Chiral Discrimination Ability of Peptide-Based Chiral Ionic Liquids

Abstract

This proposal describes a project that aims to develop peptide based chiral ionic liquids that exhibit better chiral discrimination abilities than previously studied amino acid based chiral ionic liquids. The peptide based chiral ionic liquids will be synthesized of Di- or Tri-peptides to be studied in both the anion and cation position of the salts. Circularly polarized luminescence spectroscopy will be used to understand the chiral discrimination ability of these peptide based chiral ionic liquids with a luminescent chiral molecule dissolved in them. Chiral discrimination ability of these peptide based ionic liquids will then be compared against previously studied amino acid based chiral ionic liquids. The results of this study will provide a foundation for the further study of peptide based chiral ionic liquids and will add to the knowledge of the use of solvents as chiral discriminators.

Significance of Project

Chirality is the reason why your nose smells spearmint versus caraway or why a certain drug treats morning sickness in pregnant women versus causing serious birth defects. Chirality is the term used to describe objects that are non-superimposable with their mirror images. A classic example of chirality is a right and left human hand. Many molecules such as amino acids also exhibit chirality. The difference in 3-dimensional arrangement of similar groups coming off of a central carbon atom determines whether they are D (right handed) or L (left handed) amino acids. It is important to be able to select for certain chiral molecules. For example, in the pharmaceutical industry it is necessary to separate out a certain handed molecule that serves a therapeutic purpose from the opposite handed molecule with an ill effect. Returning to the left and right human hand analogy, during a hand shake it is noticeably more comfortable when a right hand shakes another right hand than when a left hand shakes a right hand. In chemistry, this recognition of a certain handedness of a molecule over the opposite handedness is known as chiral discrimination.

Recent studies have shown that ionic liquids can perform chiral discrimination.[1,2,3] Much like NaCl (table salt), ionic liquids are salts composed of oppositely charged ions. Unlike NaCl, though, ionic liquids form anion/cation pairs with much weaker ionic interactions and form liquids at normal (room) temperatures. In these studies, researchers have synthesized various chiral ionic liquids (CILs), meaning one of the two ions of the ionic liquid itself is chiral. This property gives the ionic liquid an overall molecular handedness. When a chiral molecule (both left and right handed) is dissolved in the chiral ionic liquid (only one handed), the liquid interacts with one of the handed molecules more than the other due to intermolecular interactions. Using the hand shake analogy, the CILs can play the role of guiding right hands to other right hands so that more handshakes are comfortable.

Amino acid based CILs have exhibited chiral discrimination.[4,5,6] Amino acids are naturally chiral, therefore their use in the synthesis of CILs is not unexpected. Another important aspect of the use of amino acids for CILs is the ability to select their functional groups. The different functional groups of the various amino acids cause different intermolecular interactions between added chiral molecules, which accounts for the differing levels of chiral discrimination amongst amino acid based CILs in the literature. A property of amino acids that has not yet been studied in terms of CILs is the linking of multiple amino acids together. These chains of amino acids, known as peptides, offer an increased number of functional groups, which increases the number of possible intermolecular interaction sites

between CILs and dissolved chiral molecules. An increase of intermolecular interaction between CIL and dissolved chiral molecules also increases the chiral discrimination potential of the ionic liquid. The result will be an overall increase in chiral discrimination by peptide based CILs compared to amino acid based CILs. If successful, peptide-based CILs could offer a better means to separate different handed chiral molecules than standard methods in industry, which tend to be both expensive and dangerous to the environment and human health. Peptide based CILs could be used as a solvent to selectively synthesize one hand of a chiral molecule over the other, or they could be used as a stationary phase in gas chromatography to physically separate one hand of a chiral molecule from the other.

Statement of Central Objectives

One central objective of the project described in this proposal is to develop peptide based chiral ionic liquids that are better at chiral discrimination than amino acid based chiral ionic liquids. A second central objective is to gain significant research experience that will help further my future educational goals.

Methods

Synthesis: The synthesis of peptide based CILs will be much the same as the synthesis performed for amino acid based CILs.[5,7] Peptides will be used as both anions and cations in order to explore different chiral discrimination properties of peptide based CILs. Using H_2O as the solvent, anionic peptide based CILs will be synthesized via a reaction between TBA OH (tetrabutylammonium hydroxide) and the C-terminus carboxylic acid of the peptide to be studied.[8] The products of this reaction are the peptide based CIL and H_2O (Figure 1). The resulting product will be heated to drive off any remaining H_2O.

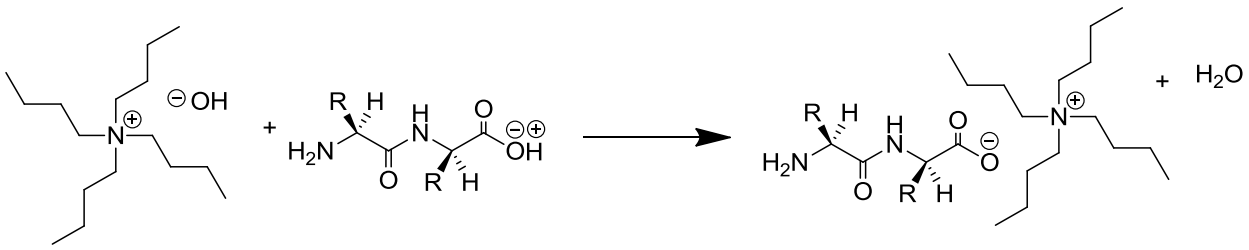

Figure 1. Preparation of TBA/peptide CIL from TBA OH and peptide.

