Lithium Ion-selective Electrodes Containing TOPO: Determination of Serum Lithium by Flow Injection Analysis

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Trioctylphosphine oxide (TOPO) acts as a neutral lithium carrier in lithium ion-selective electrode membranes. When TOPO was used with 1% potassium tetrakis(*p*-chlorophenyl) borate in NPOE - PVC membranes, the electrodes exhibited a nearly Nernstian response and had a lithium to sodium selectivity of 1 : 60, which is better than some electrode sensors reported earlier. TOPO was also added to 14-crown-4, ETH 1810 and UWXC 10 electrode membranes, and the lithium to sodium selectivity of the 14-crown-4 electrode was dramatically improved. However, TOPO had a negative effect on the selectivities of the ETH 1810 and UWXC 10 electrodes. Diluted serum samples were analysed for lithium using the 14-crown-4 - TOPO electrode in an FIA system. A statistical analysis of the ISE and corresponding AAS results indicated that these two methods have no statistical difference at the 95% confidence level. Because of the improved selectivity of the electrode and the elimination of the dialysis membrane from our original FIA design, the precision and accuracy of this determination were both improved, and the measurement time decreased.

Keywords: *Lithium ion-selective electrodes; TOPO; lithium to sodium selectivity; serum lithium determination; flow injection analysis*

In the early 1970s, trioctylphosphine oxide (TOPO) and a β-diketone, dibenzoylmethane, in *p*-xylene were suggested as an extraction system for the separation of lithium ions from other alkali metal ions.[1] In 1983, TOPO was incorporated in a PVC membrane with the β-diketone in this laboratory to produce a lithium ion-selective electrode (ISE); however, the performance of this electrode was unsatisfactory. In 1985, Kitazawa *et al.*[2] added 1–2% of TOPO to their 14-crown-4 lithium ion-selective membrane and the lithium to sodium selectivity of this membrane electrode was dramatically improved. In searching for a better lithium ion-selective electrode for the determination of serum lithium, we studied a series of existing lithium ion-selective membranes and the effect of TOPO in these. We found that TOPO, a commercially available and inexpensive compound, when used only with a small percentage of potassium tetrakis(*p*-chlorophenyl) borate (KTpClPB) in a PVC membrane, exhibited a good lithium to sodium selectivity (Table 1). However, comparison showed that the best lithium ion-selective electrode investigated was the 14-crown-4 - TOPO electrode.

Although the determination of serum lithium had been successfully performed in a FIA - dialysis system,[3] a better lithium selectivity was still required. The elimination of the dialysis membrane was preferred because the membrane reduced the over-all lithium to sodium selectivity.[3] A flow design was therefore constructed in which the direct injection of diluted serum samples was performed. The results of this determination were in agreement with atomic absorption spectrometry (AAS) results. The advantages and disadvantages of the direct sample injection and dialysis systems are discussed in this paper.

Experimental

Chemicals

N,N-Dicyclohexyl-*N',N'*-diisobutyl-*cis*-1,2-cyclohexane-1,2-dicarboxyldiamide (ETH 1810) was obtained from the Department of Organic Chemistry, Swiss Federal Institute of Technology (ETH). *N,N'*-Diethyl-5,5-dimethyl-*N,N'*-bis(3-oxapentyl)3,7-dioxanonanediamine (UWXC 10) and 3-dodecyl-3-methyl-1,5,8,12-tetraoxacyclotetradecane (14-crown-4) were synthesised in our laboratory. The procedures of these syntheses are reported elsewhere.[4,5] TOPO was obtained from Aldrich Chemical and all the other chemicals are the same as those reported in our earlier papers.[3,6]

Apparatus

Fig. 1 illustrates the flow design of the FIA - ISE system. As many as four electrodes of the same or different composition may be mounted in the carrier stream for simultaneous investigations. The 3 M KCl stream forms a flow salt bridge between the sample carrier stream and the reference electrode (channel B–A in Fig. 1). This design reduces the junction potential at point A by 3 mV compared with the 140 mM NaCl

Table 1. Performance of the TOPO lithium ion-selective electrode

	Electrode			
	1	2	3	4
	TOPO, 1%; KTpClPB, 1%	TOPO, 3%; KTpClPB, 1%	TOPO, 6%; KTpClPB, 1%	TOPO, 10%; KTpClPB, 1%
Selectivity*				
$K^{pot}_{Li,Na}$	0.017	0.023	0.027	0.029
$K^{pot}_{Li,K}$	0.0017	0.0015	0.0015	0.0016
$K^{pot}_{Li,Mg}$	0.013	0.038	0.23	0.20
$K^{pot}_{Li,Ca}$	0.15	0.71	1.4	1.0
Slope/mV decade^{-1}	46.4	45.5	53.4	54.4
Correlation coefficient	0.999	0.995	0.997	0.996

