การแยกอิแนนทิโอเมอร์ของอิพ็อกไซด์ด้วยแก๊สโครมาโทกราฟีที่ใช้อนุพันธ์แอลฟาไซโคลเดกซ์ทรินเป็นเฟสคงที่

นางสาวอัญญรัตน์ คล้ายโพธิ์ทอง

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาเคมี ภาควิชาเคมี
คณะวิทยาศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2554
ลิขสิทธิ์ของจุฬาลงกรณ์มหาวิทยาลัย

ENANTIOMERIC SEPARATION OF EPOXIDES BY GAS CHROMATOGRAPHY USING DERIVATIZED ALPHA-CYCLODEXTRINS AS STATIONARY PHASES

Miss Aunyarat Claypotong

A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science Program in Chemistry
Department of Chemistry
Faculty of Science
Chulalongkorn University
Academic Year 2011

Thesis Title	ENANTIOMERIC SEPARATION OF EPOXIDES BY GAS CHROMATOGRAPHY USING DERIVATIZED ALPHA-CYCLODEXTRINS AS STATIONARY PHASES
By	Miss Aunyarat Claypotong
Field of Study	Chemistry
Thesis Advisor	Assistant Professor Aroonsiri Shitangkoon, Ph.D.

Accepted by the Faculty of Science, Chulalongkorn University in Partial Fulfillment of the Requirements for the Master's Degree

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อัญญรัตน์ คล้ายโพธิ์ทอง : การแยกอิแนนทิโอเมอร์ของอิพ็อกไซด์ด้วยแก๊สโครมาโทกราฟีที่ใช้อนุพันธ์แอลฟาไซโคลเดกซ์ทรินเป็นเฟสคงที่.
(ENANTIOMERIC SEPARATION OF EPOXIDES BY GAS CHROMATOGRAPHY USING DERIVATIZED ALPHA-CYCLODEXTRINS AS STATIONARY PHASES)
อ. ที่ปรึกษาวิทยานิพนธ์หลัก: ผศ.ดร.อรุณศิริ ชิตางกูร, 63 หน้า.

ได้ทำการแยกคู่อิแนนทิโอเมอร์ของแอโรแมติกอิพ็อกไซด์ 42 ชนิดและแอลิฟาติกอิพ็อกไซด์ 6 ชนิด ด้วยแคพิลลารีแก๊สโครมาโทกราฟีที่ใช้อนุพันธ์แอลฟาไซโคลเดกซ์ทริน คือ เฮกซะคิส(2,3-ได-*โอ*-เมทิล-6-*โอ*-*เทอร์ต*-บิวทิลไดเมทิลไซลิล)ไซโคลมอลโตเฮกซะโอส (หรือ ASiMe) และเฮกซะคิส(2,3-ได-*โอ*-แอซีทิล-6-*โอ*-*เทอร์ต*-บิวทิลไดเมทิลไซลิล)ไซโคลมอลโตเฮกซะโอส (หรือ ASiAc) เป็นเฟสคงที่ชนิดไครัล โดยได้ทำการศึกษาผลของชนิด จำนวน และตำแหน่งของหมู่แทนที่ของอิพ็อกไซด์ที่มีต่อค่ารีเทนชันและค่าการเลือกจำเพาะของอิแนนทิโอเมอร์ จากการทดลองพบว่าอิแนนทิโอเมอร์ของอิพ็อกไซด์ทุกตัวสามารถแยกได้ด้วยเฟสคงที่ชนิดใดชนิดหนึ่งหรือทั้งสองชนิด ยกเว้น benzyl glycidyl ether (**8**) และ 1,2-epoxydodecane (**dodec**) ที่ไม่สามารถแยกได้ คอลัมน์ ASiMe สามารถแยกอิแนนทิโอเมอร์ของสารได้ 41 ชนิด ในขณะที่คอลัมน์ ASiAc แยกได้เพียง 16 ชนิด แอโรแมติกอิพ็อกไซด์แยกได้ดีด้วยคอลัมน์ ASiMe พบว่าตำแหน่งและชนิดของหมู่แทนที่บนวงแอโรแมติกของสไตรีนออกไซด์มีความสำคัญต่อการแยกอิแนนทิโอเมอร์ นอกจากนี้ ยังได้คำนวณค่าทางเทอร์โมไดนามิกส์เพื่ออธิบายถึงแรงกระทำระหว่างอิแนนทิโอเมอร์กับเฟสคงที่และค่าการคัดเลือกจำเพาะสำหรับคู่อิแนนทิโอเมอร์ของอิพ็อกไซด์ที่นำมาศึกษา

ภาควิชา เคมี ลายมือชื่อนิสิต .....

สาขาวิชา เคมี ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก .....

ปีการศึกษา 2554

527 26292 23 : MAJOR CHEMISTRY
KEYWORDS: GAS CHROMATOGRAPHY / CHIRAL SEPARATION / EPOXIDES / DERIVATIZED CYCLODEXTRIN

AUNYARAT CLAYPOTONG: ENANTIOMERIC SEPARATION OF EPOXIDES BY GAS CHROMATOGRAPHY USING DERIVATIZED ALPHA-CYCLODEXTRINS AS STATIONARY PHASES.
ADVISOR: ASST. PROF. AROONSIRI SHITANGKOON, Ph.D., 63 pp.

Enantiomeric separations of 42 aromatic epoxides and 6 aliphatic epoxides were studied by means of capillary gas chromatography using derivatized α-cyclodextrins: hexakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltohexaose (or ASiMe) and hexakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltohexaose (or ASiAc) as chiral stationary phases. The effects of substitution types, number and position of epoxides on retention and enantioselectivity have been investigated. The results showed that all epoxides were successfully separated with either ASiMe or ASiAc or both columns, except benzyl glycidyl ether (**8**) and 1,2-epoxydodecane (**dodec**). ASiMe column could enantioseparate 41 analytes while ASiAc column could resolve only 16 analytes. Aromatic epoxides were better separated on ASiMe column. Furthermore, the position and type of substituent on aromatic ring of styrene oxide played important roles on enantioseparation. Thermodynamic data were acquired to clarify the interaction strength between analyte and stationary phase as well as the enantioselectivity towards the selected groups of epoxides.

Department Chemistry Student's Signature .....
Field of Study Chemistry Advisor's Signature .....
Academic Year 2011

ACKNOWLEDGEMENTS

First of all, I would like to express my deepest gratitude to my thesis advisor, Assistant Professor Dr. Aroonsiri Shitangkoon, for her support, suggestion, attention, continuous assistance, encouragement and critical proofreading during all step of this research.

I would like to thank my thesis committee members, Assistant Professor Dr. Warinthorn Chavasiri, Dr. Amarawan Intasiri and Assistant Professor Dr. Radchada Buntem for their comments and suggestions.

Furthermore, I am deeply indebted to Professor Gyula Vigh for his kind provision of cyclodextrin derivatives used in this research.

I would also like to thank the Department of Chemistry, Faculty of Science, Chulalongkorn University for providing equipment, facilities and financial support throughout the course of my study. I thank all the staffs in the Department of Chemistry for their helpfulness. Partial support from Center of Excellence on Petrochemical and Materials Technology is acknowledged.

My sincere thanks go to all my friends. Especially, I would like to thank all members in my research group for their help, cheerful and friendship.

Finally, my warmest thanks go to my family for their support, understanding and care during the entire course of study.

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LIST OF ABBREVIATIONS AND SIGNS

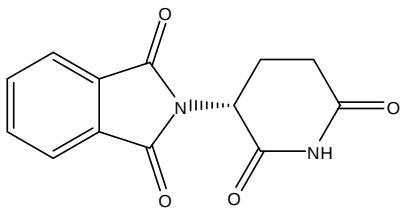
ASiAc	=	hexakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltohexaose
ASiMe	=	hexakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltohexaose
BSiAc	=	heptakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose
BSiMe	=	heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose
CD	=	cyclodextrin
CSP	=	chiral stationary phase
EN	=	electronegativity
GC	=	gas chromatography
GSiAc	=	octakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltooctaose
GSiMe	=	octakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltooctaose
i.d.	=	internal diameter
K	=	distribution coefficient
k′	=	retention factor
m	=	meter
mm	=	millimeter
OV-1701	=	7% phenyl, 7% cyanopropyl, 86% dimethyl polysiloxane
R	=	universal gas constant (1.987 cal/mol·K)
R^2	=	correlation coefficient
SD	=	standard deviation
T	=	absolute temperature (K)

Å	=	angstrom, 10^{-10} m
α	=	separation factor or selectivity
β	=	phase ratio
°C	=	degree Celsius
ΔG	=	Gibbs free energy
ΔH	=	enthalpy change of each enantiomer
$\Delta\Delta H$	=	difference in enthalpy change for an enantiomeric pair
ΔS	=	entropy change of each enantiomer
$\Delta\Delta S$	=	difference in entropy change for an enantiomeric pair
$\bar{x}$	=	mean value
μm	=	micrometer, 10^{-6} m

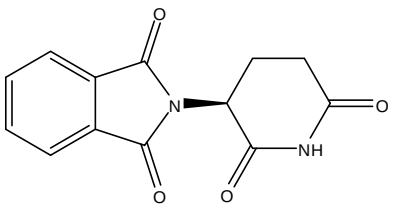
CHAPTER I

INTRODUCTION

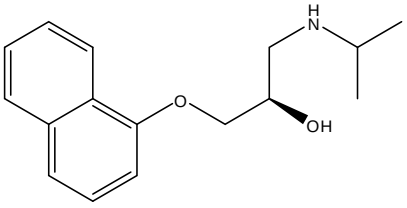
Chiral compounds are widely used in organic synthesis especially for pharmaceutical and agrochemical industries. Two stereoisomers of a chiral molecule with a non-superimposable mirror image are called enantiomers. Enantiomers have identical physical and chemical properties but may have different pharmaceutical activity, potency and toxicity in biological systems. For chiral drugs, one enantiomer may give desired property and activity, while the other enantiomer may show no activity or give undesired effects. For example, enantiomers of thalidomide have different pharmaceutical activities [1]. In the past, thalidomide was used to relieve morning sickness but babies were born with deformities due to the use of thalidomide as a racemate, equal amount of (*R*)– and (*S*)–enantiomers. Later, it was found that (*R*)–thalidomide is effective against morning sickness but (*S*)–enantiomer is teratogenic. Propanolol is another chiral drug that has identical pharmaceutical activity but different potency [1]. Both enantiomers of propanolol are used in the treatment of hypertension but (*S*)–propanolol is 130 times more active than its (*R*)–enantiomer.



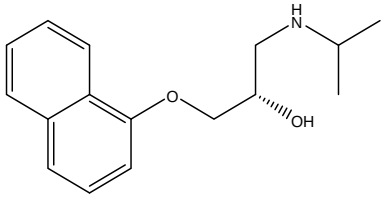
(*R*)–thalidomide



(*S*)–thalidomide



(*R*)–propanolol



(*S*)–propanolol

Figure 1.1 Structures of (*R*)– and (*S*)–enantiomers of thalidomide and propanolol

In 1992, the Food and Drug Administration (FDA, U.S.A.) and regulatory authorities in Europe, China and Japan indicated that only active enantiomer of chiral drugs could be sold in the market. The trend of marketed drug led to manufacturing the single-enantiomer drugs to replace racemic drugs. The active-enantiomer drugs can increase efficiency, decrease side effects from unwanted enantiomer and reduce waste in manufacturing. Thus, the FDA and the European committee required that manufacturers need to separate and study properties of each enantiomers before bringing drugs to the market. Hence, the separation techniques were developed for analysis of chiral intermediates or final products [1].

Common techniques for enantiomeric separation are chromatography such as gas chromatography (GC), high performance liquid chromatography (HPLC) and electrophoresis. GC is an accurate and reliable technique for separation of chiral analytes which are volatile and thermally stable organic compounds. The advantages of separation by GC are simplicity, reproducibility, high efficiency and speed of separation [2–3]. Enantiomeric separation using GC requires chiral selector or chiral stationary phase [4]. Cyclodextrins (CDs) and their derivatives are frequently used as chiral stationary phases. Enantioseparation by GC using CDs as stationary phases depends on various parameters such as size of CD, type and position of substituent on CD and structure of analytes [5].

In this study, epoxides were selected as analytes of interest because they are the building blocks in many processes of pharmaceutical, agrochemicals, flavors, fragrances, optically active polymers and chiral catalyst. An example is the synthesis of drug Solabegron [6, 7]. Styrene oxide and styrene oxide derivatives with various type and number of substituents on the aromatic ring were used as chiral analytes. Additionally, some aliphatic epoxides were studied. Since there were only a few studies on α-CDs, two types of α-CD derivatives with different types of substituent were used in this research: hexakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-α-cyclodextrin and hexakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-α-cyclodextrin. In addition, thermodynamic investigation was performed through van't Hoff equation to study the interaction between epoxides and α-CD derivatives.

Hopefully, the results from this study will provide some knowledge about the effect of analyte structure and the type of CD derivative on enantioseparation. This study would enhance the possibility of selecting the most suitable chiral stationary phase and separation condition for the chiral recognition of these epoxide analytes, including other epoxides having similar structure to the test compounds.

CHAPTER II

THEORY

2.1 Gas chromatographic separation of enantiomers

Gas chromatography (GC) is an accurate and reliable technique for separation of volatile and thermally stable compounds. The advantages of separation by GC are simplicity, reproducibility, high efficiency, sensitivity and speed of separation. Due to separation power of capillary GC, impurities and simultaneous analysis of multicomponent-mixture are separated from analyte in one analytical run. Furthermore, GC is suited for non-derivatized chiral sample and can directly separate volatile enantiomers from the vapor phase of headspace technique [2, 3]. The main application of enantioseparation by GC is concerned with the determination of enantiomeric compositions of chiral research chemicals, intermediates, auxiliaries, metabolites, precursors, drugs, pesticides, fungicides, herbicides, pheromones, flavors and fragrances [2].

The separation of enantiomers by GC can be performed either by direct or indirect approach. The indirect approach uses a chiral reagent to convert enantiomers into diastereomers which can be separated by achiral stationary phase. However, incomplete reaction between a chiral reagent and enantiomers may occur. The direct method can separate enantiomers directly on chiral stationary phase without derivatizing analytes [4]. CD derivatives are frequently used as chiral stationary phases for direct separation [5]. They are widely used in industries for enantiomers and isomers separation.

2.2 Cyclodextrins and their derivatives

CDs are natural cyclic oligosaccharide molecules composing of glucopyranose units which linked by α-(1,4) bonds. The three major CDs are α-, β- and γ-CDs which consist of 6, 7 and 8 glucose units, respectively. Their systematic names are cyclomaltohexaose, cyclomaltoheptaose and cyclomaltooctaose, respectively. The properties of three CDs are given in Table 2.1 [8, 9].

