

Reagents for Lithium Electrodes and Sensors for Blood Serum Analysis¹

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Abstract: The measurement of lithium in blood serum requires high selectivity since the blood contains about 140 mM sodium compared to the 0.5-1.5 mM lithium level in manic depressive patients under treatment with lithium salts. This review traces the development of optical and potentiometric methods for the selective measurement of lithium in the presence of sodium. Selectivities of over 1,000:1 are achievable with properly designed ionophores.

Keywords: Spectrophotometry, Fluorescence, Sensors, Ion-Selective Electrodes, Crown Ethers, Cryptands, Diamide Ionophores

Introduction

Lithium occurs naturally in blood at very low levels, at the parts per billion level (1). Administration of lithium salts for treatment of manic depressive psychosis (bipolar personality) was proposed in 1949 (2), and lithium has been used from the 1950's for the efficient treatment of this disease (3). Lithium is toxic in high concentrations (4), yet is ineffective for treatment if too low. It is therefore important to maintain the blood concentration in the 0.5-1.5 mM range (5). The upper level is near that where toxic symptoms are manifested, and 5 mM concentration may result in death (6). It is apparent that accurate measurement of lithium in the blood of patients is important to assure adequate and safe treatment.

A major challenge in developing sensors for lithium in blood is the fact that blood contains on the order of 140 mM sodium, i.e., about 100 to 300 times the concentration of lithium to be measured.

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Numerous attempts have been made to develop reagents and ionophores that exhibit high selectivity for lithium relative to sodium. In spite of the challenges, successful potentiometric and optically-based sensors have been developed. Similar compounds are often effective for both types of measurement. The evolution of these developments will be presented.

Optical Methods

The colorimetric reagent, Thoron, forms a weak complex with lithium in alkaline acetone/water solutions, which results in a bathochromic shift of its spectrum. This was used for the determination of lithium in serum by removing proteins with trichloroacetic acid, and measuring the change in absorbance at 480nm against the reagent as reference (7). It was necessary to compensate for sodium and other electrolytes by adding them to the reagent blank.

Crown ethers and cryptands can be designed to achieve high selectivity as ionophores for specific ions by varying cavity size, conformational flexibility, and different side groups to influence the size of the metal ion accommodated. TMC-crown formazane was demonstrated to provide a selectivity over sodium of about 1,400:1 under solution conditions similar to those used with Thoron (8). 14-Crown-4 ethers exhibit the best cavity size for lithium complexation. The formation of 2:1 sandwich-type sodium crown ether complexes can be inhibited by adding bulky groups to the base crown. Watanabe et al. (9) synthesized a PMT 14-crown-4 ether containing a bulky pinane and subunits at the ethano bridge of the crown that exhibited a remarkable selectivity of more than 10,000:1 for lithium over sodium. A flow-through optical sensor probe was developed by dissolving the crown, and a lipophilic anionic dye in the protonated form, in an organic liquid and then adsorbing on a pellicular-type ODS bead to serve as the sensor. Ion-pair extraction of the lithium occurs, which causes displacement of the proton, turning the color from yellow to red. Up to 0.1 M sodium had no influence on the lithium signal down to the detection limit of 10^{-5} M! Lithium was measured directly in 1:10 diluted artificial serum in Tris buffer.

A chromophoric small cavity cryptand phenol exhibits a greater than 4,000:1 selectivity for complexing lithium in an aqueous alkaline solution, with no solvent extraction required (10). It was successfully used for determination of lithium in blood serum diluted 1:40 with the reagent.

1-8 Dihydroxyanthraquinone was used as a fluorescence agent to determine lithium in deproteinized serum, in an alkaline acetone-water solution, exhibiting 480:1 selectivity over sodium (11).

Ion-Selective Electrodes

Early lithium ion-selective electrodes were based on amide-type ionophores (12-14). Metzger et al. (15) were able to determine lithium in undiluted serum with a cyclohexyl diamide compound which had a selectivity of 80:1 for lithium over sodium. Gadzekpo et al. (16) prepared a series of diamide-based ionophores with pyridine, furan, and dioxanone backbones, while Attiyat and coworkers (17) synthesized cyclic dioxadiamides and acyclic monoxadiamides, used in ISEs. One of the cyclic ionophores exhibited a selectivity of over 100 for lithium relative to sodium (17).

14-Crown-4 ethers have proved to be excellent ionophores for lithium ISEs, particularly when containing bulky groups to prevent formation of the 2:1 sodium complex. Dodecylmethyl-14-crown-4 exhibits a selectivity for lithium over sodium of 150 (18), and was used to measure lithium in undiluted serum in a flow injection analysis system containing a dialysis membrane (19). An acyclic formazane exhibited lithium selectivity of 160:1 in an ISE (20).

A bulky dibenzo-14-crown-4 ether exhibited a preference for lithium of 800:1 in an ISE, and was used to measure lithium in undiluted serum by placing a dialysis membrane over the electrode (21). A di-n-butylamide 14-crown-4 ionophore exhibited a selectivity of 800:1 and could be used to measure lithium in serum diluted 1:10 with a buffer (22).

A series of 14-crown-4 ethers with bulky groups were synthesized and tested in ISEs by Wen et al. (23), and a selectivity of 700:1 was obtained for a tribenzo compound, double that obtained with the dibenzo compound (21) under the same measurement conditions. The decalin 14-crown-4 ether reported by Suzuki et al. (24) exhibited 1,000:1 selectivity for lithium, and a decalino 14-crown-4 ether (25) topped the ISE selectivity at 2,000:1.

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