Synthesis of cationic peptide based CILs will require two steps. The first step will require Fischer esterification of the C-terminus carboxylic acid of the peptide that yields an esterified peptide/chloride salt. In H_2O, the esterified peptide will have an overall positive charge under correct pH conditions.[8] The next step involves a metathesis reaction between Li Tf_2N (lithium bis

trifluoromethanesulfonyl amide) dissolved in H_2O and the N-terminus of the peptide. This reaction yields the peptide based CIL, as well as aqueous Li^+ and Cl^- (Figure 2). The aqueous layer, as well as the contained Li^+ and Cl^- ions, will be removed from the ionic liquid using a separation funnel. The ionic liquid will then be heated to drive off remaining H_2O. Overall, Di-peptide based CILs to be studied during the nine week BSI period will be TBA/L-Valine-L-Serine, L-Alanine-L-Alanine/Tf_2N, and L-Leucine-L-Leucine/Tf_2N. Tri-peptide based CILs of study will be TBA/L-Alanine-L-Alanine-L-Alanine, L-Alanine-L-Alanine-L-Alanine/Tf_2N, and L-Alanine-L-Alanine-L-Leucine/Tf_2N.

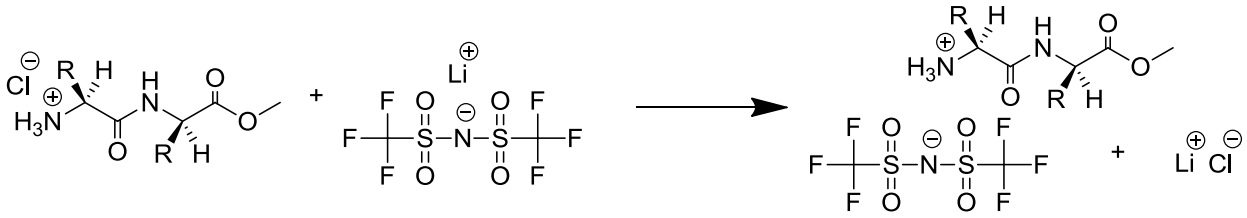

Figure 2. Metathesis of peptide/ Tf_2N CIL from esterified peptide Cl salt and Li Tf_2N.

In both the anionic and cationic synthetic procedures, the identity of the synthesized peptide based CILs will be verified using ^1H NMR spectroscopy. To keep the peptides intact, the peptide based CILs will be kept in a vacuum desiccator so that hydrolysis of the peptide bonds will be minimized.

Chiral Discrimination Measurement: Chiral discrimination of the peptide based CILs will be determined by measurement of the luminescent characteristics of a chiral Europium complex using a circularly polarized luminescence (CPL) spectrometer. Equal amounts of right and left handed $Eu(dpa)_3^{3-}$ (Europium 2,6-pyridinedicarboxylate dianion) molecules will be dissolved in the peptide based CILs. When $Eu(dpa)_3^{3-}$ is struck by ultraviolet (UV) radiation it emits CPL. The handedness of the $Eu(dpa)_3^{3-}$ molecule that is struck by UV light dictates whether the emitted CPL will rotate to the right or the left, also known as the CPL polarization (Figure 3).

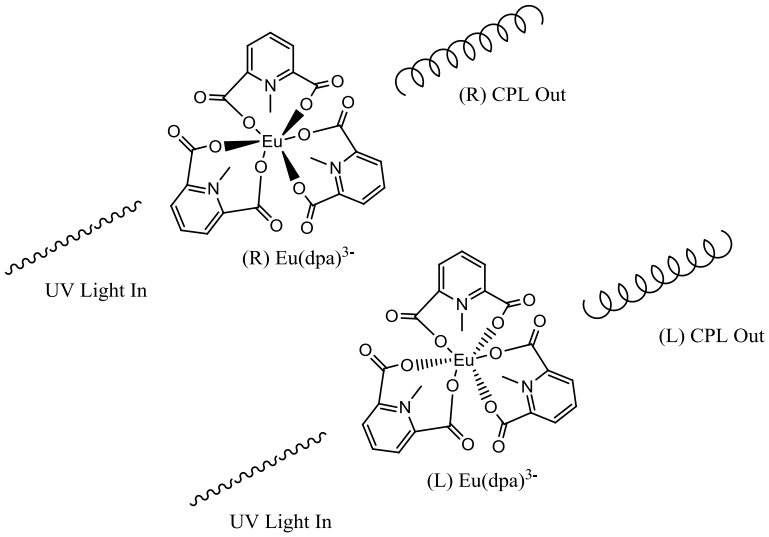

Figure 3. CPL emission characteristics of chiral $Eu(dpa)_3^{3-}$ molecules.

