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Enantiomeric separation of isochromene derivatives by high-performance liquid chromatography using cyclodextrin based stationary phases and principal component analysis of the separation data

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ABSTRACT

Isochromene derivatives are very important precursors in the natural products industry. Hence the enantiomeric separations of chiral isochromenes are important in the pharmaceutical industry and for organic asymmetric synthesis. Here we report enantiomeric separations of 21 different chiral isochromene derivatives, which were synthesized using alkynylbenzaldehyde cyclization catalyzed by chiral gold(I) acyclic diaminocarbene complexes. All separations were achieved by high-performance liquid chromatography with cyclodextrin based (Cyclobond) chiral stationary phases. Retention data of 21 chiral compounds and 14 other previously separated isochromene derivatives were analyzed using principal component analysis. The effect of the structure of the substituents on the isochromene ring on enantiomeric resolution as well as the other separation properties was analyzed in detail. Using principal component analysis it can be shown that the structural features that contribute to increased retention are different from those that enhance enantiomeric resolution. In addition, principal component analysis is useful for eliminating redundant factors from consideration when analyzing the effect of various chromatographic parameters. It was found that the chiral recognition mechanism is different for the larger γ-cyclodextrin as compared to the smaller β-cyclodextrin derivatives. Finally this specific system of chiral analytes and cyclodextrin based chiral selectors provides an effective format to examine the application of principal component analysis to enantiomeric separations using basic retention data and structural features.

1. Introduction

Isochromene derivatives exist in variety of natural products. They have very important biological effects including antitumor properties, hence they play a vital role in natural products research [1,2]. The isolation of isochromene based compounds from living systems, such as various types of fungi, is a common practice [3]. Isochromenes also are useful as intermediates in the synthesis of other natural products and pharmaceuticals. Consequently some organic chemists tend to produce isochromene derivatives in bulk quantities using asymmetric synthesis [4,5]. In these cases, it is important to efficiently determine the enantiomeric excess (%ee) as well as to separate chiral products or intermediates in larger quantities.

HPLC continuous to be the most dominant chiral separation technique available. Here we present chiral HPLC methodologies for the separation of isochromene derivatives using Cyclobond HPLC columns. The Cyclobond series is the original line of cyclodextrin based chiral selectors. Cyclodextrin is made of 1–4 linked α-D-glucopyranosides. The number of glucose units for bonded cyclodextrins are 6, 7 and 8 (named α, β, and γ respectively) [6–14]. Among the Cyclobond columns used in this study, with the exception of the Cyclobond II column, the cyclodextrin hydroxyls have been partially derivatized with various functional groups to enhance enantioselectivity. Previously, neutral hydrophobic molecules with few polar functional groups have been shown to separate particularly well on Cyclobond chiral stationary phases [13,15–18].