* Selectivity coefficients were calculated by matched potential method.[9]

liquid junction when diluted serum samples are injected into the system. It also avoids problems such as contamination and liquid junction blocking, which are commonly associated with some conventional salt bridge designs.[7] An attempt at passing 3 M KCl through the reference electrode (channel B–C in Fig. 1) failed as the reference Ag - AgCl electrode was unstable in such a high chloride ion concentration. The flow-rates of the streams were adjusted to the values shown in Fig. 1 in order to obtain a fast response and a stable base line. The flow meters were purchased from Cole Parmer. The other apparatus was the same as reported in our earlier papers,[3,6] in which the construction of the electrodes and microconduits are also described.

The membrane compositions of the electrodes were 33 mg of PVC and 65 mg of *o*-nitrophenyl octyl ether (NPOE), with different mass percentages of neutral carriers and additives as indicated in Tables 1 and 2. (The mass percentages in the tables are equivalent to milligrams of each component added to the above masses of PVC and NPOE.)

Standards and Samples

Lithium-free serum and serum from manic-depressive patients on lithium treatment were obtained from the University of Washington Hospital. Equal volumes of five normal blood sera were mixed (*i.e.*, pooled serum samples) and diluted 10-fold with 2.5 mM $Na_2B_4O_7$ buffer solution as blanks. Serum lithium standards were prepared by 10-fold dilution of the pooled normal serum with a series of LiCl standards in 2.5 mM $Na_2B_4O_7$ solution. The serum samples from manic-depressive patients were also diluted 10-fold with 2.5 mM $Na_2B_4O_7$ before analysis. The buffered standards and diluted sample solutions had a pH of 9.2.

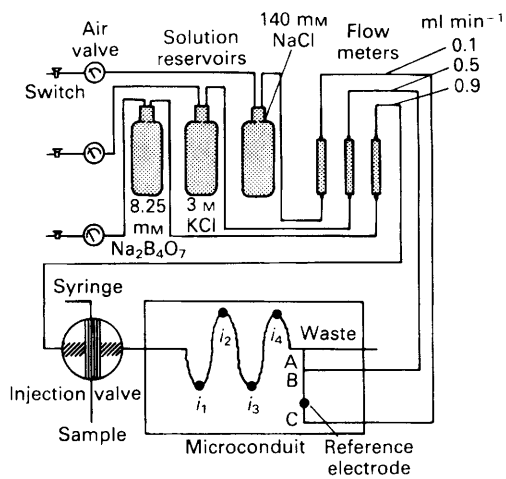

Fig. 1. Design of flow injection analysis ISE system

Selectivity Coefficients

Fixed interference[8] and matched potential[9] methods were used to measure the selectivity coefficients, $k^{pot}_{Li,M}$. A discussion of this subject has been given in our earlier papers.[3,6]

Results and Discussion

TOPO as a Neutral Lithium Carrier

TOPO with dibenzoylmethane has been successfully used for the extraction of lithium from other alkali metal ions and the lithium complex formed is probably $PhCOCH_2COPh–Li^+–(TOPO)_2$.[1] Because liquid membrane ion-selective electrodes are based on the same complexation - extraction phenomenon, our first step was to make lithium ISEs with 2% TOPO

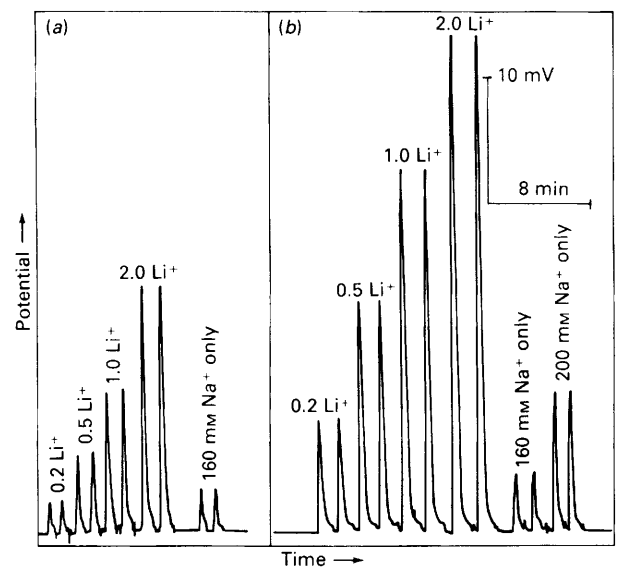

Fig. 2. Response of the 14-crown-4 electrodes with (*b*) and without (*a*) 1% TOPO. Li^+ in 140 mM Na^+, concentration in mM

