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ENANTIOMERIC SEPARATION BY CLOUD POINT PRECIPITATION OF CYCLODEXTRINS

Deanna L. Schmid

Abstract

Certain cyclodextrins exhibit a diminishing solubility in water when heated. This phenomena of cloud point precipitation in conjunction with cyclodextrin's ability to form an inclusion complex with many compounds, can be used as a method of chemical separation. These cyclodextrins can be removed from the solution after precipitation by a hot filtration technique and the remaining solution analyzed by HPLC. Enantiomeric separations, concentration of compounds and removal of hazardous organic materials are all possible applications of cloud point extraction using cyclodextrins.

Introduction

Surface active agents have been used for years in many separation processes.¹ These processes are classified as either micellar or nonmicellar methods. A nonmicellar process is one in which no aggregation of the surfactant is required for the separation method to be effective. Examples of nonmicellar processes are foam flotation, precipitation and ion interaction chromatography.² A micellar process is one in which the surfactant must reach the critical micellar concentration and form micelles to be effective as a separation technique.³ Examples of micellar techniques are liquid-liquid extractions and membrane techniques.⁴ Cyclodextrins are surface active agents that form cloudpoint precipitates in a nonmicellar manner.⁵ Cloud point extractions have one other critical property that must be met. The temperature of the aqueous solution must reach the point where precipitation of the aggregated surfactant occurs. This temperature is called the cloud point temperature.

Cyclodextrins are cyclic oligosaccharides which have a toroidal shape. The interior of the cyclodextrin is hydrophobic, while the outside is lined with hydroxyl groups which are hydrophilic. These properties give cyclodextrin the capability of forming inclusion complexes with many organic molecules. Molecules that have been shown to form the best inclusion complexes with cyclodextrins have at least one aromatic ring.⁶ Cyclodextrins are also capable of chiral recognition and have become popular in that respect within the last decade.⁷

Experimental

The cyclodextrins were tested for cloud point precipitation at various temperatures and concentrations using the following method. Cyclodextrin was added to the specified amount of water in a test tube. That test tube was placed in a beaker filled with water. A magnetic stir bar was put into the beaker. The beaker was then placed on a hot plate/magnetic stirrer which was the source of temperature control and heat distribution. A thermometer was placed in the beaker to record the exact temperature.

The filtration was done using a Pyrex vacuum filtration apparatus, Nylon 66 0.45 micron filters and a standard oven set at 120 degrees Celsius. The filtration apparatus was heated for 20 minutes and quickly used for filtering. Before filtering the cyclodextrin was added to 10 ml of water and heated as previously described for 20 minutes at 65 degrees Celsius water bath.

The method to determine enhancement of the enantiomeric compounds was done using 0.005M permethyl-2-hydroxypropyl- β -CD and 0.005M compound. One filtration was done using only the compound in solution with water. This run was used as the standard to compare to the filtrate of the solution with the compound and cyclodextrin. Both filtrations were done as

described in the previous paragraph. HPLC with a B-cyclodextrin analytical column was used to analyze the standard and CD solutions after filtration. A mobile phase of methanol/1% TEAA (pH 4.1) was used in different ratios for all compounds. A flow rate of 1 ml/min was used. Ultraviolet detection at 254 nm was used for all compounds.

Results

Cyclodextrin	Critical Concentration	Cloud Point Temperature
Beta-Cyclodextrin	----	----
Hydroxyethyl-beta-CD	----	----
Hydroxypropyl-beta-CD	----	----
Methyl-beta-CD	----	----
Permethyl-2-hydroxypropyl-gamma-CD	0.0016	45
Permethyl-2-hydroxypropyl-alpha-CD	0.0017	49
Permethyl-2-hydroxypropyl-beta-CD	0.0016	45

Compound	Mobile Phase	Percent Enhancement
Mephobarbital	20/80	0
Mephénytoin	20/80	0
Dansyl-DL-leucine	35/65	0
Dansyl-DL-phenylalanine	35/65	0
Dansyl-DL-valine	35/65	0
Dansyl-DL-norleucine	35/65	0

Conclusions

All members of the permethyl-2-hydroxypropyl-cyclodextrin family were found to exhibit the cloud point precipitation phenomena. A hot filtration method was devised to filter off the precipitated cyclodextrin. Although no enantiomeric enhancement was evident in this limited study, further experimentation is underway to provide more complete results. There are also many other possible uses for the cyclodextrins that form a cloud point precipitate, many of which are currently being investigated.

Acknowledgments

Dr. Daniel W. Armstrong, Faculty Advisor for OURE Project, Professor of Chemistry, University of Missouri-Rolla.

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