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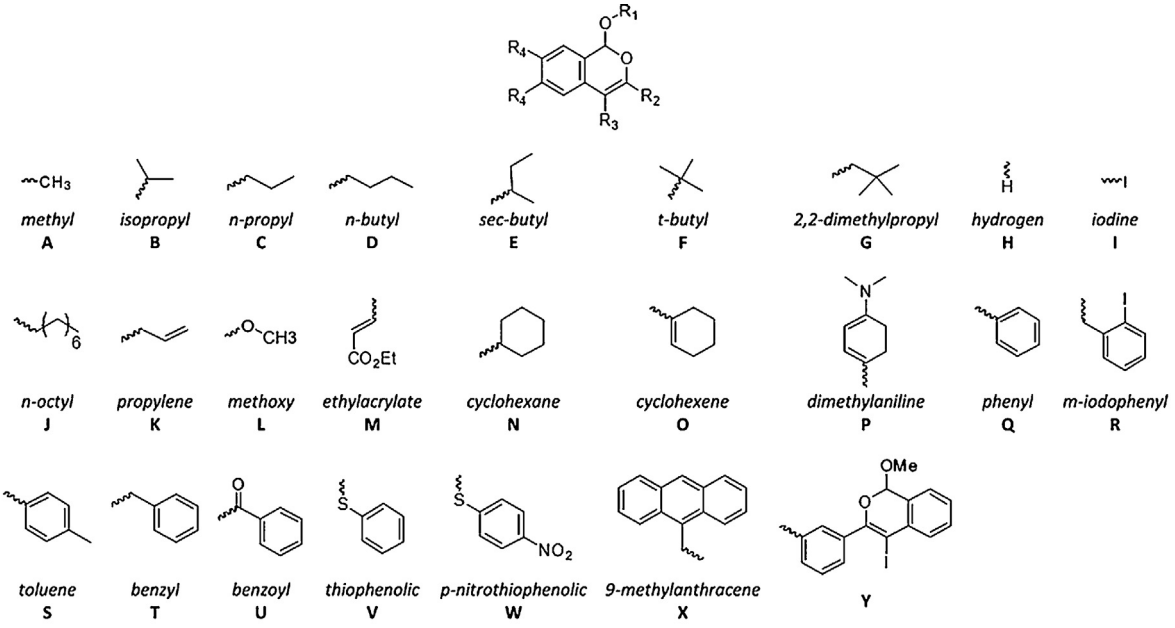
Recently a series of chiral isochromene derivatives were synthesized using a new class of chiral Au^{I}/acyclic diaminocarbene (ADC) catalysts [19]. These analytes were synthesized by asymmetric alkynylbenzaldehyde cyclization [19]. Most of these have not been separated previously on any HPLC chiral stationary phase. We then employed principal component analysis (PCA) to analyze the separation data of these chiral isochromene derivatives along with the separation data of 14 other related compounds that had been reported previously [20]. Principal component analysis (PCA) is a powerful tool that can be used to understand the differences between calculated and measured separation data, to determine the external variables that significantly affect separation and to reduce the number of chromatography systems/analytes to solve specific practical and theoretical problems in chromatography [21]. PCA was employed previously in two chiral separations studies by Camilleri et al. and Montanari et al. [22,23]. Camilleri et al. used quantitative structure–property relationships (QSPR) whereas Montanari et al. used molecular interaction fields (MIF). Hence both of those studies had complex molecular modeling and complex electronic property estimation. However in our study we used common chromatographic variables such as retention factor, resolution and substitution position as well as the volume of the substituted group. Hence, to our knowledge, this is the first report which uses PCA with simple common variables to help understand HPLC enantiomeric separations. Also this is the first report on the use of PCA to analyze the chiral separation data of isochromene derivatives.

2. Experimental

HPLC grade acetonitrile, methanol, 2-propanol and heptane were purchased from EMD chemicals (Gibbstown, NJ). Deionized water was prepared using a Millepore© Synergy 185 system (Billerica, MA). Cyclobond columns were obtained from Supelco© (Bellefonte, PA). LARIHC columns were obtained from AZYP LLC (Arlington, TX). The chiral stationary phases used in this study consisted of Cyclobond II (underivatized, native γ-cyclodextrin), Cyclobond AC (acetylated β-cyclodextrin), Cyclobond RSP ((R,S)-hydroxypropyl modified β-cyclodextrin), Cyclobond DM (dimethylated β-cyclodextrin) and LARIHC



Compound	Substituted Groups			
	R1	R2	R3	R4
IC1	B	Q	H	H
IC2	C	Q	H	H
IC3	D	Q	H	H
IC4	A	Q	H	H
IC5	B	C	H	H
IC6	D	C	H	H
IC7	J	C	H	H
IC8	A	C	H	H
IC9	X	S	H	H
IC10	X	Q	H	H
IC11	E	Q	H	H
IC12	B	S	H	H

Compound	Substituted Groups			
	R1	R2	R3	R4
IC13	K	S	H	H
IC14	G	S	H	H
IC15	N	Q	H	H
IC16	T	Q	H	H
IC17	F	Q	H	H
IC18	N	S	H	H
IC19	A	S	H	H
IC20	J	S	H	H
IC21	J	Q	H	H
IC22	A	Q	W	H
IC23	D	Q	I	H
IC24	R	Q	I	H

Compound	Substituted Groups			
	R1	R2	R3	R4
IC25	U	Q	I	H
IC26	A	Q	Q	H
IC27	A	O	V	H
IC28	A	D	W	H
IC29	A	Q	M	H
IC30	A	O	I	H
IC31	A	Y	I	H
IC32	P	O	I	H
IC33	F	Q	I	H
IC34	A	Q	I	L
IC35	A	Q	W	L

Fig. 1. General structure and the ring numbering conventions for studied chiral compounds. R1 and R2 can be either aliphatic or aromatic substituents. R3 can be an iodine, a sulfur group, an aliphatic group or an aromatic group. R4 can be either hydrogen or methoxy group.