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Analytical strategies for the measurement of lithium in biological samples[1]

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Abstract

Therapeutic lithium levels in the treatment of manic depressive psychosis must be maintained in the range of 0.5–1.5 mM in the blood, which also contains 140 mM sodium. This paper reviews spectrophotometric, fluorometric, and ion-selective electrode (ISE) reagents and methods for achieving high lithium selectivity over sodium and their use in blood lithium measurement. These include aromatic organic reagents, crown ethers and amide ionophores. Crown ethers and cryptands provide the best lithium selectivity. A chromophoric small-cavity cryptand phenol exhibits greater than 4000:1 selectivity due to rigid configuration of a well preorganized binding site for lithium complexation. It is water soluble, making it easy to apply for blood analysis. Crown ethers with bulky groups inhibit formation of the 2:1 crown:sodium complex, while allowing formation of the 1:1 lithium complex. A PTM 14-crown-4 having a bulky pinane and subunits at the ethano bridge exhibits at least 10 000:1 selectivity for lithium in a flow-through optical sensor probe. Bulky crown ethers used in PVC membrane ion-selective electrodes exhibit lithium selectivities of 1–2000:1. Methods of evaluating selectivities are discussed, along with the correlation of solvent extraction of crown ether complexes and solvent membrane ISE selectivities.

Keywords: Analytical strategies; Biological samples; Lithium

1. Introduction

Gade reported in 1949 on the treatment of manic depressive psychosis with lithium salts [1]. The efficacy of such lithium treatment was subsequently firmly established [2]. Blood normally contains only parts per billion levels of lithium [3,4]. Lithium is normally administered in the form of lithium carbonate or other salts. The concentration of lithium in the blood must be maintained over a narrow range of about 0.5–1.5 mM [5], near the toxic level. Below 0.5 mM, the therapy may not be effective, and if the concentration exceeds 1.5 mM, toxicity is manifested [6]. A level of 5 mM can be lethal [7]. Hence, the measurement and accurate monitoring of lithium levels is important. A suitable technique should be capable of measuring therapeutic serum lithium levels in the range 0.2–2 mM, in the presence of about 140 mM sodium in the blood.

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Traditionally, lithium is readily measured by flame emission or flame atomic absorption spectrometry [8,9], and results are reliable. However, because of the high instrumentation and operation cost, the bulkiness of the instrumentation and the desire to avoid compressed gases and flames in the clinical laboratory, alternative measurement procedures have been investigated over the years. A major effort has been made to identify or create reagents that possess high selectivity for lithium relative to sodium. Few are sufficiently selective to ignore the presence of sodium. This report identifies several of the techniques and reagents used for the measurement of lithium, with examples from this laboratory and others.

2. Techniques and reagents used for measurement of lithium

2.1. Spectrometric methods

Aromatic organic reagents with $AsO(OH)_2$ or $PO(OH)_2$ ortho to an azo group have been reported as spectrophotometric agents for lithium due to the bathochromic shift of the reagent spectrum caused by the weak complex formation with lithium [10]. Thoron is a colorimetric reagent that forms a complex (Fig. 1) with lithium in alkaline acetone/water solutions, and a bathochromic shift in the thoron spectrum results. Trautman et al. [11] used this reagent to determine lithium in blood serum, by measuring the change in absorbance at 480 nm against the reagent as reference. Proteins are removed with trichloroacetic acid, and the effect of serum electrolyte is compensated for by adding a synthetic serum electrolyte to the reagent blank. Results of analysis of serum samples from manic depressive patients by this method agreed with atomic absorption spectroscopy results with an average error of −1.1% for 40 samples, with a correlation coefficient of 0.987.