Table 2.1 Molecular dimensions and physical properties of CDs

	α-CD	β-CD	γ-CD
number of glucopyranose units	6	7	8
anhydrous molecular weight (g/mol)	972	1135	1297
number of chiral centers	30	35	40
cavity diameter (Å)	4.7–5.3	6.0–6.5	7.5–8.3
cavity volume ($Å^3$)	174	262	427
height of torus (Å)	7.9	7.9	7.9
outer diameter (Å)	14.6	15.4	17.5
water solubility (g/100 mL, 25 °C)	14.50	1.85	23.20
decomposition temperature (°C)	278	299	267

The native CD is a conical cylinder or wreath-shape truncated cone. There are two kinds of hydroxyl groups in CDs (Figure 2.1), one is the secondary hydroxyl groups (C2 and C3) located on the wider rim of the ring and the other is the primary hydroxyl groups (C6) on the narrow rim. CD cavity is relatively hydrophobic while the outside is hydrophilic. CDs are able to form inclusion complexes with a variety of analyte molecules. CDs can be modified by substituting hydroxyl groups at C2, C3 and C6 with alkyl or acyl groups. The derivatized CDs have changed size, shape and separation abilities owing to their substituents [2, 4, 10].

(a) (b)

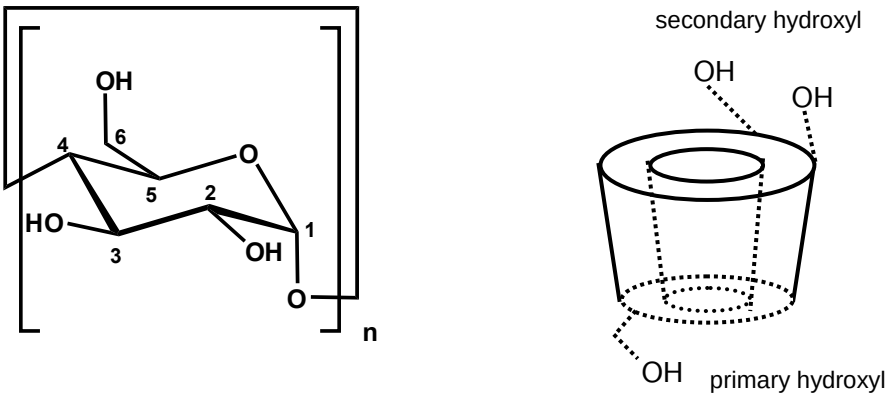


Figure 2.1 (a) Structure of cyclodextrin with n glucose units; (b) Side view of cyclodextrin showing primary and secondary hydroxyls

2.3 Gas chromatographic separation of enantiomers with cyclodextrin derivatives

Native CDs are unfavored for using as chiral stationary phases because they decompose instead of melting and have low solubility in polysiloxane diluent. Native CD column had a limited life time and poor efficiency. Hence, the native CDs were modified to improve their properties such as decomposition temperature and increased efficiency by substituting at the hydroxyl groups. The hydroxyl groups at C2 and C3 positions were substituted with small alkyl or acyl groups and hydroxyl groups at C6 position were substituted with longer alkyl or bulky groups [2, 4, 5]. CD derivatives show increased enantioselectivity over native CDs [8, 11].

Most enantioseparations occur by generating a transient diastereomeric intermediate between chiral analyte and chiral stationary phase. The recognition processes involve various interactions such as hydrogen bonds, dispersion forces, dipole-dipole interactions, electrostatic interactions and hydrophobic interactions [2]. The most characteristic property of CDs is ability to form inclusion complexes (host-guest complexes) with wide variety of guest molecules. The binding of guest molecules within the host cavity of CDs is not fixed or permanent but is a dynamic equilibrium. There are two factors affecting inclusion complex stability: the first is the

relative size between guest and host molecules and the second is thermodynamic interaction.

Enantioseparation by GC using CD derivatives as chiral stationary phases based on several parameters such as cyclodextrin ring size, position and type of substituent on cyclodextrin and analyte structures. Results from previous studies can be summarized as follow:

Vetter *et al.* [12] studied enantiomeric separation of 26 organochlorines by GC using pure heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrin (or purified β-TBDM) or randomly silylated β-TBDM as chiral stationary phases. The randomly β-TBDM resolved 24 enantiomers while the purified β-TBDM resolved only 6 compounds. Aromatic compounds showed shorter retention time on the randomly β-TBDM column while aliphatic showed shorter retention time on the purified β-TBDM column.

Takahisa and Engel [13] studied the separation of 125 enantiomers, including alcohols, ketones, esters, lactones and aromatic compounds by GC using 2,3-di-*O*-methoxymethylsilyl-γ-CD as a chiral stationary phase. The results showed that this column could separate various types of compounds, but could not separate tertiary alcohols and less volatile esters.

Špánik *et al.* [14] studies the enantioseparation of 7 *N*-trifluoroacetyl-*O*-alkyl amino acids (Figure 2.2) by GC using 2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl-α-, β-and γ-CDs (column 1, 2 and 3); 2,6-di-*O*-pentyl-3-*O*-butyryl-γ-CD (column 4) and 2,6-di-*O*-pentyl-3-*O*-propionyl-γ-CD (column 5) as chiral stationary phases. Amino acids with varied length of R_1 were better separated with larger CD of column 3 than columns 1 and 2. However, amino acids with varied length of R_2 were better separated with column 2. Changing the size of CD (columns 1-3) did not change the enantioseparation orders (D, L) of amino acids. Columns 3, 4 and 5 had the same size of CD but different substituent at C3-position. The results showed that column 3

resolved enantiomers better than columns 4 and 5. When increasing alkyl chain length, enantioselectivities were decreased.

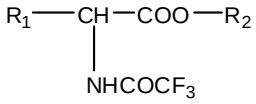
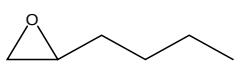


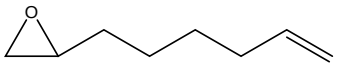
Figure 2.2 *N*-trifluoroacetyl-*O*-alkyl amino acids studied by Španik *et al.* [14]

Enantioseparation of epoxides by GC using derivatized CDs as chiral stationary phases were reviewed as follow:

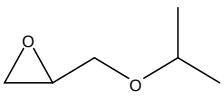
Armstrong *et al*. [15] studied the effect of size of CDs on enantiomeric separation by GC using three type of 2,6-di-*O*-pentyl-α-, β- and γ-CDs as chiral stationary phases. Most of 65 enantiomers studied, including alcohols, amino alcohols, amines, lactones, epoxides, haloalkanes, were separated on derivatized β-CD column. However, seven epoxides in their study were separated on derivatized α-CD column.



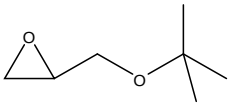
1,2-epoxyhexane



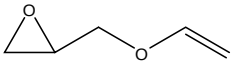
1,2-epoxyoct-7-ene



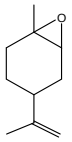
glycidyl isopropyl ether



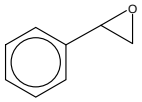
tert-butyl glycidyl ether



allyl glycidyl ether



limonene oxide



styrene oxide

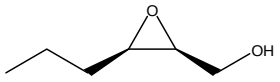
Figure 2.3 Epoxides studied by Armstrong *et al*. [15]

Li *et al*. [16] studied the effect of size of cyclodextrins on enantiomeric separation by GC using 2,3-di-*O*-pentyl-3-*O*-trifluoroacetyl-α-, β- and γ-CDs as chiral stationary phases. More than 150 enantiomeric pairs such as alcohols, amino alcohols, amines, haloalkanes, epoxides and lactones were resolved. About 80 % of tested compounds were resolved on γ-CD column, 60 % on β-CD column and 30 % on α-

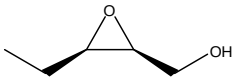
CD column. For separations of epoxides, the results could not be concluded as the structures of epoxide were varied and a small change in their structures affected enantioseparation.

Reiher and Hamann [17] studied the effect of structure of aliphatic and aromatic epoxides and alcohols on enantiomeric separation by GC using 2,3,6-tri-*O*-pentyl-α-CD as chiral stationary phase. From twelve epoxides in their study, this column could not separate most of aliphatic epoxides: 1,2-epoxyheptane; 1,2-epoxyoctane; 1,2-epoxydecane and 2,3-epoxy-1,1-dimethyl-propan-1-ol. Aromatic epoxides, such as styrene oxide and 1,2-epoxy-3-phenylpropane, could not be separated as well.

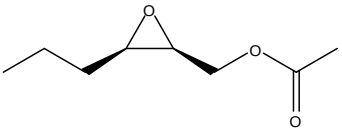
Shi *et al*. [18] studied the effect of substituent type and position on CD ring on enantiomeric separation of 7 aliphatic epoxides by GC on four types of β-CD derivatives: 2,6-di-*O*-benzyl-3-*O*-heptanonyl-β-CD (column 1); 2,6-di-*O*-benzyl-3-*O*-octanonyl-β-CD (column 2); 2,3-di-*O*-benzyl-6-*O*-heptanonyl-β-CD (column 3) and 2,3-di-*O*-benzyl-6-*O*-octanonyl-β-CD (column 4). Columns 1 and 2 had different substituent at C3-position, while columns 3 and 4 had different substituent at C6-position. The results showed that column 1 could resolve enantiomers of 6 epoxides while column 2 resolved only 1 epoxide. Columns 3 and 4 showed similar enantioseparation abilities.



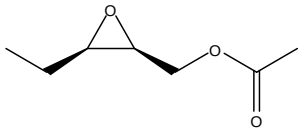
cis-2,3-epoxy-1-hexanol



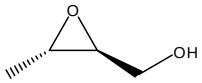
cis-2,3-epoxy-1-pentanol



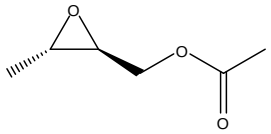
cis-2,3-epoxy-1-hexyl acetate



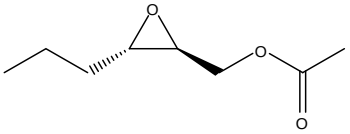
cis-2,3-epoxy-1-pentyl acetate



trans-2,3-epoxy-1-butanol



trans-2,3-epoxy-1-butyl acetate



trans-2,3-epoxy-1-hexyl acetate

Figure 2.4 Aliphatic epoxides studied by Shi *et al*. [18]

Systematic enantioseparation of epoxides by GC using derivatized CDs as chiral stationary phases were reviewed as follow:

Yanchinda [19] studied enantioseparation of 43 styrene oxides by GC using 2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl-β-CD (BSiMe) and 2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-β-CD (BSiAc) as chiral stationary phases. The trend for the enantioseparation was quite obvious for mono-substituted styrene oxides. The substituent position strongly affected the separation of enantiomers than the substituent type. The substituent at *ortho*- or *para*-substituted styrene oxides were well separated on BSiMe column whereas *meta*-substituted styrene oxides were resolved well on BSiAc column.

Assavachartthongchai [20] studied enantioseparation of 43 styrene oxides and 6 aliphatic epoxides by GC using 2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl-γ-CD (GSiMe) and 2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl-γ-CD (GSiAc) as chiral stationary phases. For 43 styrene oxides, GSiMe column resolved 35 compounds while GSiAc column resolved 40 compounds. Both columns showed similar

enantioseparation abilities and resolved *ortho*-substituted styrene oxides better than mono-substituted styrene oxides at *meta*- or *para*-position. For aliphatic epoxides, GSiAc column separated only 1 epoxide (1,2-epoxy-5-hexene) while GSiMe could not separate any aliphatic epoxides studied.

2.4 Thermodynamic investigation of enantiomers separation by gas chromatography

Although the enantioseparation mechanism is still unclear, some mechanic aspects can be derived from thermodynamic investigations involving thermodynamic parameters (e.g. enthalpy, entropy, Gibb free energy, etc.). Temperature is the important factor influencing the retention factor, enantioselectivity and resolution. Thus, a change in temperature can be used to optimize enantioseparation.

In the direct enantiomer separation, the formation of reversible diastereomeric associates or complexes are created by intermolecular interactions of enantiomers with a chiral selector. This formation process can be characterized by Gibbs-Helmholtz thermodynamic parameters [2, 21].

From van't Hoff equation [21], the difference in Gibbs free energy, $\Delta\Delta G$, is calculated form the separation factor (α) obtained from enantiomeric separation on a chiral column at a given temperature according to general equation (1):

$$-\Delta\Delta G = RT \cdot \ln \alpha = RT \cdot \ln \left(\frac{k'_2}{k'_1}\right) \qquad (1)$$

where α is the separation factor or selectivity and is calculated from the ratio of k' of two enantiomers

k' is the retention factor or capacity factor of each enantiomer calculated from solute retention time according to

$$\frac{t_R - t_M}{t_M}$$

t_R is the retention time of an enantiomer or analyte

t_M is the time for unretained compound to travel at the same distance as analyte

R it the universal gas constant (1.987 cal/mol·K)

T is the absolute temperature (K)

1,2 refer to the less and the more retained enantiomers.

Combining equation (1) with the Gibbs-Helmholtz relationship, equation (2), leads to equation (3):

$$-\Delta\Delta G = -\Delta\Delta H + T \cdot \Delta\Delta S \quad (2)$$

$$RT \cdot \ln \alpha = -\Delta\Delta H + T \cdot \Delta\Delta S \quad (3)$$

From equation (3), the following equation can be rewritten

$$\ln \alpha = \frac{-\Delta\Delta H}{RT} + \frac{\Delta\Delta S}{R} \quad (4)$$

where $\Delta\Delta H$ is the difference in enthalpy values for enantiomeric pairs

$\Delta\Delta S$ is the difference in entropy values for enantiomeric pairs

According to equation (4), $\Delta\Delta H$ and $\Delta\Delta S$ could be evaluated from the slope and y-intercept of the ln α versus 1/T plot. However, the calculations of thermodynamic parameters from these plots are not possible, as a result of curvatures observed in many cases. This is due to the nonlinear dependence of selectivity on the concentration in diluted stationary phase. Therefore, this method is only valid for undiluted chiral selectors [21].

Alternatively, thermodynamic parameters can be calculated from retention factors (k′) instead of separation factors (α). The linear relationship between ln k′ and 1/T can be derived from the combination of equations (5) and (6) resulted in equation (7). Thermodynamic parameters of individual enantiomers can be obtained from van’t

Hoff plot of ln k′ against 1/T. Subsequently, the differences in enthalpy and entropy of two enantiomers can be achieved.

$$-\Delta G = RT \cdot \ln K = RT \cdot \ln (k' \cdot \beta) \tag{5}$$

$$\Delta G = \Delta H - T \cdot \Delta S \tag{6}$$

$$-\Delta H + T \cdot \Delta S = RT \cdot \ln (k' \cdot \beta)$$

$$\frac{-\Delta H}{RT} + \frac{\Delta S}{R} = \ln k' + \ln \beta$$

$$\ln k' = \frac{-\Delta H}{RT} + \frac{\Delta S}{R} - \ln \beta \tag{7}$$

where K is the distribution constant of chiral analyte (selectand) between the gas and the liquid phases.

