Resolution of Enantiomeric Helicenes by β-Cyclodextrin Association

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Abstract

This project focuses on the resolution of enantiomers (chemically equivalent, spatially different molecules), specifically the synthesis and resolution of [7] helicene. To achieve this chiral separation, a boronic acid moiety will be placed on the helicene, and \( \beta \)-cyclodextrin will be used as a mobile phase in reverse-phase HPLC. Boronic acids are known to form association complexes with carbohydrates, and it is our hope that these associative properties will provide resolvable enantiomers using traditional chromatographic techniques. These resolved enantiomers would prove useful in the production of LEDs, selective DNA recognition, and the new resolution method holds interminable applications.

Introduction

Due to the tetrahedral nature of a carbon atom, when many organic molecules are synthesized, they can be produced with the same bonds between the same atoms, but in different positions in 3-D space. These molecules are known as stereoisomers. Stereoisomers that are mirror images of each other and cannot be superimposed onto one another are known as enantiomers. Enantiomers possess the same individual chemical and physical properties as one another, such as melting point, boiling point and spectral properties, and thus can be very difficult to separate. This is the exact case with [7] helicene (Figure 1). There is no known way to control which direction the molecule will wind around itself during photocyclization. Molecules will arbitrarily cyclize in different directions, resulting in a mixture of enantiomers, similar to right and left handed screws (Figure 2).

![Figure 1 Crystal Structure of [7] Bromohelicene](image1.png)  
![Figure 2](image2.png)

If stereoisomers are not mirror images of one another, they are known as diastereomers. Diastereomers possess different properties and can be separated in a number of ways.

These sometimes extremely subtle differences can make for drastic differences in the behavior of a molecule in a system, especially biological. A very well known example of this is thalidomide, which was given to pregnant women to combat morning sickness. While one enantiomer of the molecule serves its intended purpose, the other causes severe birth defects. The ability to obtain enantiomerically pure compounds is
increasingly vital. The modern routes to achieve this separation are expensive, time consuming, and often difficult.

It has been shown that boronic acids and esters form association complexes with carbohydrates. These complexes are commonly fluorescent, and boronic acids are increasingly used as carbohydrate sensors.

β-cyclodextrin, seven glucose molecules arranged in a ring, is known well in the field of chiral resolution. It is most commonly used as a stationary phase in HPLC columns.

**Objective**

[7] Bromohelicene was synthesized by known literature methods.¹,²

![Fig. 3 Synthesis of stilbene derivative](image1)

![Fig. 4 Stilbene photocyclization](image2)
The bromine moiety was then converted into a boronic ester by metal halogen exchange using $n$-BuLi followed by quenching with 2-isoproxy-4,4,5,5-tetramethyl-1,3,2-dioxaboralane.

**Fig. 5** Synthesis of boronic ester

The boronic ester can then be reduced to a boronic acid by means of a trifluoroborate intermediate and subsequent hydrolysis.

**Fig. 6** Conversion to trifluoroborinate
The boronic ester intermediate is used for its stability to ease isolation and purification. It cannot be loaded onto the column itself, however, for the same reasons. It does not interconvert, is insoluble in common HPLC solvents, and will not associate with β-cyclodextrin. Yuen\textsuperscript{10} outlined a simple procedure to create the potassium trifluoroboronate intermediate (Fig. 6) as well as the subsequent basic hydrolysis to the boronic acid (Fig. 7). This painless method is extremely useful due to its simplicity, efficacy and stability.

The final reaction mixture will be placed directly onto a reverse phase HPLC column. β-Cyclodextrin will be eluted through the column. It is our hope that associations between the helicene and the cyclodextrin will form diastereomers, which will elute through the column at different rates.

This simplified resolution method will greatly reduce the cost and complications of isolating stereoisomers. Following successful chiral resolution, reduction will convert the products into [7] helicene, and we will have two enantiomerically pure compounds, which will be characterized by means of nuclear magnetic resonance spectroscopy and x-ray crystallography.

**Preliminary Results**

[7] Bromohelicene has been synthesized\textsuperscript{1-2} (Figures 3 and 4). The bromine moiety has been successfully converted to a boronic ester (Figure 5). Hydrolysis to a boronic acid by means of a potassium trifluoroborate intermediate is currently being optimized. Boronic esters were not able to be loaded directly onto columns due to lack of solubility. HPLC conditions will subsequently be optimized after hydrolysis to boronic acid.

**References**


4) Yan Xu, Hiroshi Sugiyama, Kazuhiko Tanaka, Hideji Osuga; *Nucleic Acid Symposium Series*, **2004**, *48*, 87-88


Characterization
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borylated helicene

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