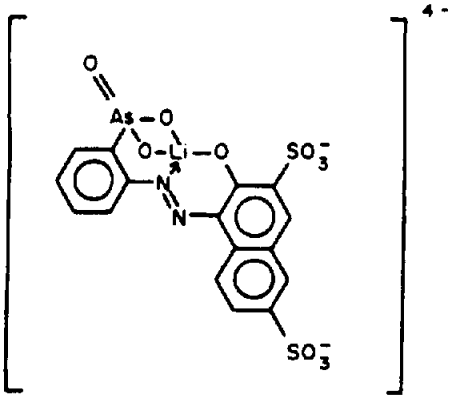

Fig. 1. Li–thoron complex (from Ref. [11])

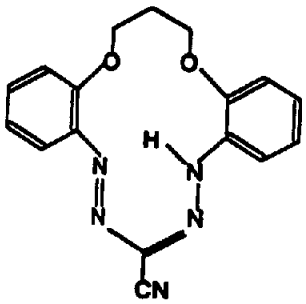

Fig. 2. TMC-crown formazane.

Crown ethers are effective complexing agents for alkali and alkaline earth metal ions. They can be designed with different cage sizes, conformational flexibility, and various side groups to influence the size of metal ion accomodated and the nature of the complex formed. 14-Crown-4 compounds are the most effective for lithium ion. Crown ether complexes may be extracted as ion pairs into organic solvents along with an appropriate anionic reagent. If the anionic reagent is colored, this can form the basis of spectrophotometric measurement. Wu and Pacey [12] developed a dinitro-chromogenic benzocrown ether which was found to be more sensitive and selective than the benzo-parent crown with a picrate ion-pairing agent. Sodium at the 130 mM level did not interfere with 40 mM lithium. This reagent was used to accurately determine lithium ion in deproteinated blood serum samples, in both batch and flow-injection methods, at the relatively high levels of 3.6–36 mM, using solvent extraction at pH 13 (with rubidium hydroxide) into 1,2-dichloroethane.

Sitnikova et al. [13] reported TMC-crown formazane, a dibenzo compound with a 14-mem-

bered ring containing two oxygens and four nitrogens (Fig. 2) as a spectrophotometric reagent for lithium. Sodium as high as 5000 times the lithium content (w/w) purportedly did not interfere with the measurement (this corresponds to about 1500:1 on a molar basis). Attiyat et al. [14] modified the synthesis of the compound and investigated it further as a potential reagent for measuring low millimolar levels of lithium in the presence of 140 mM sodium. Sodium depresses the lithium signal and influences the background absorbance, and so calibration must be done in the presence of sodium. In a background solution containing 140 mM sodium, a 10 mM increment of sodium is equivalent to 0.007 mM lithium, an apparent selectivity of 1:1400. Hence, by careful calibration, it should be possible to apply this reagent for serum lithium measurement. Solvent conditions are 85% acetone/15% water containing 50 mM sodium hydroxide, similar to the conditions for the thoron reagent.

A challenge with crown ether reagents for the selective measurement of lithium is to inhibit the formation of the sodium complex. This is best accomplished by adding bulky groups to the base crown ring to inhibit the formation of the 2:1 sandwich type crown:sodium complex that is typical with large cations that do not fit the cavity of the 14-crown-4. Lithium generally forms a 1:1 complex. Suzuki and co-workers [15] developed a flow-through optical sensor probe based on PTM 14-crown-4 having a bulky pinane and subunits at the ethano bridge of the crown (Fig. 3). The crown and a lipophilic anionic dye in the protonated form are dissolved in an organic liquid such as bis(2-ethyl hexyl)sebacate, which is then adsorbed on a pellicular-type ODS bead to prepare the optical sensor. This gives an ion-pair extraction system for the lithium ion. The color of the

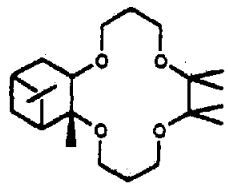

Fig. 3. PTM 14-crown-4 ether (from Ref. [15]).