Table 2. Evaluation of 14-crown-4 and ETH 1810 lithium ISEs. M.P. = matched potential method; F.I. = fixed interference method

	Electrode*				
	1	2	3	4	5
	A, 1%; B, 1%; crown, 3%	A, 3%; B, 0%; crown, 3%	A, 0%; B, 0.5%; crown, 1.5%	A, 0%; B, 0.4%; ETH, 1.4%	A, 1%; B, 1%; ETH, 2%
Selectivity					
$K^{pot}_{Li,Na}$ (M.P.)	0.0042	0.0088	0.012	0.014	0.019
(F.I.)	0.0025	0.0086	0.0080	0.0071	0.011
$K^{pot}_{Li,K}$ (M.P.)	0.0062	0.0013	0.013†	0.0025‡	0.0034
$K^{pot}_{Li,Mg}$ (M.P.)	0.0010	0.0054	0.000016†	0.00010‡	0.0027
$K^{pot}_{Li,Ca}$ (M.P.)	0.0015	0.073	0.000077†	0.0020‡	0.026
Slope/mV dec^{-1}	59.0	59.9	58.9	59.9	45.3
Correlation coefficient	1.000	0.999	0.999	0.999	0.996
Linear range§/ mM	2–200	2–200	5–200	5–200	5–200

* A, TOPO; B, KTpClPB.
† Data from reference 2.
‡ Data from reference 12.
§ In the presence of 140 mM Na^+.

and 1% dibenzoylmethane in PVC membranes. Although different plasticisers were used to prepare the electrodes, none of the electrodes responded to lithium ions. However, when TOPO was used with 1% of KTpClPB in NPOE - PVC membranes, the electrodes exhibited a nearly Nernstian response (Table 1) and the lithium to sodium selectivity of the electrode was better than for some of the electrode sensors reported earlier.[10] These results imply that the function of a complex extraction system in an organic solvent cannot be assumed to be completely applicable to electrode membranes, and that the selectivity for metal ion extraction in electrode liquid membranes is a combined effect of all the membrane materials. However, TOPO, like other neutral carriers, plays a key role in the electrode.

Table 1 shows that the best combination in the electrode is 1% of TOPO and 1% of KTpClPB. The lithium selectivity decreases with an increasing percentage of TOPO in the membrane, and calcium and magnesium interferences also increase with increasing TOPO percentage. Potassium selectivity remains about the same. It should be noted that the $k^{pot}_{Li,M}$ values in the tables have uncertainties of approximately 10%. However, these values do indicate trends in the performance of the electrode.

Effect of TOPO in Existing Lithium ISEs

Among the many reported lithium ISEs,[5,10–13] 14-crown-4, ETH 1810 and UWXC 10 are the best three lithium ion-selective electrodes. We constructed 14-crown-4 electrodes with and without TOPO in order to compare the selectivities of the two electrodes in 140 mM NaCl. The results are shown in Fig. 2. The lithium response of the electrode with TOPO was three times more sensitive than that of the electrode without TOPO, whereas the sodium response was nearly the same. Therefore, the lithium to sodium selectivity of the electrode was also tripled ($k^{pot}_{Li,Na}$ = 0.0025). Our selectivity value compares favourably with the results of Kitazawa *et al.*,[2] who prepared the electrodes in a conventional manner (membrane-body type) and performed batch-wise selectivity measurements. It is important to point out that the reported sensitivity loss (higher detection limit) of this electrode in pure lithium solution[2] has no realistic meaning in most electrode applications, as real samples, *e.g.*, serum samples, generally contain a high background of interfering sodium ions. Here, the higher lithium selectivity results in a better detection of lithium in the presence of sodium. Thus, the restriction of sensitivity loss[14] is not applicable when the electrode is designed for application purposes.

A higher percentage of TOPO was then added to the electrode membranes. The selectivity change (Table 2) followed the same trend observed in Table 1. This change also agreed with the previous report.[2] TOPO was also added to the ETH 1810 electrode membranes for comparison purposes. The selectivity and sensitivity of the resulting electrode were somewhat inferior to those of the ETH 1810 electrode without TOPO (Table 2). TOPO added to the UWXC 10 electrode suppressed the lithium response of the electrode and the lithium to sodium selectivity of the electrode was reduced to 40; this is approximately one-third of the original selectivity of the UWXC 10 electrode.[11]

TOPO electrode and TOPO additive studies support the suggestion that the selectivity of liquid membrane electrodes is not governed solely by the neutral carrier itself; the chemical nature of additives and liquid phases also greatly affects the selectivity of the electrodes. At present the best lithium ion-selective electrode for determinations in the presence of sodium is the 4-crown-4 - TOPO electrode. Therefore, we used this electrode for serum lithium determinations.