Depending on the intermolecular interactions between $Eu(dpa)_3^{3-}$ and the peptide based CIL, one of the $Eu(dpa)_3^{3-}$ molecules (right or left) will interact more with the CIL and emit less of its handed CPL. These small differences in CPL between right and left handed $Eu(dpa)_3^{3-}$ can be detected by the CPL spectrometer.

The CPL spectrometer detects the polarization (right versus left polarization) and intensity (the overall amount of each handed CPL), which can be expressed as I_L and I_R, of the emitted CPL. These measurements can be used to calculate an emission dissymmetry factor (g_{em}), which can be expressed as:[9]

$$g_{em} = \frac{2(I_L - I_R)}{I_L + I_R}$$

g_{em} values give both quantitative and qualitative information about the chiral discrimination characteristics of the peptide based CILs. The g_{em} value reveals the magnitude of chiral discrimination between $Eu(dpa)_3^{3-}$ molecules by the CIL, and the sign of the value explains which hand of $Eu(dpa)_3^{3-}$ is interacting more with the CIL. Overall, if the g_{em} value is nonzero, chiral discrimination is occurring. The experimentally determined g_{em} values of the peptide based CILs will be compared to control g_{em} values of amino acid based CILs to determine which exhibit better chiral discrimination ability. The g_{em} values of $Eu(dpa)_3^{3-}$ in D,L-Alanine, L-Leucine, and D,L Serine amino acid based CILs have previously been recorded in our research lab. These amino acid based CIL studies will serve as a control of chiral discrimination ability to compare against peptide based CILs. In our previous amino acid based CIL studies, the observed g_{em} values were typically measured around +/- 0.01. If peptide based CILs have

better chiral discrimination ability than amino acid based CILs, the observed g_{em} value will be greater in magnitude than +/- 0.01.

Progression of Project

Week 1: Synthesis of stock Di-peptide based CILs (TBA/L-Val-Ser, L-Ala-Ala/ Tf_2N, and L-Leu-Leu/ Tf_2N)
Week 2: Physical measurements and molecular determination of synthesized Di-peptide CILs
Week 3: Perform chiral discrimination screening on Di-peptide CILs
Week 4: Perform chiral discrimination screening on Di-peptide CILs
Week 5: Synthesis of stock Tri-peptide based CILs (TBA/L-Ala-Ala-Ala, L-Ala-Ala-Ala/ Tf_2N, and L-Ala-Ala-Leu/ Tf_2N)
Week 6: Physical measurements and molecular determination of synthesized Tri-peptide CILs
Week 7: Perform chiral discrimination screening on Tri-peptide CILs
Week 8: Perform chiral discrimination screening on Tri-peptide CILs
Prepare for presentation
Week 9: Prepare for presentation
Give Presentation

Feasibility

The CPL spectrophotometer is in place and ready for use in Dr. Hopkins' lab. The chemistry department also has numerous Di- and Tri-peptides that are at our disposal, and there are additional commercially available peptides we can use. Because we will be synthesizing ionic liquids with no known reference data, we will use the Butler University Chemistry Department's ^1H NMR Spectrometer to determine our synthesized species' chemical identity.

Working on Campus

All aspects of this research can be performed at Butler University and do not require me to be away from campus.

Personal

My interest in scientific research is based on the belief that scientific discovery leads to the advancement of the human condition. Ionic liquids are a new and relatively unstudied field that holds the potential to improve existing technology. For example, the further study of ionic liquids as a solvent could eventually lead to the replacement of conventional organic solvents, which tend to be both hazardous for the environment and human health. This proposed project in particular interests me because these ionic liquids serve as both solvent and chiral discriminator, eliminating the need for costly and potentially dangerous catalysts.

As a Chemistry major at Butler, I've had numerous courses that have prepared me for this project. General Chemistry (CH106), Organic Chemistry (CH 351 and CH 352) and Biological Investigations (BI 121) have given me important lab experience, and Biochemistry (CH 361) gave me the necessary skills to work with amino acids and peptides. In addition, I've also had 2 semesters of lab experience in Dr. Hopkins' lab to familiarize myself with the equipment and techniques necessary to carry out this project.

My participation in the Butler Summer Institute will also aid me in my future educational goals. Using the data generated from my work during BSI, I plan on writing a Butler University Honors thesis. After graduation, I would like to apply to a post-baccalaureate research program with the intention of enrolling in either medical school or chemistry graduate school. Eventually, I would like to start a career in biomedical research. By participating in BSI, I will gain key experience in writing research proposals, performing research under a specific timeframe, and presenting scientific research.

Presentation

- Butler University Community Presentation
- Butler Undergraduate Research Conference
- 2012 American Chemistry Society Spring National Meeting
- 2012 American Chemistry Society – Green Chemistry Conference
- Butler University Honors College Thesis Presentation

- The Journal of Physical Chemistry
- Chirality (Journal)
- Butler University Honors College Thesis

Research Approvals

No official research approvals are required for the proposed project.

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