000 different chemical environments of a large test set can be predicted. The time required to estimate a single chemical shift is in the order of ms.

3.3. Automatic Spectra-Structure Compatibility Tests

Based on NMR chemical shift predictions, the automatic ranking of solutions produced by structure generators is made possible [54][57]. For IR spectra, a method developed by *Clerc* and coworkers has been implemented [58][59]. As to MS, although a reliable spectra prediction is not feasible, heuristic methods can be used for testing the compatibility of a mass spectrum with a proposed structure [46].

Mainly driven by the demands of combinatorial chemistry and by new possibilities of automatic sample processing and spectra recording, the number of spectra to be interpreted is increasing rapidly. A program for the fully automatic compatibility check of a proposed structure with a 1H -NMR, ^{13}C -NMR, IR, or mass spectrum is, therefore, being developed.

3.4. Automatic Spectra Interpretation

In cases where no proposed structure is available, a new program serving as a front-end of structure generators [60] automatically extracts relevant information from various spectra [61]. This new rule-based spectra interpretation system has been developed considering the strengths and weaknesses of different techniques [62][63]. By making simultaneous use of several spectroscopic methods, both high reliability and good performance are achieved. For small- and medium-sized molecules, the system is capable of automatically reducing the solution space to under 3%.

3.5. Design of Genetic Algorithms

Stochastic automatization methods such as genetic algorithms (GAs) are the optimization method of choice for complex search spaces of high dimensions and multiple minima. A GA has been designed to find unbiased starting structures for molecular mechanic calculations [64]. There is a wide range of possibilities as to the specific design and parameter settings of a GA for a given task. Unfortunately, no objective means is yet available to judge the performance of stochastic optimization techniques. Therefore, various quality criteria have been developed very recently [65] which make use of the whole evolving population and allow to judge both the coverage of search space and the reproducibility of the optimization.

The projects described have been partly supported by the *Swiss National Foundation*, the *Eidgenössische Stiftung zur Förderung Schweizerischer Volkswirtschaft durch wissenschaftliche Forschung* (Zürich), the *Bundesministerium für Bildung, Wissenschaft, Forschung und Technik* of the Federal Republic of Germany, by *Chemical Concepts* (Weinheim), *Hitachi Ltd.* (Tokyo), and *Orion Research, Inc.* (Beverly, MA). The author thanks Dr. D. Wegmann for careful reading of the manuscript.