β is a constant called phase ratio (the ratio of mobile phase volume to stationary phase volume).

ΔH is enthalpy change resulting from the interaction of the enantiomer with the stationary phase. ΔH value describes the degree of the strength of the interaction. The more negative the ΔH value, the higher the strength of the interaction and larger the retention in the column.

ΔS is entropy change resulting from the interaction of the enantiomer with the stationary phase. ΔS value describes the degree to which the structure of the solute influences the interaction.

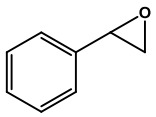
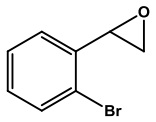
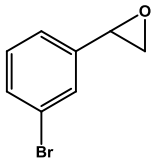
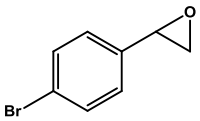
CHAPTER III

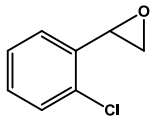
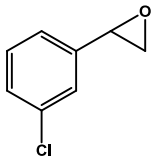
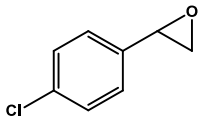
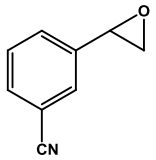
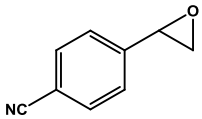
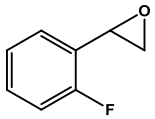
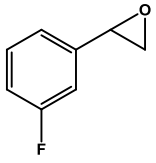
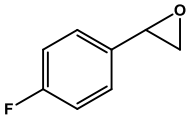
EXPERIMENTAL

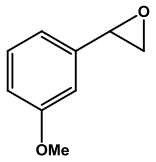
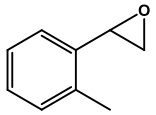
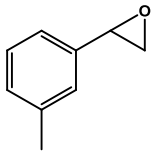
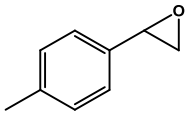
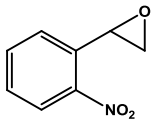
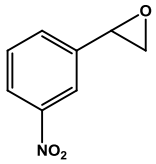
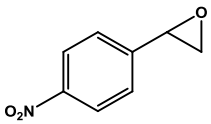
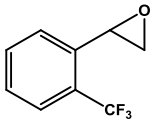
3.1 Epoxides

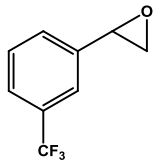
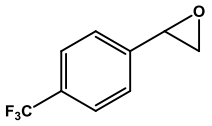
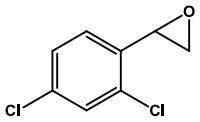
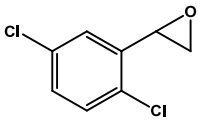
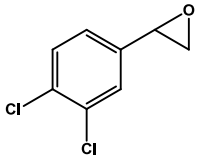
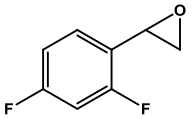
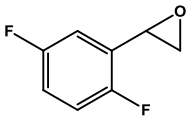
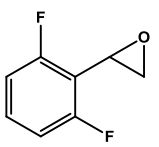
Most of styrene oxides used in this study were obtained from the study of Yanchinda [19]. Some aromatic epoxides and all aliphatic epoxides were purchased from Aldrich, U.S.A. The compound names, abbreviations and chemical structures of epoxide derivatives were shown in Table 3.1.

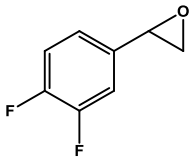
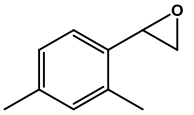
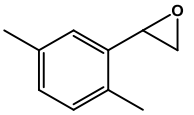
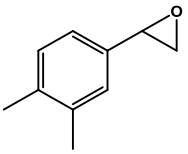
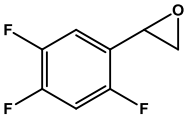
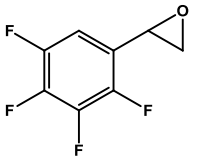
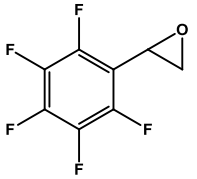
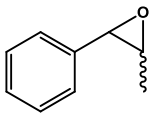
Table 3.1 Chemical structures and abbreviations of epoxides

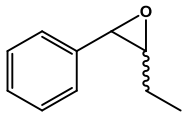
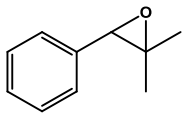
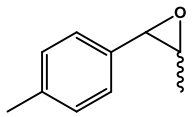
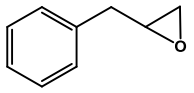
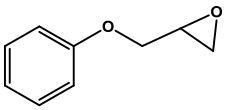
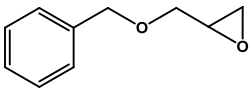
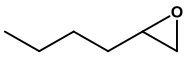
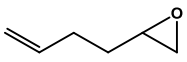
compound	abbreviation	chemical structure
styrene oxide [96-09-3], 97%, Fluka	**1**	
Group 1: mono-substituted styrene oxides		
2-bromostyrene oxide	**2Br**	
3-bromostyrene oxide	**3Br**	
4-bromostyrene oxide	**4Br**	

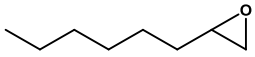
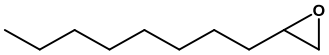
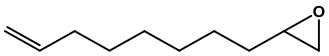
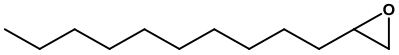
compound	abbreviation	chemical structure
2-chlorostyrene oxide	**2Cl**	
3-chlorostyrene oxide	**3Cl**	
4-chlorostyrene oxide	**4Cl**	
3-cyanostyrene oxide	**3CN**	
4-cyanostyrene oxide	**4CN**	
2-fluorostyrene oxide	**2F**	
3-fluorostyrene oxide	**3F**	
4-fluorostyrene oxide	**4F**	

compound	abbreviation	chemical structure
3-methoxystyrene oxide	**3OMe**	
2-methylstyrene oxide	**2Me**	
3-methylstyrene oxide	**3Me**	
4-methylstyrene oxide	**4Me**	
2-nitrostyrene oxide	**2NO**	
3-nitrostyrene oxide	**3NO**	
4-nitrostyrene oxide	**4NO**	
2-(trifluoromethyl)styrene oxide	**2CF**	

compound	abbreviation	chemical structure
3-(trifluoromethyl)styrene oxide	**3CF**	
4-(trifluoromethyl)styrene oxide	**4CF**	
Group 2: di-substituted styrene oxides		
2,4-dichlorostyrene oxide	**24Cl**	
2,5-dichlorostyrene oxide	**25Cl**	
3,4-dichlorostyrene oxide	**34Cl**	
2,4-difluorostyrene oxide	**24F**	
2,5-difluorostyrene oxide	**25F**	
2,6-difluorostyrene oxide	**26F**	

compound	abbreviation	chemical structure
3,4-difluorostyrene oxide	**34F**	
2,4-dimethylstyrene oxide	**24Me**	
2,5-dimethylstyrene oxide	**25Me**	
3,4-dimethylstyrene oxide	**34Me**	
Group 3: other aromatic epoxides		
2,4,5-trifluorostyrene oxide	**triF**	
2,3,4,5-tetrafluorostyrene oxide	**tetraF**	
2,3,4,5,6-pentafluorostyrene oxide	**pentaF**	
phenylpropylene oxide	**2**	

compound	abbreviation	chemical structure
phenylbutylene oxide	**3**	
phenylisopropylene oxide	**4**	
4-methylphenylpropylene oxide	**5**	
(2,3-epoxypropyl)benzene [4436-24-2], 98%	**6**	
1,2-epoxy-3-phenoxypropane [122-60-1], 99%	**7**	
benzyl glycidyl ether [89616-40-0], 99%	**8**	
Group 4: aliphatic epoxides		
1,2-epoxyhexane [1436-34-6], 97%	**hexa**	
1,2-epoxy-5-hexene [10353-53-4], 97%	**5hexe**	

compound	abbreviation	chemical structure
1,2-epoxyoctane [2984-50-1], 96%	**octa**	
1,2-epoxydecane [2404-44-6], 95%	**deca**	
1,2-epoxy-9-decene [85721-25-1], 96%	**9dece**	
1,2-epoxydodecane [2855-19-8], 95%	**dodec**	

3.2 Gas chromatographic analysis

All chromatographic analyses were performed on an Agilent 6890 gas chromatograph equipped with a split injection at 250 °C and a flame ionization detector (FID) at 250 °C. Carrier gas was hydrogen at average linear velocity of 50 cm/s. The separation was carried out on the 15 m × 0.25 mm i.d. capillary column coated with 0.25 μm thick film of stationary phase. Two types of stationary phase were used in this study:

- ASiMe column : 26.7% hexakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltohexaose in polysiloxane OV-1701
- ASiAc column : 30.2% hexakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltohexaose in polysiloxane OV-1701

These chiral columns were conditioned at 220 °C until a stable baseline was observed. Each epoxide was dissolved in hexane. Approximately 0.2–0.4 μL of solution was injected at least in duplicate with a split ratio of 100:1.

All thermodynamic studies were performed isothermally in the temperature range of 50–210 °C at 10 °C interval. From chromatograms, retention factors and enantioselectivities of all analytes were calculated. Plots of ln k′ *vs.* 1/T were constructed and used to determine thermodynamic parameters from van't Hoff equation.

CHAPTER IV

RESULTS AND DISCUSSION

4.1 Gas chromatographic separation of epoxides

All enantiomers of aromatic epoxides and aliphatic epoxides were analyzed on ASiMe and ASiAc columns. They were performed isothermally in the temperature range of 50–210 °C with 10 °C increments. The retention factor (k') and enantioselectivity (α) could be obtained from chromatograms at each operating temperature. All racemic epoxides could be separated into their enantiomers on at least one column except benzyl glycidyl ether (**8**) and 1,2-epoxydodecane (**dodec**).

The trends of enantioselectivity values were depending on type, number, and position of analyte substituent. Since the physical properties of analytes, such as boiling point or polarity, were varied, retention factors, and enantioselectivities of analytes at a specific temperature could not be directly compared. Therefore, thermodynamic parameters (enthalpy and entropy values) obtained over a temperature range would be investigated to provide better understanding about interactions between analytes and stationary phases.

4.2 Thermodynamic investigation

Thermodynamic parameters associated with the analyte and stationary phase interactions could be acquired through the van't Hoff plot. All ln k´ versus 1/T plots were linear with correlation coefficient (R^2) values greater than 0.9988. The enthalpy (ΔH) and entropy (ΔS) values for each enantiomer could be calculated from the slope and y-intercept of these plots, respectively. When the enantiomers were separated, the enthalpy and entropy differences ($\Delta\Delta H$ and $\Delta\Delta S$) could be calculated from the differences in ΔH and ΔS values of two enantiomers.

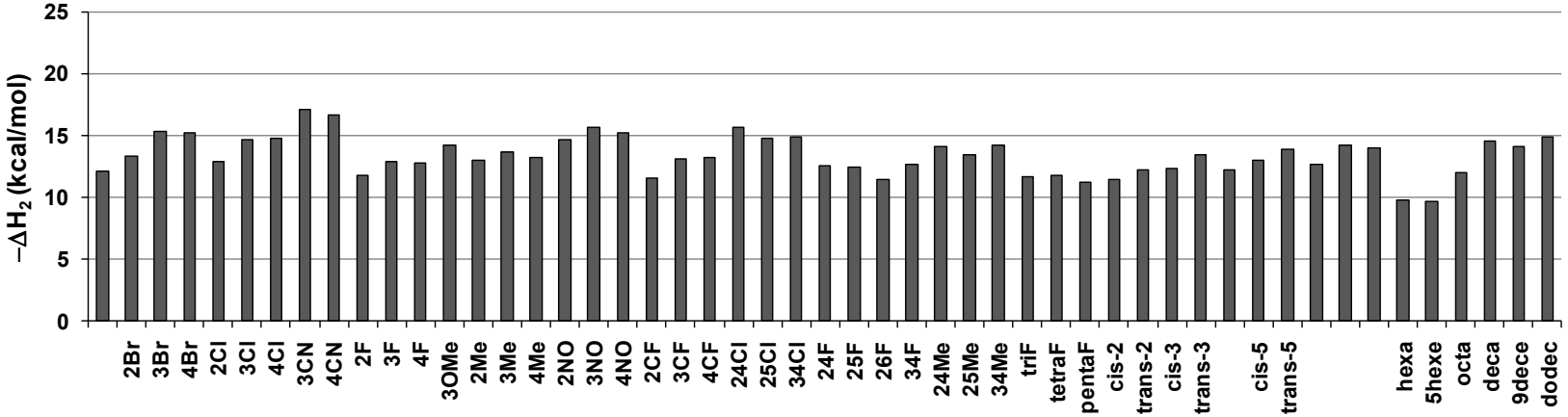
In order to better understand the influence of size of CD ring, thermodynamic values of epoxides obtained from ASiMe and ASiAc columns in this study were compared with results obtained from β- and γ-cyclodextrin derivatives (BSiMe, BSiAc, GSiMe, and GSiAc) [19, 20].

4.2.1 Enthalpy change (−ΔH) and entropy change (−ΔS)

The enthalpy change (−ΔH) represents the strength of interaction between an analyte and a stationary phase. The larger the −ΔH value (more negative value), the stronger the interaction. The entropy change (−ΔS) is the loss of degree of freedom associated with the interaction between an analyte and a stationary phase.

The enthalpy ($-\Delta H_2$) and entropy ($-\Delta S_2$) values of more retained enantiomers of all epoxides on ASiMe and ASiAc columns were shown in Figures 4.1 and 4.2, respectively. The −ΔH and −ΔS values on the same column showed similar trend. On ASiMe column, all analytes exhibited average $-\Delta H_2$ values of 13.37 ± 1.58 kcal/mol. On ASiAc column, all analytes exhibited average $-\Delta H_2$ values of 11.55 ± 1.11 kcal/mol. The average enthalpy ($-\Delta H_2$) value attained from ASiMe column were higher than the values from ASiAc column, indicating stronger interaction towards ASiMe. Among methyl-derivatized CDs, the average $-\Delta H_2$ slightly decreased from ASiMe > BSiMe > GSiMe as the CD ring size increased. While the trend for acetyl-derivatized CDs was different, the average $-\Delta H_2$ decrease from BSiAc > GSiAc > ASiAc.