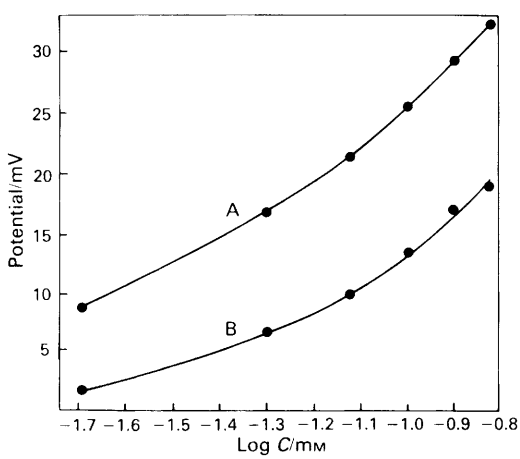

Fig. 3. Calibration graphs of (A) aqueous standards and (B) serum standards using electrode 1 of Table 2

Serum Lithium Determination

The direct injection of diluted serum samples (200 µl) was carried out in the FIA system shown in Fig. 1. Using this system, no significant base-line drift or change in response time was observed and the system was also free from blockages. Calibration graphs for standards in both aqueous solutions and serum solutions are shown in Fig. 3. Because of the matrix effects in serum samples, a significant blank response shifted the background potential in the samples and the lithium responses were slightly suppressed, therefore aqueous standards cannot be used. Even so, in the usual therapeutic lithium concentration range (0.5–1.5 mM), the observed voltage interval of diluted serum standards was 12.4 mV, a sensitivity improvement of about 2.5 times over our previous system.[3] This concentration range is in the non-linear

Table 3. Results of serum lithium determination by AAS and ISE (electrode 1 of Table 2)

Sample No.	AAS Li^+ concentration/mM	ISE Li^+ concentration/mM	Absolute error/mM	Relative error, %	ISE Na^+ concentration/mM
1	0.82	0.88	+0.06	+7	150
2	0.4	0.41	0.0	0	150
3	1.17	1.24	+0.07	+6	151
4	1.00	0.98	−0.02	−2	149
5	0.61	0.57	−0.04	−6	149
6	0.88	0.96	+0.08	+9	145
7	0.76	0.69	−0.07	−9	149
8	0.68	0.60	−0.08	−12	149
9	0.73	0.62	−0.11	−15	149
10	0.75	0.70	−0.05	−7	150
Blank	0.00	0.00	0.00	0	145
Average			−0.016	−2.9	

region of the calibration graph, owing to high background sodium. Linearity is achieved down to 2 mM serum lithium in either diluted or undiluted serum, Table 2. Precise measurements are nevertheless obtained with the system and the lithium selectivity relative to sodium is greater than with any other electrode. Hence, the lithium response in serum is at a maximum.

Ten hospital serum lithium samples were analysed by this electrode and the results are listed in Table 3. Table 3 also lists the AAS results, absolute errors, relative errors and the Na^+ content of samples. A statistical analysis of the ISE results and the AAS results indicated that at the 95% confidence level, these two methods have no statistical difference ($t = 0.76$).[15] When ISE values were plotted against AAS values, a good linearity, with a correlation coefficient of 0.970, was obtained. As the sodium contents were nearly constant in the sample and the electrode had a high lithium to sodium selectivity, sodium corrections were not needed.

Five normal individual sera blanks (diluted) were injected into the system. The standard deviation of the potential values of these separate blanks was ±0.97 mV. If we assume that the average sodium concentration, C_{Na}, in the serum samples is 140 mM and the lithium concentration, C_{Li}, is 1.0 mM, then according to the equation

$$dE = \frac{S}{C_{Li} + k^{pot}_{Li,Na} C_{Na}} dC_{Li}$$

this potential uncertainty corresponds to a ±0.05 mM lithium concentration fluctuation (S is the slope of the electrode response, which is 59 mV decade^{-1}). Thus, an average ±5% relative error could be observed in this determination (at the 1.0 mM level), owing to uncertainties in the background reading of the prepared serum standards. This essentially agrees with our observations (Table 3).

The precision for six measurements of an individual serum sample at 0.5 mM lithium is ±0.17 mV or ±0.0049 mM lithium. Therefore, the uncertainties in the serum lithium determination are mainly from the sample matrix uncertainties rather than the instrumentation.

Previously we determined serum lithium in a FIA - dialysis system.[3] The advantages of this system are that it is free from serum protein interferences and free from the risk of electrode poisoning. Also, it is possible to use aqueous standards and little sample preparation is needed. The disadvantages are the reduced lithium to sodium selectivity and the slow sampling rate due to the dialysis process. The elimination of the dialysis membrane in this study increased the over-all lithium to sodium selectivity by five-fold and tripled the sampling speed. As a better electrode was employed, the precision and accuracy were also improved.

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