Received: July 30, 1997

- [1] D. Ammann, P. Anker, P.C. Meier, W.E. Morf, E. Pretsch, W. Simon, *Ion-Select. Electrode Rev.* **1983**, 5, 3.
- [2] U. Oesch, D. Ammann, W. Simon, *Clin. Chem.* **1986**, 32, 1448.
- [3] P. D'Orazio, The Pittsburgh Conference, Chicago, IL, 1994, Book of Abstracts, No. 152.
- [4] W.E. Morf, 'The Principles of Ion-Selective Electrodes and of Membrane Transport', Elsevier, New York, 1981.
- [5] W.E. Morf, K. Seiler, B. Lehmann, C. Behringer, K. Hartman, W. Simon, *Pure Appl. Chem.* **1989**, 61, 1613.
- [6] J.T. Clerc, *Pure Appl. Chem.* **1978**, 50, 103.
- [7] P. Bühlmann, E. Bakker, E. Pretsch, *Chem. Rev.*, in preparation.
- [8] E. Bakker, R.K. Meruva, E. Pretsch, M.E. Meyerhoff, *Anal. Chem.* **1994**, 66, 3021.
- [9] E. Bakker, M. Nägele, U. Schaller, E. Pretsch, *Electroanalysis* **1995**, 7, 817.
- [10] E. Bakker, W. Simon, *Anal. Chem.* **1992**, 64, 1805.
- [11] E. Bakker, P. Bühlmann, E. Pretsch, *Chem. Rev.*, in press.
- [12] G. Eisenman, D.O. Rudin, J.U. Casby, *Science* **1957**, 126, 831.
- [13] W.E. Morf, D. Ammann, E. Pretsch, W. Simon, *Pure Appl. Chem.* **1973**, 36, 421.
- [14] E. Bakker, M. Willer, M. Lerchi, K. Seiler, E. Pretsch, *Anal. Chem.* **1994**, 66, 516.
- [15] E. Bakker, E. Pretsch, *J. Electrochem. Soc.* **1997**, 144, L125.
- [16] E. Bakker, A. Xu, E. Pretsch, *Anal. Chim. Acta* **1994**, 295, 253.
- [17] A. van den Berg, P.D. van der Waal, M. Skowronska-Ptasinska, E.J.R. Sudhölter, D.N. Reinhoudt, P. Bergveld, *Anal. Chem.* **1987**, 58, 2827.
- [18] E. Lindner, E. Gráf, Z. Nigreis, K. Tóth, E. Pungor, R.P. Buck, *Anal. Chem.* **1988**, 60, 295.
- [19] P. Bühlmann, S. Yajima, K. Tohda, Y. Umezawa, *Electrochim. Acta* **1995**, 40, 3021.
- [20] M. Nägele, E. Pretsch, *Mikrochim. Acta* **1995**, 121, 269.
- [21] W.E. Morf, W. Simon, *Anal. Lett.* **1989**, 22, 1171.
- [22] U. Schaller, E. Bakker, U.E. Spichiger, E. Pretsch, *Anal. Chem.* **1994**, 66, 391.
- [23] U. Schaller, E. Bakker, U.E. Spichiger, E. Pretsch, *Talanta* **1994**, 41, 1001.
- [24] E. Bakker, E. Malinowska, R.D. Schiller, M.E. Meyerhoff, *Talanta* **1994**, 41, 881.
- [25] U. Schaller, E. Bakker, E. Pretsch, *Anal. Chem.* **1995**, 67, 3123.
- [26] T.A. Nieman, G. Horvai, *Anal. Chim. Acta* **1985**, 170, 359.
- [27] D. Ammann, E. Pretsch, W. Simon, E. Lindner, A. Bezegh, E. Pungor, *Anal. Chim. Acta* **1985**, 171, 119.
- [28] B.K. Oh, C.Y. Kim, H.J. Lee, K.L. Rho, G.S. Cha, H. Nam, *Anal. Chem.* **1996**, 68, 503.
- [29] M. Nägele, Y. Mi, E. Bakker, E. Pretsch, *Anal. Chem.*, submitted.
- [30] X. Li, S. Petrovic, D.J. Harrison, *Sens. Actuators, B* **1990**, 1, 275.
- [31] Z. Li, X. Li, S. Petrovic, D.J. Harrison, *Anal. Chem.* **1996**, 68, 1717.
- [32] B. Schneider, T. Zwickl, B. Federer, E. Pretsch, E. Lindner, *Anal. Chem.* **1996**, 68, 4342.
- [33] E. Lindner, T. Zwickl, E. Bakker, B.T.T. Lan, K. Tóth, E. Pretsch, *Anal. Chem.*, submitted.
- [34] T. Zwickl, B. Schneider, E. Lindner, T. Sokalski, U. Schaller, E. Pretsch, *Anal. Sciences*, submitted.