(a)



(b)

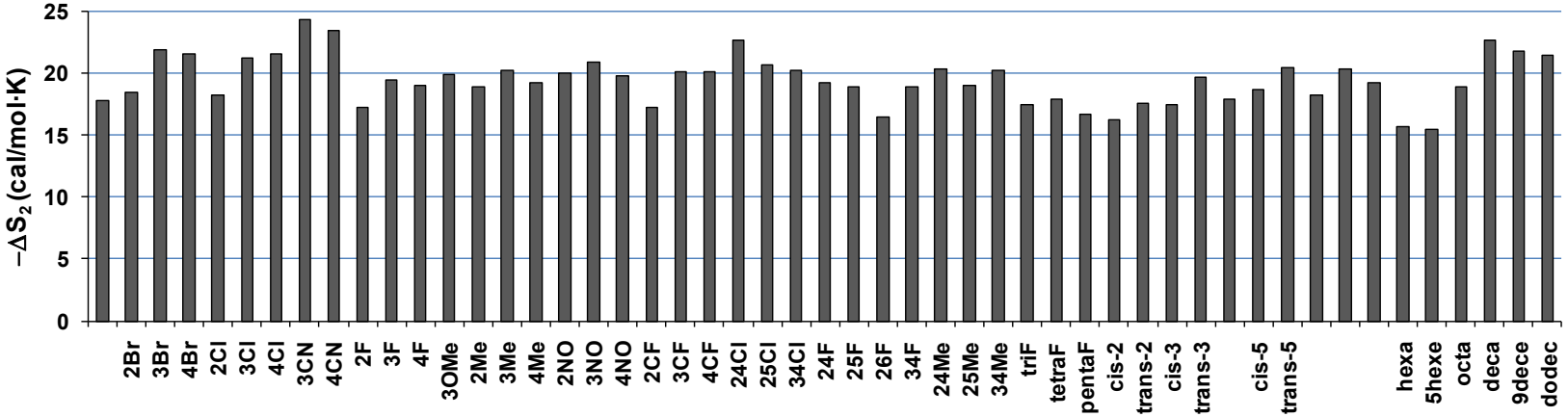
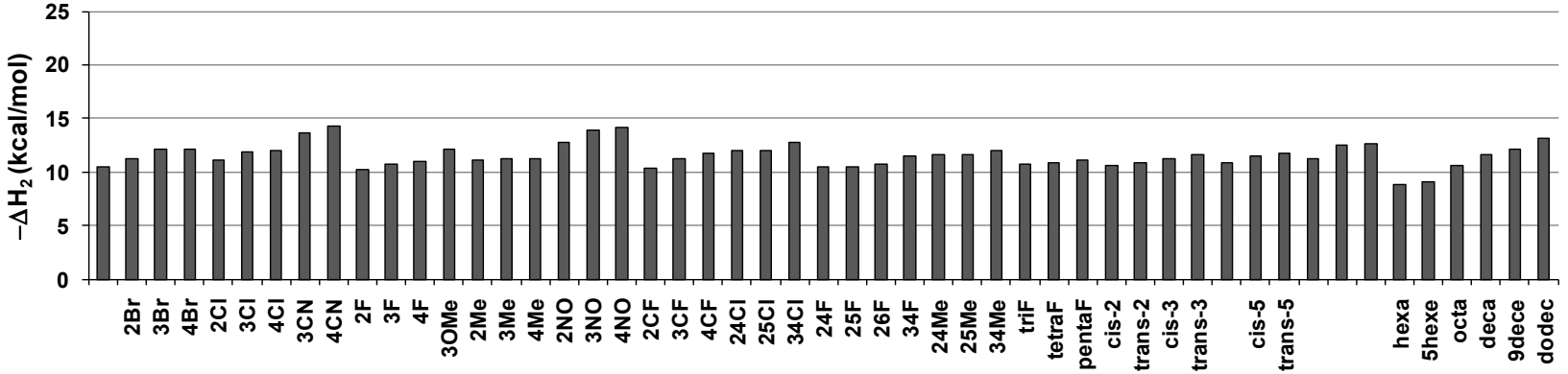


Figure 4.1 Thermodynamic values of the more retained enantiomers of epoxide on ASiMe column: (a) enthalpy change ($-\Delta H_2$), $\bar{x}$ = 13.37 ± 1.58 kcal/mol; (b) entropy change ($-\Delta S_2$), $\bar{x}$ = 19.46 ± 1.95 cal/mol·K.

(a)



(b)

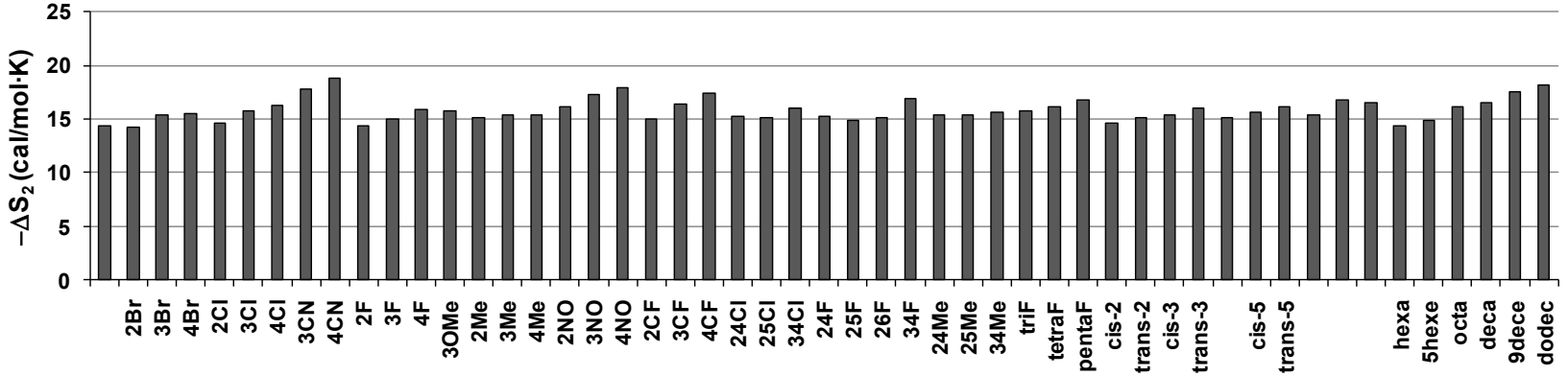
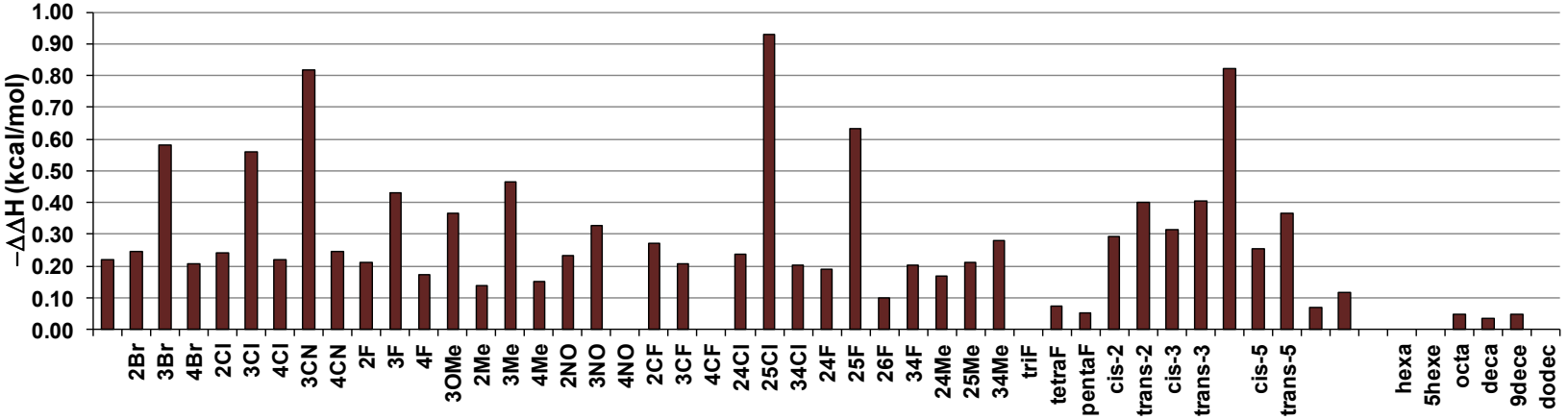


Figure 4.2 Thermodynamic values of the more retained enantiomers of epoxide on ASiAc column: (a) enthalpy change ($-\Delta H_2$), $\bar{x}$ = 11.55 ± 1.11 kcal/mol; (b) entropy change ($-\Delta S_2$), $\bar{x}$ = 15.84 ± 1.05 cal/mol·K.

4.2.2 Enthalpy difference (−ΔΔH) and entropy difference (−ΔΔS)

The −ΔΔH and −ΔΔS values were calculated from the difference in −ΔH and −ΔS values of each enantiomer obtained from van't Hoff plot. The −ΔΔH and −ΔΔS values of all epoxides on ASiMe and ASiAc columns were shown in Figures 4.3 and 4.4, respectively. Styrene oxide (compound **1**) was regarded as a reference analyte among aromatic epoxides. The influence of type, number, and position of substituent on enantioseparation was systematically explored and discussed through the thermodynamic values. The −ΔΔH and −ΔΔS values from the same column showed the similar trend on both columns; therefore, the discussion on enantioseparation would be mentioned through −ΔΔH values only. Due to the difference in analyte structure of all epoxides, the discussion on enantioseparation would be classified into four groups according to the similarity of analyte structure.

(a)



(b)

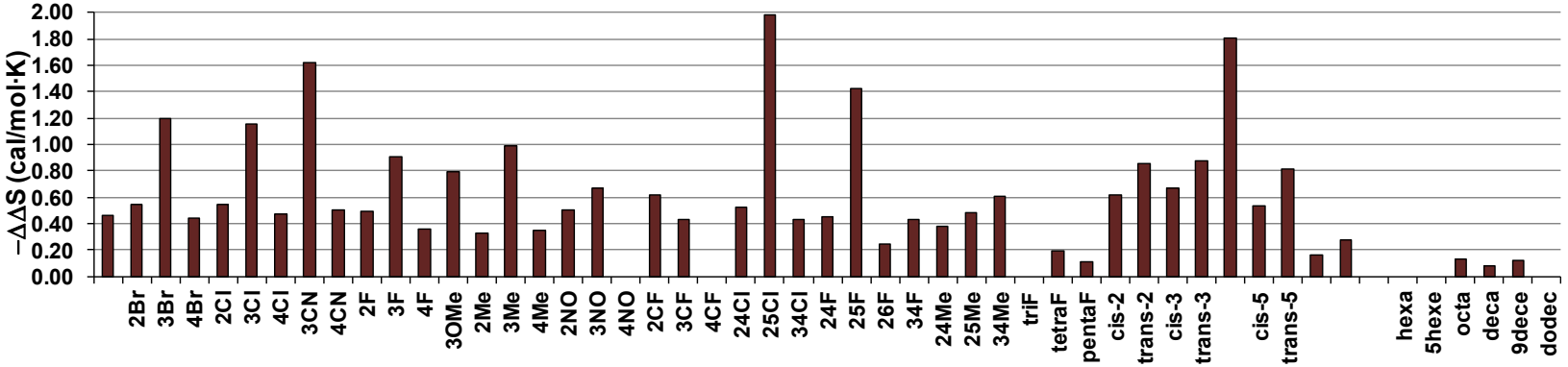
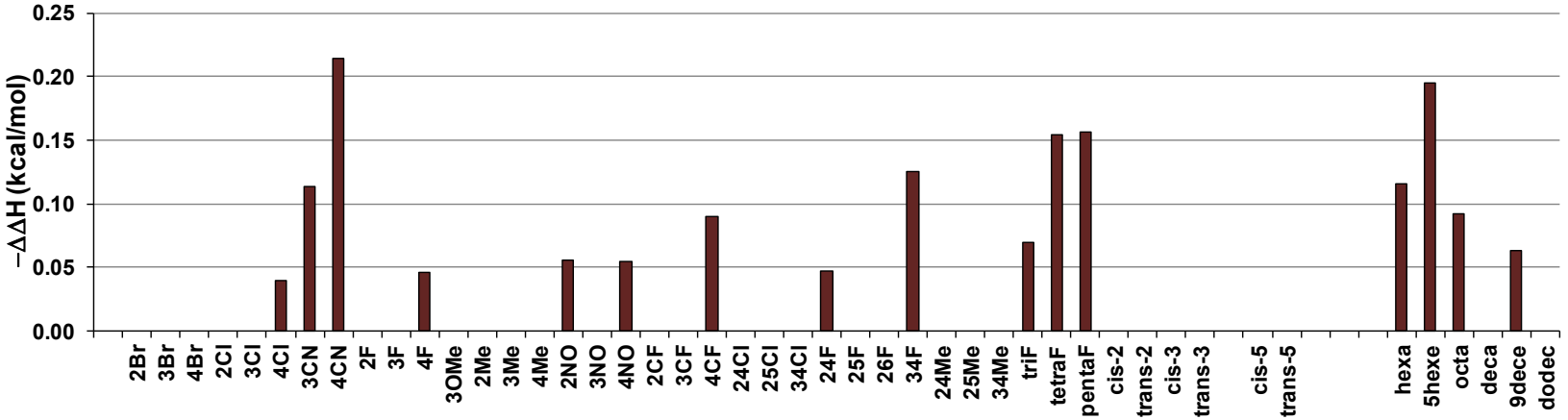


Figure 4.3 (a) Enthalpy difference (–ΔΔH) and (b) entropy difference (–ΔΔS) of the enantiomers of epoxide on ASiMe column.