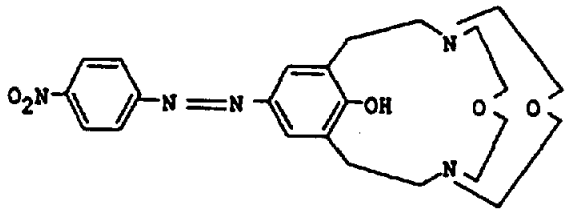

Fig. 4. Chromophoric cryptand phenol (from Ref. [16]).

dye ion pair, with a displaced proton, differs from that of the protonated dye form, turning from pale yellow to red. This sensor exhibits remarkable selectivity for lithium ion, having absolutely no response to other alkali metal and alkaline earth cations up to 0.1 M, so the selectivity coefficients of the sensor are at least less than 1:10 000 since the lithium detection limit is 1×10^{-5} M. Hence, the sensor should be capable of measuring lithium in serum without interference from sodium. A calibration curve prepared with 1:10 diluted artificial serum in Tris buffer was identical to one prepared from aqueous lithium solution in the same buffer. About 15 min was required for a measurement, but proper design of the flow-through cell should improve response times.

Chapoteau et al. [16] reported a chromophoric small-cavity cryptand phenol (Fig. 4) which could be applied for the determination of lithium in blood serum without sample pretreatment or solvent extraction steps. The chromogenic ionophore exhibits very high selectivity ($>4000:1$) for lithium over sodium, due to rigid configuration of a well-preorganized binding site for lithim complexation. The lithium reagent contains 0.2 mM chromoionphore, surfactant (to decrease interaction of the chromoionophore with serum proteins), and antioxidant (to increase reagent stability) in 100 ml l^{-1} diethylene glycol monoethyl ether in water, containing 1 M tetrahylammonium hydroxide, since the chromoionophore must be ionized (pH > 12) to complex lithium. Serum was diluted 1:40 with the reagent, and measurements made at 500 nm. Results for serum spiked with lithium agreed well with flame photometry measurements.

2.2. Fluorometric methods

Ceba et al. [17] used the reagent 1,8-dihydroxyanthraquinone for the fluorometric measurement of 50–450 ppb lithium in predominately alkaline acetonic medium. Wheeling and Christian [18] successfully applied this reagent for the fluorometric determination of serum lithium. Serum samples are deproteinized with an equal volume of acetone and 20 μl of the filtrate is added to 1 ml of 2.5×10^{-4} M KOH and 1.0×10^{-4} M reagent in 90% (v/v) acetone. Single-point calibration was performed with spiked serum, using unspiked serum as the blank. The lithium response in the serum matrix was 44% of that in water, and was 480 times that of sodium. Fluorometry results for 30 lithium-containing samples from manic depressive patients agreed with atomic absorption results, with an average relative difference of 0.2%, and a relative standard deviation of 0.3%. The sample preparation and calibration procedure utilized here should be suitable for the spectrophotometric thoron and TMC-crown formazane reagents above, which have similar solution conditions.

2.3. Ion-selective electrodes

A great deal of effort has been directed at developing lithium ion-selective electrodes that exhibit high selectivity with respect to sodium ions. For an earlier review of lithium ion-selective electrodes, see Gadzekpo et al. [19]. Okorodudu et al. [20] have compared the performance of three commercially available lithium electrodes, marketed by ADMEN, NOVA and AVL, for serum analysis, noting systematic errors and random interferences. The compositions of these commercial electrodes are generally proprietary.

Ion-selective electrode solvent membranes are commonly prepared by dissolving a lipophilic ionophore, an appropriate plasticizer, and poly(vinyl)chloride (PVC) matrix in a solvent such as tetrahydrofuran, pouring on a glass plate or placing on a contact wire and allowing the solvent to evaporate. A convenient way of performing rapid and precise potentiometric measurements using microliter volumes of samples is by the use of flow-injection analysis [21].