- [35] U. Schefer, D. Ammann, E. Pretsch, U. Oesch, W. Simon, *Anal. Chem.* **1986**, 58, 2282.
- [36] P. Bühlmann, S. Yajima, K. Tohda, K. Umezawa, S. Nishizawa, Y. Umezawa, *Electroanalysis* **1995**, 7, 811.
- [37] E. Bakker, *Anal. Chem.* **1997**, 69, 1061.
- [38] T. Sokalski, A. Ceresa, T. Zwickl, E. Pretsch, *J. Am. Chem. Soc.*, submitted.
- [39] M. Kuratli, E. Pretsch, *Anal. Chem.* **1994**, 66, 85.
- [40] M. Lerchi, E. Reitter, W. Simon, E. Pretsch, D.A. Chowdhury, S. Kamata, *Anal. Chem.* **1994**, 66, 1713.
- [41] M. Lerchi, F. Orsini, Z. Cimerman, E. Pretsch, D.A. Chowdhury, S. Kamata, *Anal. Chem.* **1996**, 68, 3210.
- [42] S. Röösl, E. Pretsch, W.E. Morf, E. Tsuchida, H. Nishide, *Anal. Chim. Acta* **1997**, 338, 119.
- [43] E. Pretsch, J.T. Clerc, J. Seibl, W. Simon, 'Spectral Data for Structure Determination of Organic Compounds', Springer-Verlag, Heidelberg, 1989.
- [44] M. Cadisch, M. Farkas, J.T. Clerc, E. Pretsch, *J. Chem. Inf. Comput. Sci.* **1992**, 32, 286.
- [45] M. Cadisch, E. Pretsch, *Fresenius J. Anal. Chem.* **1992**, 344, 173.
- [46] T. Brodmeier, A. Gloor, M. Cadisch, R. Bürgin, E. Pretsch, *Anal. Chim. Acta* **1993**, 277, 297.
- [47] A. Gloor, M. Cadisch, T. Kocsis, R. Bürgin Schaller, H.-J. Hediger, J.T. Clerc, E. Pretsch, *Anal. Chim. Acta* **1994**, 295, 93.
- [48] C.L. Macher, M. Cadisch, J.T. Clerc, E. Pretsch, *Chemom. Intell. Lab. Syst.* **1995**, 28, 213.
- [49] C.L. Macher, R.P. Schwarzenbach, E. Pretsch, in 'Software Development in Chemistry 10; Proceedings of the 10th Workshop 'Computer in Chemistry', Hochfilzen, 1995'; J. Gasteiger, Ed., Gesellschaft Deutscher Chemiker, Frankfurt am Main, 1996, p. 97.
- [50] M. Junghans, E. Pretsch, *Fresenius J. Anal. Chem.* **1997**, 359, 88.
- [51] A. Fürst, E. Pretsch, *Anal. Chim. Acta* **1990**, 229, 17.
- [52] A. Fürst, W. Robien, E. Pretsch, *Anal. Chim. Acta* **1990**, 233, 213.
- [53] E. Pretsch, A. Fürst, W. Robien, *Anal. Chim. Acta* **1991**, 248, 415.
- [54] E. Pretsch, A. Fürst, M. Badertscher, R. Bürgin, M.E. Munk, *J. Chem. Inf. Comput. Sci.* **1992**, 32, 291.
- [55] R. Bürgin Schaller, E. Pretsch, *Anal. Chim. Acta* **1994**, 290, 295.
- [56] R. Bürgin Schaller, C. Arnold, E. Pretsch, *Anal. Chim. Acta* **1995**, 312, 95.
- [57] R. Bürgin Schaller, M.E. Munk, E. Pretsch, *J. Chem. Inf. Comput. Sci.* **1996**, 36, 239.
- [58] J.T. Clerc, A.L. Terkovic, *Anal. Chim. Acta* **1990**, 235, 93.
- [59] K. Baumann, C. Affolter, E. Pretsch, J.T. Clerc, *Mikrochim. Acta [Suppl.]* **1997**, 14, 275.
- [60] M. Badertscher, K. Bischofberger, E. Pretsch, *Trends Anal. Chem (TrAC)* **1997**, 16, 234.
- [61] H. Schriber, E. Pretsch, *J. Chem. Inf. Comput. Sci.*, in press.
- [62] C. Affolter, K. Baumann, J.T. Clerc, H. Schriber, E. Pretsch, *Mikrochim. Acta [Suppl.]* **1997**, 14, 143.
- [63] H. Schriber, E. Pretsch, *J. Chem. Inf. Comput. Sci.*, in press.
- [64] T. Brodmeier, E. Pretsch, *J. Comput. Chem.* **1994**, 15, 588.
- [65] R. Wehrens, E. Pretsch, L. Buydens, *J. Chem. Inf. Comput. Sci.*, submitted.