(a)



(b)

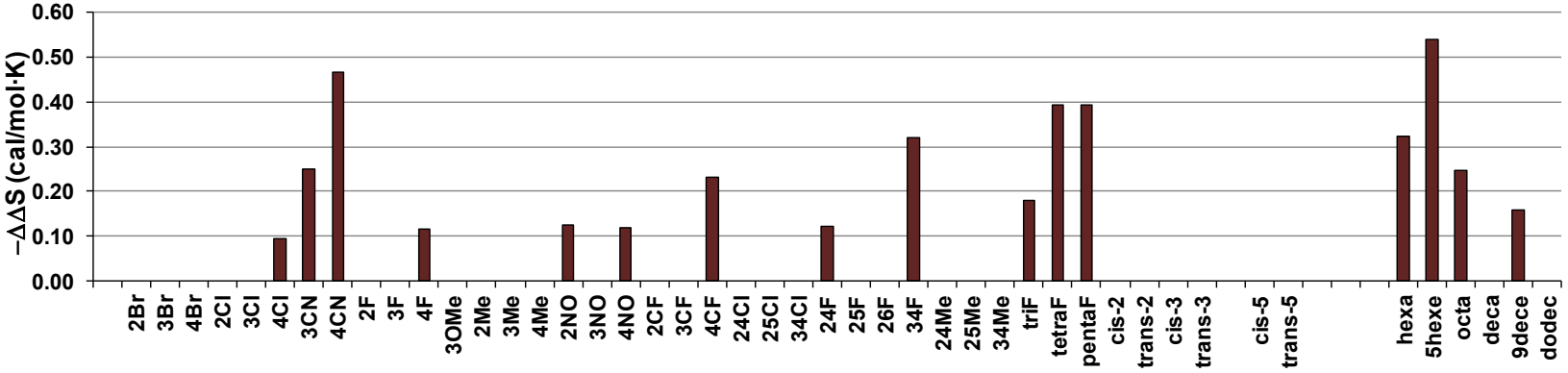
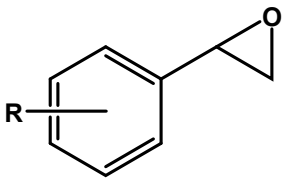


Figure 4.4 (a) Enthalpy difference (−ΔΔH) and (b) entropy difference (−ΔΔS) of the enantiomers of epoxide on ASiAc column.

Group 1: Styrene oxides with mono-substitution on the aromatic ring

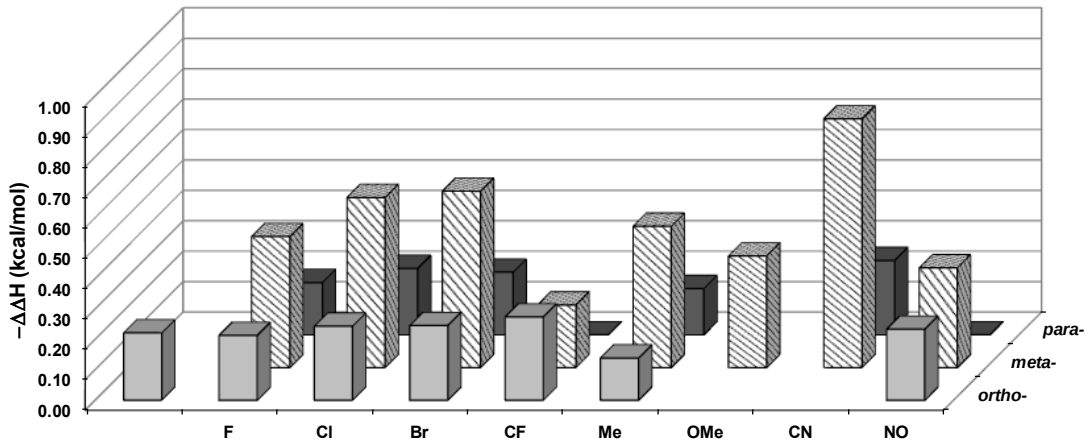


R = F, Cl, Br, CF_3, CH_3, OCH_3, CN, NO_2

Group 1 epoxides contain twenty-one styrene oxides with mono-substitution on the aromatic ring at *ortho*-, *meta*-, or *para*-position as shown above. The $-\Delta\Delta H$ values of enantiomers of all analytes in this group on ASiMe and ASiAc columns were displayed in Figure 4.5.

From Figure 4.5, it was clear that enantioseparation of group 1 epoxides mainly depended on the position of substitution on both columns. Using ASiMe column, all analytes were enantioseparated except for 4-(trifluoromethyl) styrene oxide (**4CF**) and 4-nitrostyrene oxide (**4NO**), both with substitution at *para*-position. Compared to styrene oxide (**1**), most analytes with mono-substitution exhibited higher $-\Delta\Delta H$ values than **1**, however, the degree of enantioseparation varied depending on type and position of substitution. Considering the influence of substitution position, styrene oxides with *meta*-substitution showed higher $-\Delta\Delta H$ values than *ortho*- or *para*-substituted styrene oxides. Among eight *meta*-substituted analytes, 3-cyanostyrene oxide (**3CN**) showed the highest $-\Delta\Delta H$ value and the best enantioseparation. The $-\Delta\Delta H$ values were mostly in the order of *meta* >> *ortho* > *para*. Exception was found for trifluoromethyl-substituted styrene oxides with $-\Delta\Delta H$ values in the order of *ortho* > *meta* > *para*. Attempts were made to correlate $-\Delta\Delta H$ values to physical properties of analytes. It was found that $-\Delta\Delta H$ values might relate to electronegativity (EN) value only for halogen-substituted styrene oxides at *meta*-position. The $-\Delta\Delta H$ values of **3F**, **3Cl**, and **3Br** increased from 0.43, 0.56, and 0.58 kcal/mol, respectively, with the decreasing EN values (EN_F = 3.95, EN_{Cl} = 3.03, EN_{Br} = 2.80) [22].

(a)



(b)

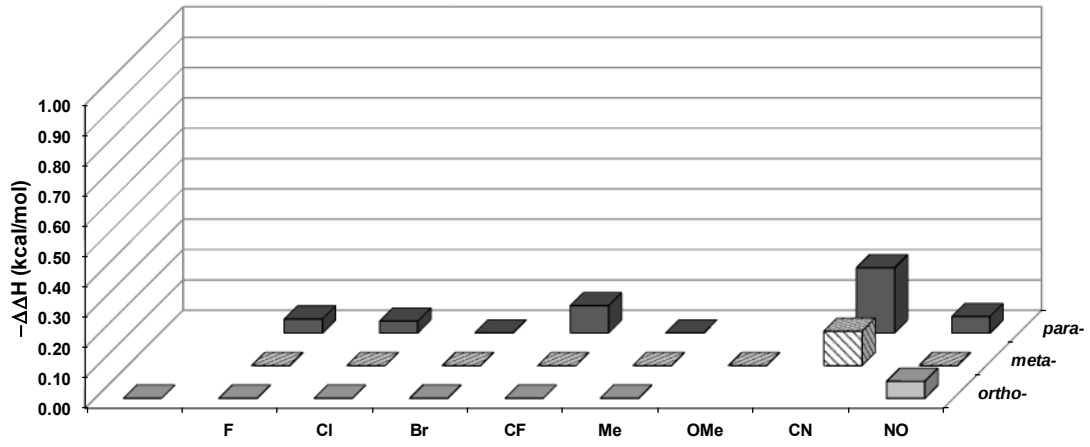


Figure 4.5 Enthalpy differences of the enantiomers of mono-substituted styrene oxides on (a) ASiMe and (b) ASiAc columns.

Enantioseparation on ASiAc column was quite different from those on ASiMe column. Enantiomers of styrene oxide and several mono-substituted styrene oxides could not be separated on ASiAc column. Only seven mono-substituted styrene oxides (**4F**, **4Cl**, **4CF**, **3CN**, **4CN**, **2NO**, and **4NO**) could be enantioseparated, most of them were *para*-substituted styrene oxides. Furthermore, styrene oxide as well as all bromo-, methyl-, and methoxy-substituted styrene oxides could not be enantioseparated on this column. In addition, the $-\Delta\Delta H$ values obtained from ASiAc column were less than those from ASiMe column.

The influences of temperature towards retention (k′) and enantioselectivity (α) of analytes on ASiMe column were demonstrated in Figures 4.6–4.7. As seen from Figure 4.6, plots of $\ln k'_2$ versus 1/T of three bromo-substituted styrene oxides on ASiMe column were compared. At the same temperature, **3Br** and **4Br** were more retained than **2Br** (higher k'_2 values) and, thus, leading to longer analysis time. However, the retention of analytes did not always correlate to enantioselectivity. As seen from Figure 4.7, plots of $\ln \alpha$ versus 1/T of three bromo-substituted styrene oxides on ASiMe column were compared. The highest enantioselectivity was observed for **3Br** at all temperature studied. As the temperature decreased, the enantioselectivities of all three analytes improved. However, temperature has more influence on the enantioselectivity of **3Br** than on **2Br** or **4Br**, as seen from its sharper slope. As shown in Figure 4.8, the temperature decrease by 10 °C could significantly improve the enantioselectivity of **3Br**, compared to **2Br** or **4Br**. While **4Br** retained the longest, its enantioselectivity was similar to that of shortest-retained analyte, **2Br**.

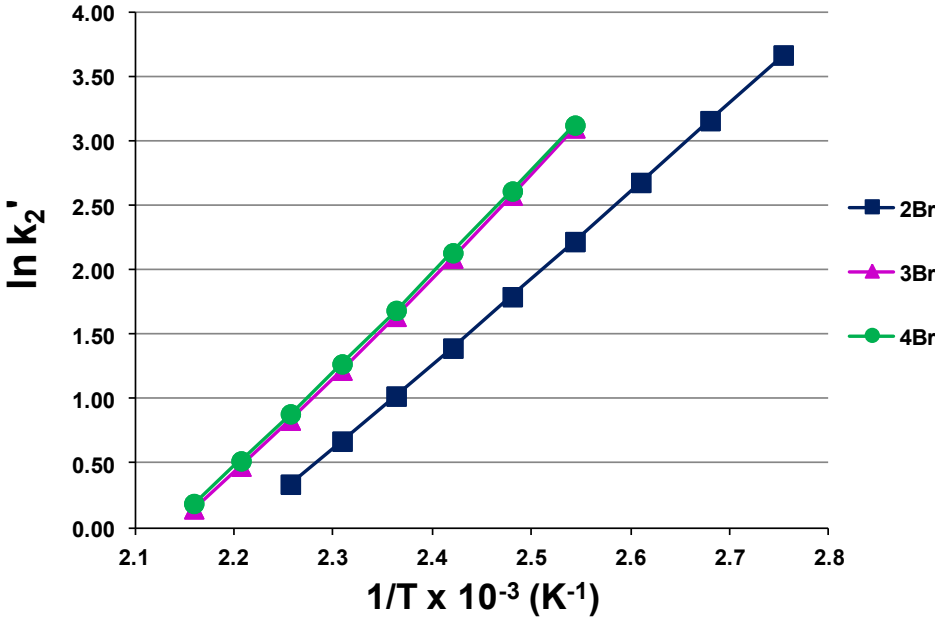


Figure 4.6 Plots of ln k_2' versus 1/T of **2Br**, **3Br**, and **4Br** on ASiMe column.

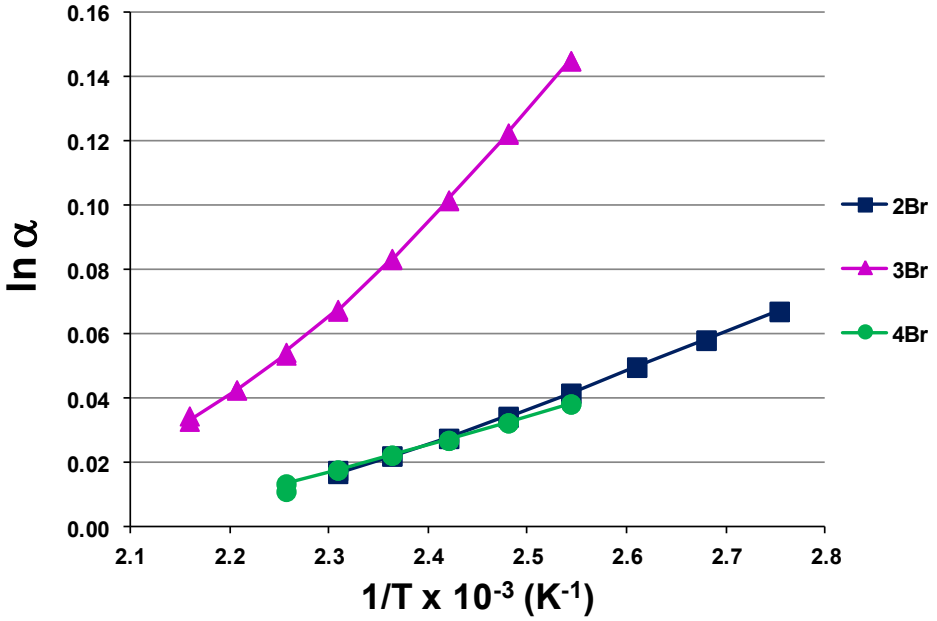


Figure 4.7 Plots of ln α versus 1/T of **2Br**, **3Br**, and **4Br** on ASiMe column.

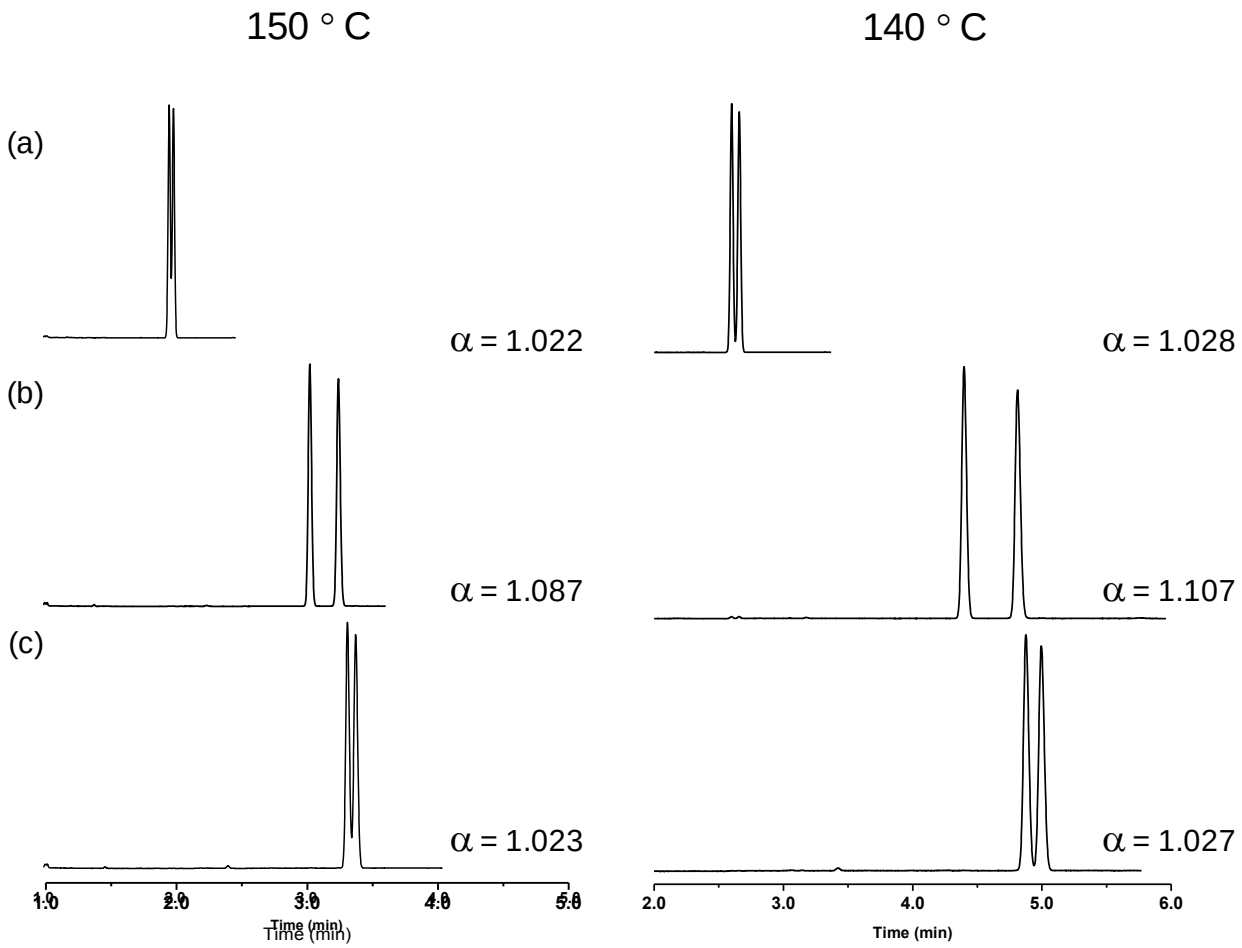


Figure 4.8 Chromatograms of (a) **2Br**, (b) **3Br**, (c) **4Br** on ASiMe column at (left) 150 °C and (right) 140 °C.