2.4. Matrix/solution composition and selectivity coefficients

The selectivity of an ion-selective electrode is usually expressed by the selectivity coefficient, K_{ij}^{pot}, which represents the relative response of the secondary ion, j, compared with that of the primary ion, i. The apparent selectivity and the response for solvent membrane electrodes depends on factors such as the matrix and solution composition, the charges on the ions, and the method of evaluating the selectivity coefficient [22]. For example, the relative concentration of the interfering ion may markedly influence the numerical value of the selectivity coefficient [23]. The plasticizer often has a dramatic effect. Zhou et al. [24] found that the plasticizer o-nitrophenyl octyl ether (o-NPOE) enhances the selectivity for lithium with respect to sodium only with a specific sidechain on different lipophilic diamide iono-phores, irrespective of the backbone. Attiyat et al. [25] compared the plasticizers o-NPOE and o-nitrophenyl pentyl ether (NPP'E) in various crown-ether-based electrodes from 14-C-4 to 21-C-7. The latter solvent enhanced the slope and linearity of the calibration curve in all cases, and generally enhanced the selectivity toward the primary ion.

The conventional methods for measuring selectivity coefficients are the separate solution method [26] and the fixed interference or mixed solution method [27]. The latter is generally more representative of analytical measurement conditions, but numerical values may still vary with solution conditions. Gadzekpo and Christian [22] developed an empirical 'matched potential' method that provides a numerical value applicable under experimental conditions and which is not dependent on the ionic charges nor on an ideal nernstian response. Bakker et al. [28] developed a quantitative model for this system based on ionic equilibrium at the membrane/sample interface which is applicable to ions of different charge, and Umezawa et al. [29] have proposed the matched potential method as an official IUPAC method. Sáez de Viteri and Diamond [30] proposed an empirical method for arrays of electrodes, using mixed standard solutions.

2.5. Solvent extraction and solvent membrane electrodes

The potentiometric selectivity and response with solvent membranes often depend on the specific membrane composition, for example the plasticizer. Crown ethers are used in the solvent extraction of alkali and alkaline earth metal ions, as well as others, and are used as ionophores in PVC membrane electrodes for measuring these ions. The ability to complex the metal ions, the efficiency and selectivity of solvent extraction, and the potentiometric response and selectivity depend on a number of factors, such as the polyether cavity size [31,32], the metal ion size [31], the stability constant [33], the stoichiometry of the complex [19], the lipophilicity, position and nature (ionizable or not) of the sidearm [34,35], the composition of the extracting or membrane matrix [19,32,36], and the number and positioning of the crown ether oxygens and the conformational flexibility of the crown ether ring [37–39]. The presence of coordination sites in the sidearm may produce marked changes in the selectivity and extent of metal complexation [40,41].

It has been demonstrated that a correlation exists between liquid membrane electrode selectivities and ion association solvent extraction parameters [42–44]. Such a correlation for other solvent membrane electrodes has been only rarely noted [45].

This laboratory, in collaboration with the laboratory of Bartsch at Texas Tech University, has investigated a number of crown-ether-based ion-selective electrodes in PVC membranes, and compared selectivity coefficient data with solvent extraction selectivity for the metal–crown ether picrates. A study of benzo-18-crown-6 and its lariat ether derivatives showed that the nature of the sidearm in the lariat ether derivatives influenced the selectivities toward different ions in different ways [46]. Addition of oxygen-containing sidearms diminishes the selectivity toward potassium ion, presumably due to enhanced coordination to other alkali and alkaline earth metal ions. However, a sidearm containing two or more ether oxygens markedly enhances the response toward strontium ion. All of the ionophores exhibited good selectivity for lead ion with respect to the alkaline earths, irrespective of the sidearm.

Crown ether compounds for lithium ion that contain either acidic or neutral sidearms exhibit small hydrogen ion response [35]. Addition of the solvent trioctylphosphine oxide (TOPO) often enhances both the sensitivity for lithium ion and the selectivity over sodium ion. Comparison of selectivity coefficient data with solvent extraction data demonstrates that solvent extraction selectivity data can aid in the design and performance prediction of electrode ionophores. Crown ethers with neutral sidearms exhibit good selectivity for lithium over other ions, while those with acidic sidearms exhibit good potassium selectivity [47]. There was no correlation between potentiometric and solvent extraction selectivities for 12-crown-4 compounds, but for the larger and more appropriate 13-crown-4 and dibenzo 14-crown-4 compounds there was perfect correlation.

