Design and synthesis of coumarin-based lithium fluoroionophores

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Introduction

The development of fluorescent probes for detecting low concentrations of cations in aqueous solution with high selectivity is an endeavor with significant biological implications. For example, lithium cations are of interest due to their undetermined pharmacological mechanism in treating acute mania and bipolar disorder. Although progress has been made in the field of lithium-specific fluorescent probe synthesis, many of these developed probes are unsuitable for in vivo applications due to poor solubility or inclusion of toxic and expensive metals in the metallacrown ionophore.

Objective

In order to develop a fluorescent probe with maximum in vivo feasibility, coumarin was chosen as a relatively pH stable fluorophore that could potentially penetrate a cell membrane. A methylene-substituted 12-crown-4 unit was chosen as the Li⁺ ionophore, as studies have shown that this crown is nearly size-fitted to the lithium cation. A synthetic strategy was developed to produce fluorescent probes that incorporate these features in a direct and inexpensive manner.

Synthetic Strategies

The most direct route to 3-substituted coumarins involves inducing Perkin-type condensations on salicylaldehyde derivatives such as 1,2,3,4. The first process uses a one-step microwave-accelerated protocol, while the second involves the isolation of the Baylis-Hillman adduct, which is then easily converted to the corresponding coumarin derivative. Both of these halide-substituted coumarins easily undergo nucleophile substitution withaza-12-crown-4 in the presence of triethylamine, a technique also used for the 4-substituted coumarin synthesis.

A modification can be made to the synthetic protocol to produce fluorophore probes that utilize 3-amide as opposed to 3-methylene tethers. This two-step procedure is shown below, where the coumarin ester 4 (produced via Knovenagel condensation onto 3) is converted to the crown-amide 5 via activation by trimethylaluminum.

Other Probe Designs

Other possibilities of lithium specific-fluorionophores are also under consideration in our laboratory. For example, the coumarin-based crystal 6 is being developed from a literature precedent in which a similar R⁺ probe was produced. This target contains what effectively is a cryptand 2,1,1, which has been shown to be selective for lithium ions. Highlights of this synthesis are shown below.

Probe electronics

There are two main photoelectronic considerations at play in these coumarin fluorionophores. First, the photoinduced electron transfer phenomenon is related to the interaction between the electron and coumarin system. As shown on the left hand side of Figure 5, the amine lone pair of electrons can quench the fluorescence of the coumarin ring. If this lone pair of electrons forms a coordinate covalent bond with Li⁺, there should be an increase in emission when the PET is relevant. Second, as previously alluded to, the potential coordination between lithium ion and coumarin carbonil can create a larger HOMOLUMO gap that would create a shift in shorter wavelengths of absorption. This shift in wavelength would be proportional to the amount of bound lithium ion, which would be quite a useful proposition for pharmacological applications.

Future Directions

In order to produce a lithium sensor with maximum in vivo suitability, it would be optimal to achieve water solubility of the fluorophore product. In order to manipulate the solubility of probes such as 5, an approach we plan to employ is protecting the amine group with phosphine or "Gabriel" type protection. This strategy would protect the amine group from coumarin-forming condensations, but could be ultimately deprotected and stabilized with an array of poly alkyhalides or other groups that could be screened for water solubility. Efforts toward the development of this and other aspects of the coumarin-based probes are underway in our laboratory.

References


Acknowledgement

The authors extend gratitude to the faculty and staff of the University of Wisconsin-Madison chemistry department for their support and assistance with summer research conducted on this project. Travel funds for the 241st ACS National Meeting were graciously provided by the Carol Dannell Freund and Experiential Learning Funds of Allegheny College.