From Figure 4.9, plots of ln α versus 1/T of **2Cl** and **4CN** on ASiMe column were parallel with the same slope. That means temperature has the same influence on the enantioselectivity of both **2Cl** and **4CN**, as indicated by similar –ΔΔH values (Figure 4.5(a)). However, the enantioselectivity of **4CN** was higher than that of **2Cl** at every temperature, indicating better enantioseparation. The results suggested that several parameters must be considered simultaneously in selecting appropriate separation condition.

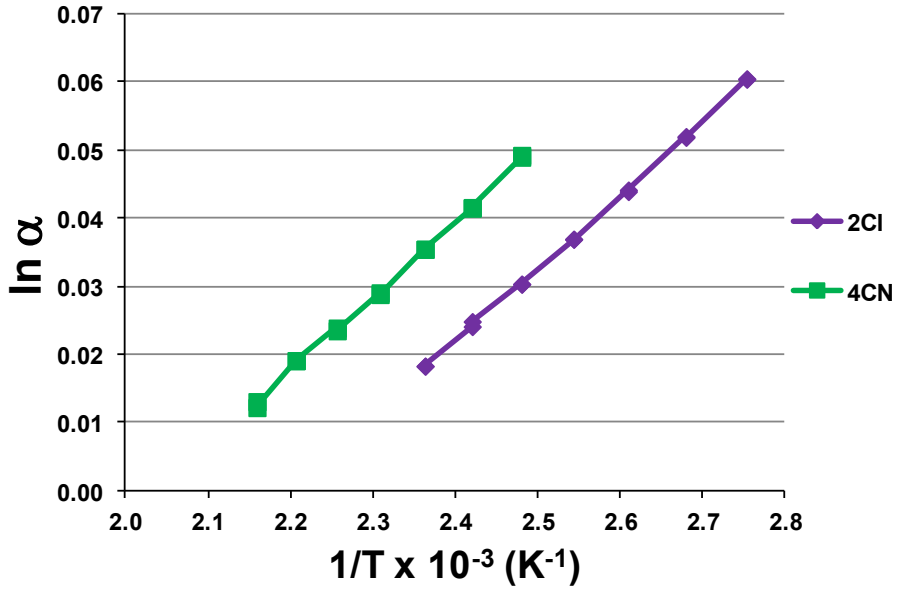
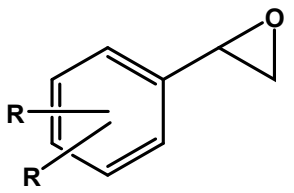


Figure 4.9 Plots of ln α versus 1/T of **2Cl** and **4CN** on ASiMe column.

Thermodynamic values of group 1 epoxides obtained from ASiMe and ASiAc columns in this study were compared to values obtained from larger CD derivatives (BSiMe, BSiAc, GSiMe, and GSiAc columns) obtained previously [19, 20]. Considering the analyte structure, it was found that the position of substitution had more influence on enantiosepartion than the type of substitution. For example, *meta*-substituted analytes were better enantioseparated with ASiMe column, they showed poor enantioseparation on BSiMe column. GSiMe column gave good enantioseparation towards *ortho*-substituted analytes. For acetyl-substituted CDs, BSiAc and GSiAc columns could enantioseparated most analytes, ASiAc column showed poor enantioseparation towards most analytes. The results obtained also suggested the influence of the size of CD ring as well.

Group 2: Styrene oxides with di-substitution on the aromatic ring

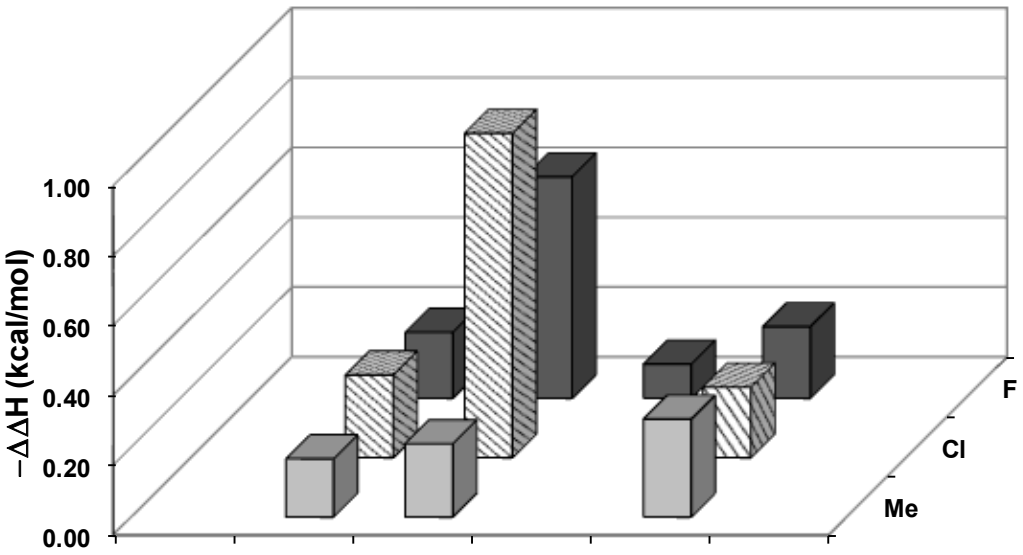


R = CH_3, Cl, F

Group 2 epoxides contain ten styrene oxides with di-substitution of chloro-, fluoro-, or methyl-groups on the aromatic ring as shown above. All isomers of di-substituted analytes could not be attained due to the unavailability of starting materials. The $-\Delta\Delta H$ values of di-substituted styrene oxides on two columns were compared in Figure 4.10.

All di-substituted styrene oxides could be enantioseparated on ASiMe column. On the contrary, only two analytes (**24F** and **34F**) could be enantioseparated on ASiAc column. On ASiMe column, the $-\Delta\Delta H$ values of all di-substituted styrene oxides were similar to or better than $-\Delta\Delta H$ value of reference epoxide (**1**). Notably, high $-\Delta\Delta H$ values were observed for chloro- and fluoro-substituted styrene oxides at 2,5-position (**25Cl** and **25F**), but not for methyl derivative (**25Me**). The effects of type and position of substituent of di-substituted styrene oxides were not apparent as those of mono-substituted styrene oxides.

(a)



(b)

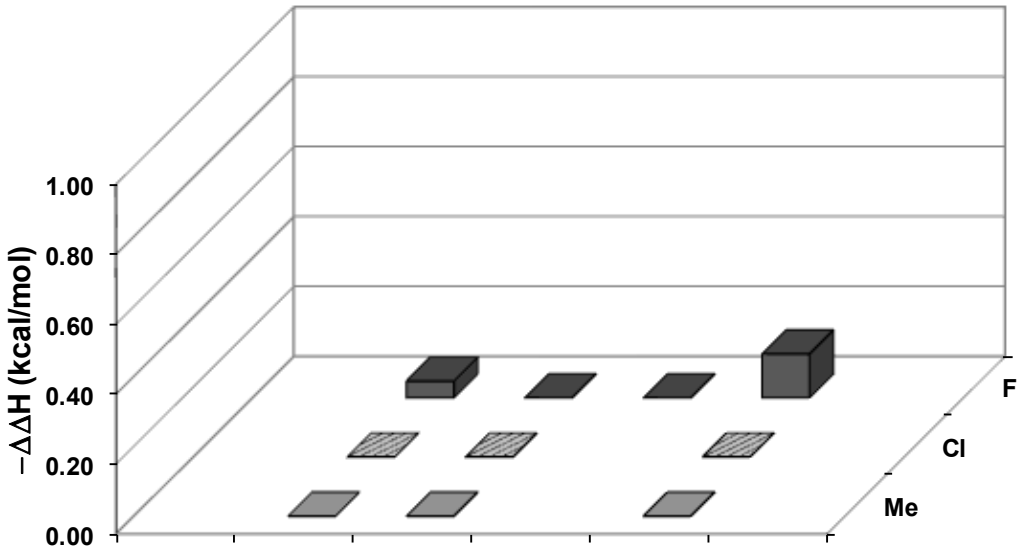
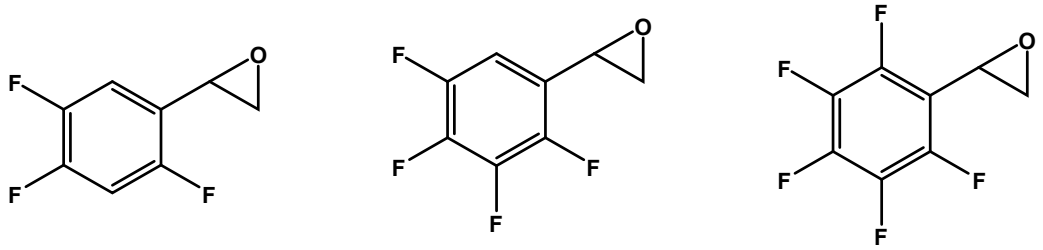


Figure 4.10 Enthalpy differences of the enantiomers of di-substituted styrene oxides on (a) ASiMe and (b) ASiAc columns.

Group 3: Other aromatic epoxides

Group 3 epoxides are derivatives of styrene oxide and are further divided into two subgroups as follows:

Group 3.1: Polyfluoro-substituted styrene oxides



triF **tetraF** **pentaF**

For this group, trifluoro-, tetrafluoro-, and pentafluoro-substituted styrene oxides were studied as shown above. Their $-\Delta\Delta H$ values on ASiMe and ASiAc columns were compared with monofluoro- and difluoro-substituted styrene oxides (Figure 4.11).

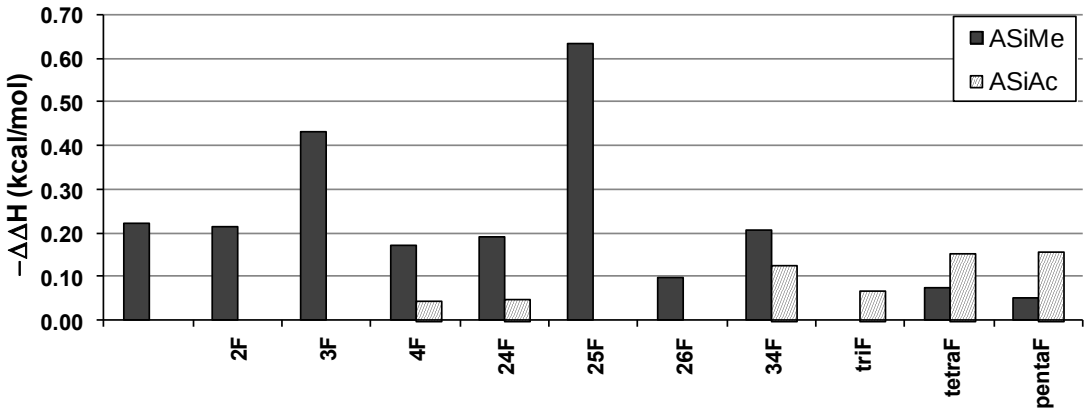


Figure 4.11 Enthalpy differences of the enantiomers of fluoro-substituted styrene oxides on ASiMe and ASiAc columns.

From Figure 4.11, ASiMe column could enantioseparated all fluoro-substituted styrene oxides, except for **triF**. However, ASiAc column separated about half of analytes tested with low $-\Delta\Delta H$ values. The influence of number of fluorine atoms on the aromatic ring was demonstrated. Compared to analyte **1**, when all protons on the aromatic ring of styrene oxide were replaced with fluorine atoms as in **pentaF**, its $-\Delta\Delta H$ value decreased. On the other hand, ASiAc column could not enantioseparated analyte **1**, but showed separation for **pentaF**. Enantioseparation of **triF**, **tetraF**, and **pentaF** on both columns at 80 °C were compared in Figure 4.12.