The bis(*tert*-butylbenzo)-21-crown-7 ionophore exhibits high selectivity for cesium ion, and there is good agreement between potentiometric response and solvent extraction, especially when the solvent TOPO is present in the electrode membrane, which acts as an extractant [48].

Only weak lithium and sodium cation binding and low selectivity was observed in both picrate solvent extraction and polymeric membrane electrode systems for a series of benzo-13-crown-4 compounds [49]. However, for a 14-crown-4 series, there was less close correlation, as opposed to the dibenzo-14-crown-4 compounds, with relatively smaller extraction selectivity for lithium as opposed to electrode selectivity.

2.6. Amide lithium ionophores

The early lithium ionophores for ion-selective electrodes were neutral lipophilic diamide compounds, as first reported by Guggi et al. [50]. Zhukov et al. [51] reported a selectivity coefficient of 0.010 for sodium relative to lithium for a diamide carrier, and Gadzekpo et al. [52] found a selectivity coefficient of 0.063 for a compound reported by Shanzer et al. [53] to be an efficient carrier for lithium. Metzger et al. [54] reported a high selectivity of 1/280 for the diamide iono-

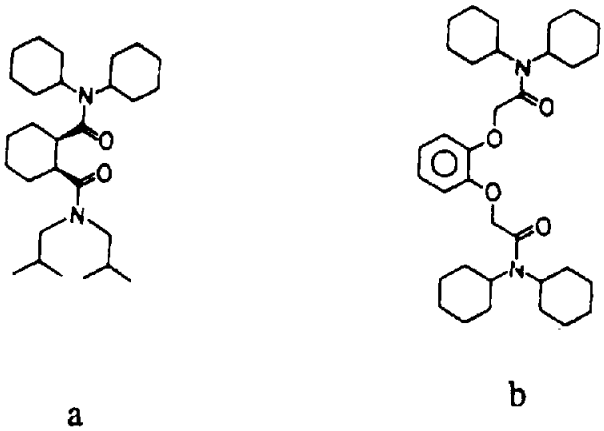

Fig. 5. Lipophilic diamides (from Ref. [55]).

phore shown in Fig. 5a, and used this electrode to measure lithium in undiluted serum, although an ionophore (Fig. 5b) used with BBPA plasticizer with a lower selectivity (1/80) exhibited better response time and reproducibility and was preferred for serum measurements [55]. Pooled serum spiked with lithium was used for calibration.

Gadzekpo et al. [56] prepared a series of diamide-based ionophores, with pyridine, furan, and dioxanone backbones. The best lithium selectivity found was with a furan compound containing *N*-methylhexyl sidechains, with a selectivity coefficient of 1/120 using the matched potential method. Attiyat and co-workers synthesized a series of cyclic dioxadiamides [57,58] and acyclic monoxadiamides [59]. One cyclic dioxadiamide (Fig. 6) exhibited a selectivity coefficient of 9.5×10^{-3} [55].

2.7. Crown ether ionophores

Gadzekpo and Christian [60] incorporated 12-crown-4 ionophore into a PVC membrane elec-

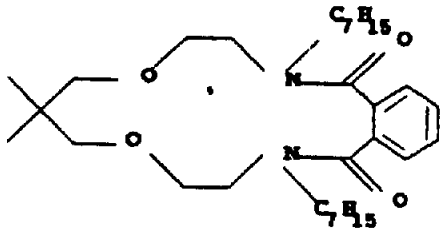

Fig. 6. Cyclic dioxadiamide (from Ref. [57]).

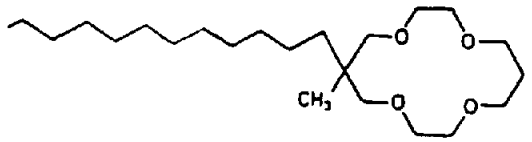

Fig. 7. Dodecylmethyl-14-crown-4 (from Ref. [61]).

trode and reported a selectivity coefficient of 0.12. 14-Crown-4 cavities are more ideally suited for lithium complexation [61]. Dodecylmethyl-14-crown-4 (Fig. 7) was used by Kitazawa et al. [62] in a PVC membrane with added TOPO to measure lithium in artificial serum samples. The preference for lithium to sodium was a factor of 150. Gadzekpo et al. [56] compared this compound with the diamide in Fig. 5a using the fixed interference and matched potential methods and found comparable lithium selectivities. Xie and Christian [63] utilized this crown ether ionophore for a coated-wire lithium electrode to measure lithium in undiluted serum by flow-injection analysis. A dialysis membrane was used to avoid protein effects. The sample was injected into a water donor stream, with a 7 mM $Na_2B_4O_7$ (pH 9.2) acceptor stream. Results for manic depressive patient samples showed an average error of -3.1% compared with atomic absorption results when using pooled serum standards and -6.6% when using aqueous standards. When 1% TOPO is added to the electrode membrane and samples are diluted 10-fold with 2.5 mM $Na_2B_4O_7$ solution for injection, the dialysis membrane is not needeed [32]. Accuracy was -2.9% when using pooled serum standards. The selectivity coefficient was 0.0025 using the fixed interference method and 0.0042 by the matched potential method. Even without the crown ionophore, a selectivity coefficient of 0.017 was obtained when adding TOPO to the membrane.

2.8. Formazane crown ionophores

As mentioned above, the TMC-crown formazane shown in Fig. 2 was reported to be a selective spectrophotometric reagent for lithium [13,14]. Attiyat et al. [64] investigated this compound as a potential lithium ion-selective electrode ionophore. Different PVC membrane

compositions of various plasticizers with and without TOPO were investigated, and most exhibited somewhat greater response to sodium than to lithium. A general trend was observed that the selectivity toward an ion decreased with a decrease of the ion size, for both alkali and alkaline earth metal ions. Membranes containing NPOE plasticizer and 200 mole% potassium tetra(*p*-chlorophenyl)borate exhibited near-nernstian response for cesium with a five fold or better selectivity for cesium over rubidium, 20-fold over potassium, more than 300-fold over sodium, strontium, calcium and hydrogen, and more than 1000-fold over lithium and magnesium.

Attiyat et al. [65] subsequently synthesized a series of acyclic formazanes in which the ether bridge in Fig. 2 was opened up and different R groups attached to the oxygens. The ionophore, 1,5-bis-(*o*-butoxyphenyl)-3-cyanoformazane (R = C_4H_4), exhibited a sodium–lithium selectivity of 6.2×10^{-3} by the matched potential method in the presence of 1% TOPO using NPPE plasticizer.

2.9. Bulky crown ether ionophores

Kimura, Shono and co-workers [66] synthesized lipophilic 14-crown-4 derivatives bearing bulky substituents or an additional binding site in the sidearm, with the goal of enhanced lithium selectivity, which was expected due to suppression of the formation of the 2:1 sandwich-type complexes with Na^+ and K^+, and from an additional binding site possessing affinity for Li^+. The dibenzyl crown shown in Fig. 8 exhibited substantially improved lithium selectivity as compared with the 6-dodecyl-6-methyl derivative (Fig. 7), with a selectivity coefficient of 1/800 by the fixed interference method in a membrane containing NPOE plasticizer and 1% TOPO. An excellent K^{pot}_{LiNa}

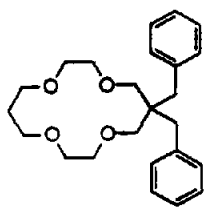

Fig. 8. Dibenzo-14-crown-4 (from Ref. [64]).

value of 1.3×10^{-3} was attained with the PVC membrane containing *o*-nitrophenyl phenyl ether/tris(2-ethylhexyl)phosphate as the solvent. Serum lithium assay was successfully achieved by utilizing a dialysis membrane, which eliminated interference by proteins in the samples [67]. Response time was about 10 min.