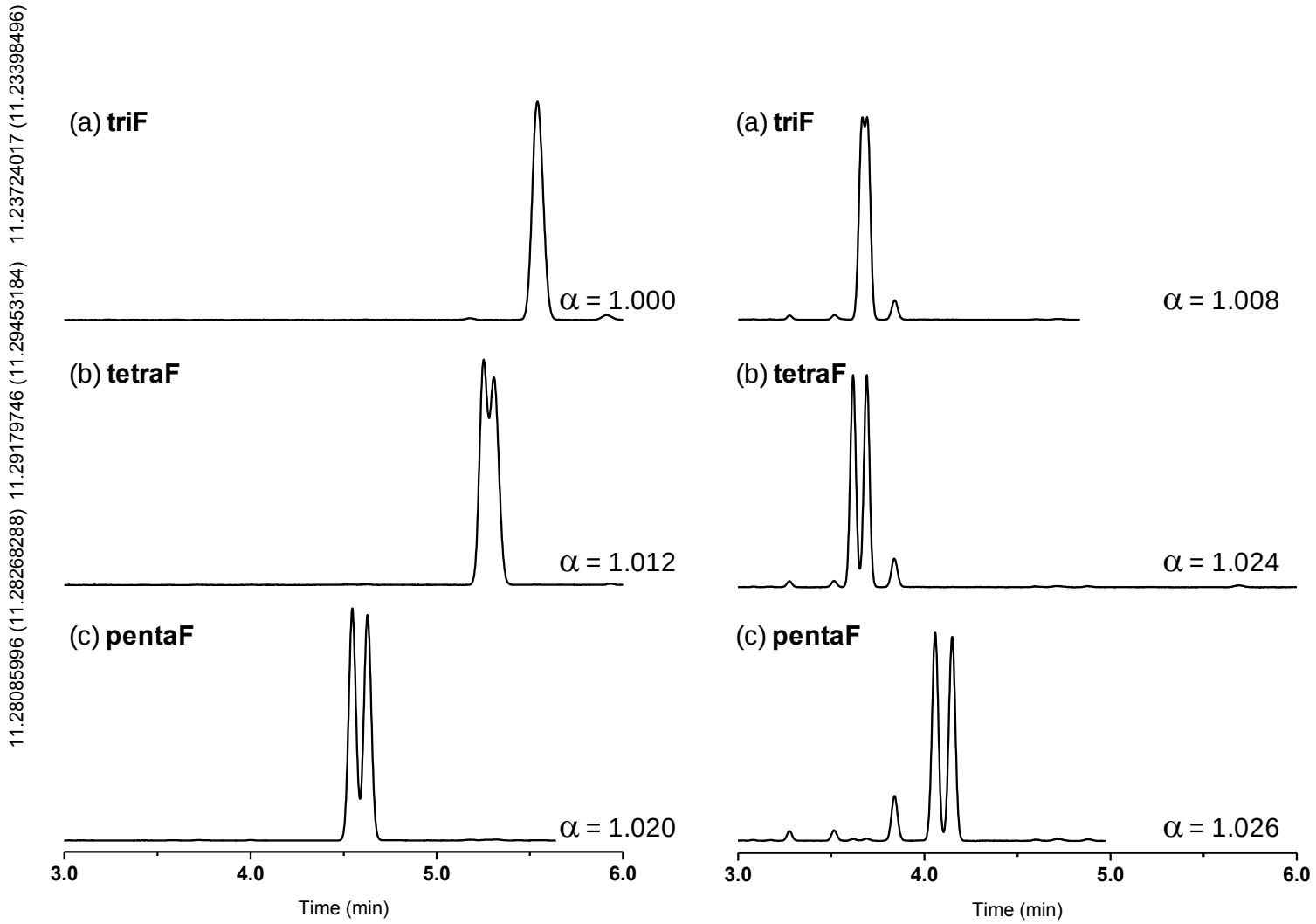
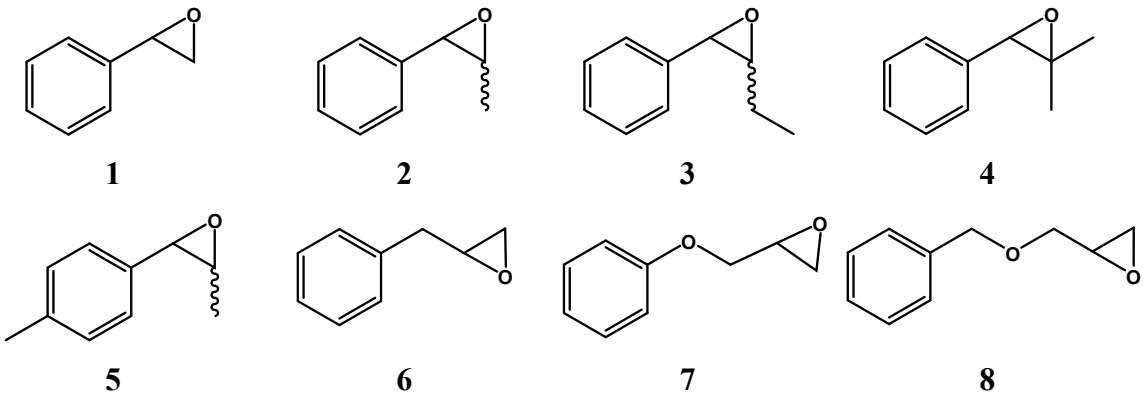


Figure 4.12 Chromatograms of (a) **triF**, (b) **tetraF**, (c) **pentaF** on (left) ASiMe and (right) ASiAc columns at 80 °C.

Group 3.2: Aromatic epoxides with different structures



Epoxides in group 3.2 included styrene oxides with different alkyl substitution on the side chain as **2**, **3**, **4**, and **5**. Compounds **2**, **3**, and **5** were present in both *cis*- and *trans*-isomers. Aromatic epoxides with different distance between aromatic ring and epoxy group were **6**, **7**, and **8**. The structures of seven aromatic epoxides were shown above. Since all analytes in this group could not be separated by ASiAc column, only the $-\Delta\Delta H$ values from ASiMe column were shown in Figure 4.13.

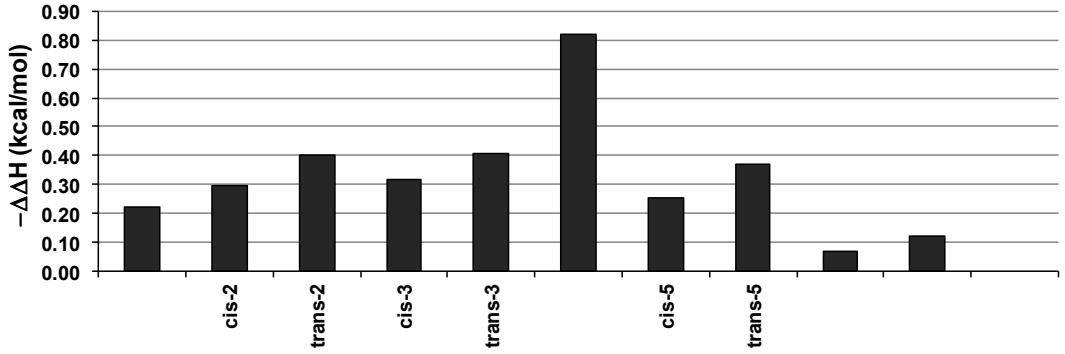


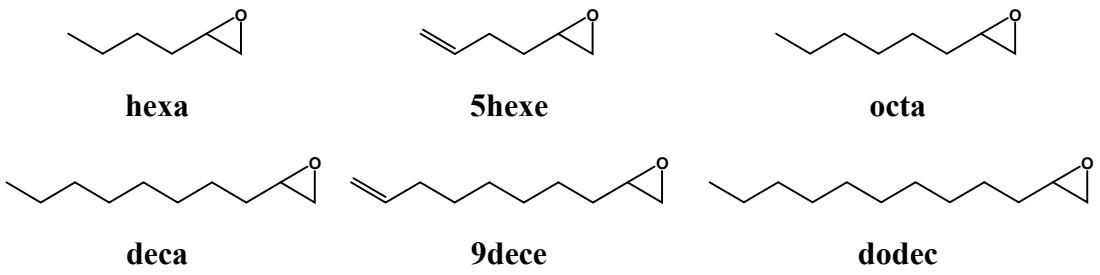
Figure 4.13 Enthalpy differences of the enantiomers of aromatic epoxides on ASiMe column.

All aromatic epoxides in this group could be enantioseparated on ASiMe column, except **8**. Compared to reference compound **1**, compounds with substitution on the epoxide ring (**2**, **3**, **4**, and **5**) had higher $-\Delta\Delta H$ values than **1**. Different substitution position led to different $-\Delta\Delta H$ values, as compound **4** (with two methyl

substitution on epoxide ring) had the highest –ΔΔH values. For compounds **2**, **3**, and **5**, where *cis*- and *trans*-isomers exist, slightly better –ΔΔH values were observed for *trans*-isomers. Where epoxide ring was further away from aromatic ring, as for compounds **6**, **7**, and **8**, no enantioseparation or lower –ΔΔH values were observed.

Enantioseparation of aromatic epoxides in this group on other CD columns (BSiMe, BSiAc, GSiMe, and GSiAc) showed different trend. Acetyl-substituted CDs (BSiAc and GSiAc) gave higher –ΔΔH values than methyl-substituted CDs (BSiMe and GSiMe). In addition, GSiAc showed better separations towards *cis*-isomers than *trans*-isomers.

Group 4: Aliphatic epoxides



Group 4 epoxides contain six aliphatic epoxides with different number of carbon atoms (from 6-12 atoms) as shown above. Their –ΔΔH values on ASiMe and ASiAc columns were compared in Figure 4.14.

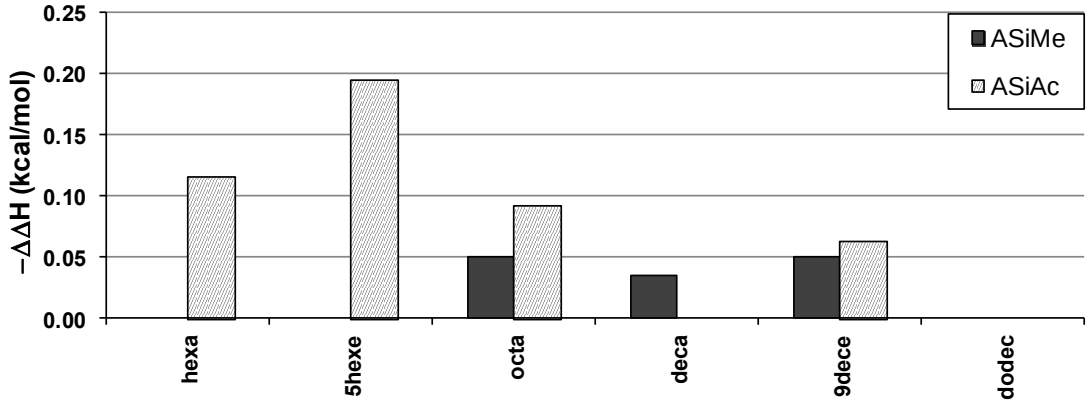


Figure 4.14 Enthalpy differences of the enantiomers of aliphatic epoxides on ASiMe and ASiAc columns.

All aliphatic epoxides could be enantioseparated with either ASiMe or ASiAc columns, except **dodec** could not be separated on any column. ASiAc column showed better enantioselectivity than ASiMe column. Comparing analytes with the same carbon numbers (**hexa** *vs.* **5hexe** and **deca** *vs.* **9dece**), analytes with double bond (**5hexe** and **9dece**) interestingly showed better enantioseparation than their alkane analogs (**hexa** and **deca**). Separation of aliphatic epoxides on γ-CDs were poor as GSiMe could not separate any aliphatic epoxides and GSiAc could only separate **5hexe**.

CHAPTER V

CONCLUSIONS

Enantioseparation of forty-two aromatic epoxides and six aliphatic epoxides were studied by GC using two chiral selectors: hexakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-α-cyclodextrin (or ASiMe) and hexakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-α-cyclodextrin (or ASiAc). Both chiral selectors possess identical ring size and substituent at C6 position, but have different substituents at C2 and C3 positions. Most epoxides could be enantioseparated with ASiMe or ASiAc or both columns. Only compounds **8** and **dodec** could not be separated by any column. Aromatic epoxides were better enantioseparated with ASiMe column.

In order to better understand the correlation between epoxide structure and CD stationary phase, thermodynamic values were calculated from van't Hoff equation. The $-\Delta H$ and $-\Delta S$ values from the same column displayed similar trend. The interactions of epoxides towards ASiMe were stronger than to ASiAc. Nonetheless, the interaction strength did not necessarily correlate with the discrimination of enantiomers. Some analytes showed strong interaction with the stationary phase but did not exhibit high enantioseparation. The $-\Delta\Delta H$ and $-\Delta\Delta S$ values must be considered. Though, there are several factors related to analyte structure and CD derivative, which lead to enantioseparation, and no definite conclusion could be made. Some observations from this study could be summarized.

On ASiMe column, the position of substituent played a major role in the enantioseparation of mono-substituted styrene oxides. The substitution at *meta*-position seemed to enhance the enantiorecognition than *ortho*- and *para*-positions. However, the enantioseparation also depended on type and number of substituent. Among all epoxides studied, 2,5-dichlorostyrene oxide (**25Cl**) showed highest degree of enantioseparation.

On ASiAc column, more than half of aromatic epoxides studied could not be enantioseparated. However, some styrene oxides (**4NO**, **4CF** and **triF**) which could not be separated on ASiMe column were separated on this column.

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APPENDICES

Appendix A

Glossary

Adjusted retention time (t'_R) is the absolute retention of a compound on a stationary phase. This value is calculated by subtracting the time of unretained compound (t_M) from the compound's retention time (t_R), according to

$$t'_R = t_R - t_M$$

Correlation coefficient (R^2) is a number between 0 and 1 indicating the degree of linear relationship between two variables.

Phase ratio (β) is defined as the ratio of the volume of mobile phase (V_M) to the volume of stationary phase (V_S) in the column. It is a unitless value and can be calculated from column dimension by the following equation.

$$\beta = \frac{r_c}{2d_f}$$

r_c = capillary column radius

d_f = stationary phase film thickness (in the same unit as r_c)

Resolution (R_s) is a value indicating the completeness of separation. This value can be calculated by following equation. $R_s \geq 1.5$ is considered complete separation.

$$R_s = 1.177 \times \left(\frac{t_{R,2} - t_{R,1}}{W_{h,2} + W_{h,1}} \right)$$

Retention factor or capacity factor (k′) is defined as the ratio of analyte masses in the stationary phase and in the mobile phase. It is equivalent to the ratio of time of analyte molecules spend in stationary phase (t'_R) to the time that they spend in mobile phase (t_M). The retention factor is calculated from:

$$k' = \frac{t_R - t_M}{t_M} = \frac{t'_R}{t_M}$$

Separation factor or selectivity (α) is a measure of the quality of peak separation expressed as a relative adjusted retention. It is calculated from the ratio of the retention factors of the two adjacent peaks, when $k'_2 \geq k'_1$.

$$\alpha = \frac{k'_2}{k'_1} = \frac{t_{R,2} - t_M}{t_{R,1} - t_M}$$

Appendix B

Thermodynamic data

Table B1 Equation and correlation coefficient of all epoxides obtained from ln k´ vs. 1/T plots on ASiMe column.