Kataky et al. [68] described a di-*n*-butylamide 14-crown-4 derivative using NPOE plasticizer that exhibited a lithium:sodium selectivity of 800:1 and performed well in blood serum diluted with an electrolyte buffer solution. A diisobutylamide derivative with a selectivtiy of 1800:1 behaved poorly in serum.

Wen et al. synthesized and characterized a series of 14-crown-4 ionophores containing bulky groups, and compared them with the 6,6-dibenzo compound in Fig. 8 (unpublished data). Compounds A, C, and D in Fig. 9 all exhibited improved lithium selectivity using NPOE plasticizer. Fig. 10 illustrates that with 1% TOPO added, compound D exhibits enhanced lithium response compared to the dibenzo compound (# 14). A selectivity coefficient of 1.4×10^{-3} by the fixed interference method (1.5×10^{-3} for the matched potential method) compared with 3.0×10^{-3} for the compound in Fig. 8 under the measurement conditions of this group.

Sugihara et al. [69] investigated 1,10-phenanthroline derivatives as lithium ionophores. The 2,9-dibutyl derivative exhibited a Li:Na selectivity of 1600:1 in aqueous solution. It responds to proton ions (H^+:Li = 250:1), and so measurements must be made above pH 4.

Suzuki et al. [70] designed highly selective ionophores for lithium based on 14-crown-4 derivatives, by introducing a bulky 'block' subunit into the ethano-bridge section of the base crown ring, which effectively prevents formation of the 2:1 or 3:1 sandwich-type complex between the crown and ions larger than Li^+. The best lithium selectivity was obtained with a compound containing a bulky decalin subunit (Fig. 11). Log $K^{pot}_{Li,Na}$ values of -3.0 and -3.1 were obtained by the separate solution and fixed interference methods respectively, using bis(1-butylphenyl)-adipate) (BBPA) plasticizer. The addition of either TOPO or tris(2-ethyl hexyl)phosphate

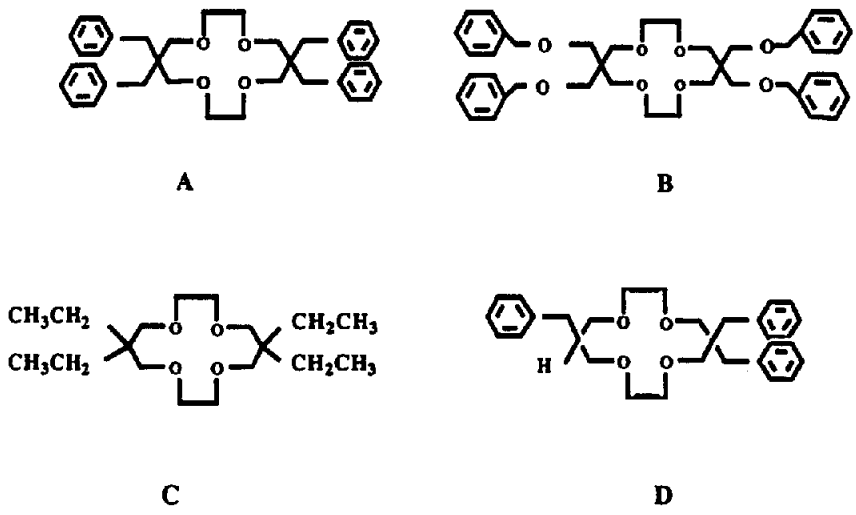

Fig. 9. Bulky 14-crown-4 ethers (from X. Wen, G.D. Christian, B.P. Czech and R.A. Bartsch, unpublished data).

(TEHP) did not enhance the lithium selectivity as reported for other ionophores. The electrodes with this ionophore was successfully applied to lithium measurement in artificial serum electrolyte solutions containing 150 mM sodium, with a measurement error of 3.4% when the background sodium concentration varied with the range 100–150 mM.

Even better lithium selectivity over sodium (2000:1) was reported for the decalino compound shown in Fig. 12 [71], again using the low polarity solvent BBPA as plasticizer (compared with about 800:1 using NPOE plasticizer). The 2000:1 selectivity for this compound compares with the literature value of about 800:1 for the dibenzo compound in Fig. 8. Given that compound D in Fig. 9 exhibited at least double the selectivity of the dibenzo compound under similar membrane and measurement conditions, it would be interesting to similarly compare this with the decalino compound. It is clear that these bulky groups provide optimum lithium selectivity with 14-crown-4 ionophores. Electrodes using these ionophores ought to provide nearly interference-free lithium measurements in serum.

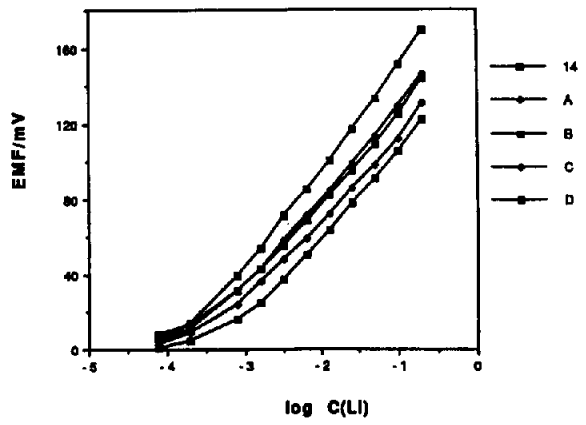

Fig. 10. Calibration curves using the ionophores in Fig. 9. Compound 14 is that shown in Fig. 8. Membranes contain NPOE plasticizer and 1% TOPO.

2.10. Lithium bronze electrodes

The term vanadium bronze has been applied to the non-stoichiometric compounds of the type $M_xV_2O_5$ where M is the univalent metal and x is a variable most frequently having a value near 0.3 [72]. The bronzes have been considered in the

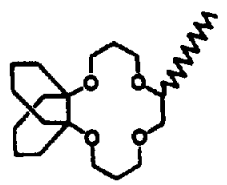

Fig. 11. Decalin 14-crown-4 ether (from Ref. [70]).

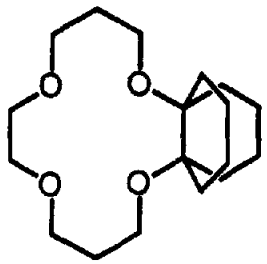

Fig. 12. Decalino 14-crown-4 ether (from Ref. [70])

search for solid-state lithium electrode materials and solid-state lithium ion electrolyte materials which require high diffusivity of lithium ions [73]. Gadzekpo [74] prepared lithium vanadium bronzes of the type $Li_xV_2O_5$ and lithium molybdenum bronze of the type Li_xMoO_3 with the possibility of using them as materials for solid-state lithium-selective electrodes. Single crystal, PVC powder membrane and silicone rubber powder membrane electrodes were prepared and evaluated. Crystalline $Li_{0.09}V_2O_5$ did not exhibit lithium response, but when the powder was in a PVC matrix, a slope of 45 mV decade^{-1} was obtained with a $K^{pot}_{Li,Na}$ value of 0.15. The silicone rubber membrane gave a nernstian slope of 59.2 mV decade^{-1} and a selectivity coefficient of 0.20. A Li_xMO_3 single crystal exhibited rapid lithium chloride response, near-nernstian at low concentrations, but nitrate or perchlorate salts exhibited a positive anion interference. The selectivity coefficient was 0.25. While functioning as lithium electrodes, these bronzes do not exhibit any advantages over more conventional ionophore solvent membrane electrodes.

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