analyte	temperature range (°C)	less retained enantiomer			more retained enantiomer		
		ln k´ = m(1/T) + c		R^2	ln k´ = m(1/T) + c		R^2
		m	c		m	c	
1	80–150	5998.7	-14.256	1.0000	6110.2	-14.488	1.0000
2Br	90–170	6591.8	-14.569	0.9997	6715.4	-14.842	0.9998
3Br	120–190	7410.2	-15.926	0.9993	7702.1	-16.528	0.9991
4Br	120–190	7551.5	-16.153	0.9994	7655.2	-16.377	0.9994
2Cl	90–160	6333.7	-14.409	0.9998	6456.3	-14.685	0.9999
3Cl	120–180	7073.7	-15.642	0.9995	7355.1	-16.225	0.9995
4Cl	100–180	7336.4	-16.160	0.9996	7446.5	-16.397	0.9997
3CN	140–200	8177.2	-16.962	0.9994	8588.7	-17.776	0.9993
4CN	130–200	8274.1	-17.108	0.9994	8397.0	-17.363	0.9995
2F	80–140	5792.1	-13.973	1.0000	5899.3	-14.223	1.0000
3F	80–150	6279.1	-14.874	1.0000	6495.8	-15.329	1.0000
4F	80–150	6330.1	-14.932	1.0000	6416.6	-15.112	1.0000
3OMe	110–180	6949.4	-15.174	0.9997	7134.0	-15.573	0.9997
2Me	80–160	6444.6	-14.854	0.9998	6514.5	-15.020	0.9997
3Me	90–160	6653.6	-15.238	0.9999	6887.4	-15.735	0.9999
4Me	80–160	6580.0	-15.035	0.9999	6656.6	-15.209	1.0000
2NO	110–190	7244.5	-15.326	0.9994	7362.0	-15.582	0.9994
3NO	120–210	7704.8	-15.695	0.9992	7869.9	-16.032	0.9992
4NO	150–210	7676.1	-15.509	0.9995	7676.1	-15.509	0.9995
2CF	80–150	5656.4	-13.893	1.0000	5794.1	-14.206	1.0000
3CF	80–150	6490.8	-15.428	0.9999	6594.3	-15.647	0.9999
4CF	80–150	6651.1	-15.673	1.0000	6651.1	-15.673	1.0000

Table B1 (continued)

analyte	temperature range (°C)	less retained enantiomer			more retained enantiomer		
		ln k′ = m(1/T) + c		R^2	ln k′ = m(1/T) + c		R^2
		m	c		m	c	
24Cl	110–190	7768.5	-16.676	0.9991	7887.8	-16.941	0.999
25Cl	110–190	6956.2	-14.967	0.9995	7424.0	-15.965	0.999
34Cl	110–190	7378.9	-15.493	0.9995	7480.5	-15.708	0.9996
24F	70–150	6202.0	-14.979	1.0000	6297.3	-15.209	1.0000
25F	70–140	5912.2	-14.321	1.0000	6231.6	-15.039	0.9999
26F	60–140	5725.4	-13.687	1.0000	5774.9	-13.809	1.0000
34F	70–150	6278.2	-14.833	0.9999	6381.5	-15.048	1.0000
24Me	90–170	7007.1	-15.596	0.9996	7091.3	-15.785	0.9997
25Me	90–170	6640.0	-14.862	0.9997	6745.7	-15.106	0.9997
34Me	90–180	7012.9	-15.429	0.9996	7154.2	-15.735	0.9996
triF	80–140	5855.2	-14.336	1.000	5855.2	-14.336	1.0000
tetraF	50–140	5888.1	-14.470	0.9999	5926.5	-14.568	0.9999
pentaF	50–130	5628.5	-13.899	1.0000	5654.9	-13.956	1.0000
***cis*-2**	80–150	5597.1	-13.373	0.9999	5745.7	-13.684	0.9999
***trans*-2**	80–150	5926.9	-13.947	1.0000	6128.2	-14.376	1.0000
***cis*-3**	80–150	6023.2	-13.978	0.9999	6181.5	-14.317	0.9999
***trans*-3**	80–150	6574.5	-14.996	0.9999	6778.8	-15.439	0.9999
4	80–150	5742.2	-13.645	0.9999	6155.5	-14.556	0.9998
***cis*-5**	100–160	6409.1	-14.663	0.9999	6536.4	-14.932	0.9998
***trans*-5**	100–160	6807.5	-15.410	0.9998	6992.6	-15.821	0.9997
6	70–150	6343.1	-14.639	0.9999	6377.7	-14.723	0.9999
7	90–190	7092.5	-15.608	0.9998	7152.2	-15.748	0.9998
8	120–180	7064.9	-15.234	0.9997	7064.9	-15.234	0.9997
hexa	50–110	4912.8	-13.418	1.0000	4912.8	-13.418	1.0000
5hexe	50–110	4866.8	-13.330	1.0000	4866.8	-13.330	1.0000
octa	50–130	6033.6	-14.998	1.0000	6058.5	-15.063	1.0000
deca	80–160	7299.8	-16.907	0.9992	7317.4	-16.949	0.9992
9dece	80–160	7095.2	-16.428	0.9994	7120.3	-16.488	0.9994
dodec	120–180	7491.0	-16.333	0.9994	7491.0	-16.333	0.9994

Table B2 Equation and correlation coefficient of all epoxides obtained from ln k′ vs. 1/T plots on ASiAc column.

analyte	temperature range (°C)	less retained enantiomer			more retained enantiomer		
		ln k′ = m(1/T) + c		R^2	ln k′ = m(1/T) + c		R^2
		m	c		m	c	
1	70–140	5242.1	-12.781	0.9999	5242.1	-12.781	0.9999
2Br	110–180	5672.0	-12.662	0.9999	5672.0	-12.662	0.9999
3Br	110–180	6075.8	-13.247	0.9998	6075.8	-13.247	0.9998
4Br	110–180	6131.8	-13.348	0.9998	6131.8	-13.348	0.9998
2Cl	80–160	5574.5	-12.880	0.9998	5574.5	-12.880	0.9998
3Cl	80–160	5964.1	-13.478	0.9997	5964.1	-13.478	0.9997
4Cl	80–160	6048.6	-13.650	0.9997	6068.3	-13.698	0.9996
3CN	110–200	6840.1	-14.348	0.9993	6897.1	-14.473	0.9992
4CN	110–200	7059.3	-14.763	0.9989	7167.4	-14.998	0.9988
2F	70–130	5159.6	-12.730	0.9999	5159.6	-12.730	0.9999
3F	70–140	5372.3	-13.067	0.9999	5372.3	-13.067	0.9999
4F	50–140	5537.4	-13.453	0.9997	5560.6	-13.512	0.9996
3OMe	120–180	6125.5	-13.486	0.9999	6125.5	-13.486	0.9999
2Me	80–140	5598.4	-13.138	0.9999	5598.4	-13.138	0.9999
3Me	80–140	5664.0	-13.280	0.9999	5664.0	-13.280	0.9999
4Me	80–140	5676.7	-13.283	0.9999	5676.7	-13.283	0.9999
2NO	100–200	6410.0	-13.596	0.9996	6438.0	-13.659	0.9995
3NO	120–210	6976.5	-14.217	0.9994	6976.5	-14.217	0.9994
4NO	120–210	7129.2	-14.469	0.9993	7156.5	-14.529	0.9992
2CF	70–120	5219.5	-13.058	0.9999	5219.5	-13.058	0.9999
3CF	70–140	5676.8	-13.759	0.9998	5676.8	-13.759	0.9998
4CF	50–140	5853.6	-14.158	0.9996	5898.9	-14.274	0.9995
24Cl	110–170	6053.0	-13.228	0.9998	6053.0	-13.228	0.9998
25Cl	120–180	6035.6	-13.121	0.9999	6035.6	-13.121	0.9999
34Cl	120–190	6446.4	-13.603	0.9997	6446.4	-13.603	0.9997
24F	50–130	5259.8	-13.144	0.9998	5283.6	-13.206	0.9998
25F	70–130	5246.4	-12.985	0.9999	5246.4	-12.985	0.9999
26F	70–140	5431.0	-13.126	0.9999	5431.0	-13.126	0.9999
34F	50–140	5739.3	-13.853	0.9996	5802.5	-14.014	0.9994

Table B2 (continued)

analyte	temperature range (°C)	less retained enantiomer			more retained enantiomer		
		ln k′ = m(1/T) + c		R^2	ln k′ = m(1/T) + c		R^2
		m	c		m	c	
24Me	100–170	5870.8	-13.257	0.9998	5870.8	-13.257	0.9998
25Me	100–170	5857.3	-13.269	0.9998	5857.3	-13.269	0.9998
34Me	100–170	6015.3	-13.413	0.9998	6015.3	-13.413	0.9998
triF	50–130	5349.4	-13.355	0.9998	5384.5	-13.446	0.9998
tetraF	50–130	5375.9	-13.445	0.9998	5453.7	-13.642	0.9998
pentaF	60–130	5534.8	-13.766	0.9998	5613.6	-13.964	0.9998
***cis*-2**	80–140	5309.2	-12.856	0.9999	5309.2	-12.856	0.9999
***trans*-2**	80–140	5481.5	-13.142	0.9999	5481.5	-13.142	0.9999
***cis*-3**	80–150	5634.5	-13.239	0.9998	5634.5	-13.239	0.9998
***trans*-3**	80–150	5857.7	-13.575	0.9998	5857.7	-13.575	0.9998
4	80–140	5457.3	-13.136	0.9999	5457.3	-13.136	0.9999
***cis*-5**	80–150	5756.0	-13.403	0.9998	5756.0	-13.403	0.9998
***trans*-5**	80–150	5925.1	-13.662	0.9998	5925.1	-13.662	0.9998
6	80–150	5661.5	-13.280	0.9998	5661.5	-13.280	0.9998
7	110–170	6276.5	-13.942	0.9998	6276.5	-13.942	0.9998
8	120–180	6376.1	-13.846	0.9998	6376.1	-13.846	0.9998
hexa	50–90	4407.4	-12.605	0.9999	4465.5	-12.768	0.9999
5hexe	50–90	4457.3	-12.732	0.9999	4555.5	-13.004	0.9999
octa	50–110	5263.8	-13.550	0.9998	5310.1	-13.674	0.9998
deca	90–150	5860.4	-13.862	0.9998	5860.4	-13.862	0.9998
9dece	60–150	6049.6	-14.302	0.9996	6081.2	-14.381	0.9995
dodec	100–170	6617.1	-14.650	0.9997	6617.1	-14.650	0.9997

Table B3 Thermodynamic parameters of all epoxides on ASiMe column

analyte	enthalpy term (kcal/mol)			entropy term (cal/mol·K)		
	$-\Delta H_1$	$-\Delta H_2$	$-\Delta\Delta H$	$-\Delta S_1$	$-\Delta S_2$	$-\Delta\Delta S$
1	11.92	12.14	0.22	17.36	17.82	0.46
2Br	13.10	13.34	0.25	17.98	18.52	0.54
3Br	14.72	15.30	0.58	20.67	21.87	1.20
4Br	15.00	15.21	0.21	21.12	21.57	0.45
2Cl	12.59	12.83	0.24	17.66	18.21	0.55
3Cl	14.06	14.61	0.56	20.11	21.27	1.16
4Cl	14.58	14.80	0.22	21.14	21.61	0.47
3CN	16.25	17.07	0.82	22.73	24.35	1.62
4CN	16.44	16.68	0.24	23.02	23.53	0.51
2F	11.51	11.72	0.21	16.79	17.29	0.50
3F	12.48	12.91	0.43	18.58	19.49	0.90
4F	12.58	12.75	0.17	18.70	19.06	0.36
3OMe	13.81	14.18	0.37	19.18	19.97	0.79
2Me	12.81	12.94	0.14	18.54	18.87	0.33
3Me	13.22	13.69	0.46	19.31	20.29	0.99
4Me	13.07	13.23	0.15	18.90	19.25	0.35
2NO	14.39	14.63	0.23	19.48	19.99	0.51
3NO	15.31	15.64	0.33	20.21	20.88	0.67
4NO	15.25	15.25	0.00	19.85	19.85	0.00
2CF	11.24	11.51	0.27	16.63	17.26	0.62
3CF	12.90	13.10	0.21	19.68	20.12	0.44
4CF	13.22	13.22	0.00	20.17	20.17	0.00
24Cl	15.44	15.67	0.24	22.16	22.69	0.53
25Cl	13.82	14.75	0.93	18.77	20.75	1.98
34Cl	14.66	14.86	0.20	19.81	20.24	0.43

Table B3 (continued)

analyte	enthalpy term (kcal/mol)			entropy term (cal/mol·K)		
	$-\Delta H_1$	$-\Delta H_2$	$-\Delta\Delta H$	$-\Delta S_1$	$-\Delta S_2$	$-\Delta\Delta S$
24F	12.32	12.51	0.19	18.79	19.25	0.46
25F	11.75	12.38	0.63	17.48	18.91	1.43
26F	11.38	11.47	0.10	16.22	16.47	0.24
34F	12.47	12.68	0.21	18.50	18.93	0.43
24Me	13.92	14.09	0.17	20.02	20.39	0.38
25Me	13.19	13.40	0.21	18.56	19.04	0.48
34Me	13.93	14.22	0.28	19.69	20.29	0.61
triF	11.63	11.63	0.00	17.51	17.51	0.00
tetraF	11.70	11.78	0.08	17.78	17.98	0.19
pentaF	11.18	11.24	0.05	16.65	16.76	0.11
***cis*-2**	11.12	11.42	0.30	15.60	16.22	0.62
***trans*-2**	11.78	12.18	0.40	16.74	17.59	0.85
***cis*-3**	11.97	12.28	0.31	16.80	17.48	0.67
***trans*-3**	13.06	13.47	0.41	18.83	19.71	0.88
4	11.41	12.23	0.82	16.14	17.95	1.81
***cis*-5**	12.73	12.99	0.25	18.16	18.70	0.53
***trans*-5**	13.53	13.89	0.37	19.65	20.47	0.82
6	12.60	12.67	0.07	18.12	18.28	0.17
7	14.09	14.21	0.12	20.04	20.32	0.28
8	14.04	14.04	0.00	19.30	19.30	0.00
hexa	9.76	9.76	0.00	15.69	15.69	0.00
5hexe	9.67	9.67	0.00	15.52	15.52	0.00
octa	11.99	12.04	0.05	18.83	18.96	0.13
deca	14.50	14.54	0.03	22.62	22.71	0.08
9dece	14.10	14.15	0.05	21.67	21.79	0.12
dodec	14.88	14.88	0.00	21.48	21.48	0.00

Table B4 Thermodynamic parameters of all epoxides on ASiAc column

analyte	enthalpy term (kcal/mol)			entropy term (cal/mol·K)		
	$-\Delta H_1$	$-\Delta H_2$	$-\Delta\Delta H$	$-\Delta S_1$	$-\Delta S_2$	$-\Delta\Delta S$
1	10.42	10.42	0.00	14.42	14.42	0.00
2Br	11.27	11.27	0.00	14.19	14.19	0.00
3Br	12.07	12.07	0.00	15.35	15.35	0.00
4Br	12.18	12.18	0.00	15.55	15.55	0.00
2Cl	11.08	11.08	0.00	14.62	14.62	0.00
3Cl	11.85	11.85	0.00	15.81	15.81	0.00
4Cl	12.02	12.06	0.04	16.15	16.25	0.10
3CN	13.59	13.70	0.11	17.54	17.79	0.25
4CN	14.03	14.24	0.21	18.36	18.83	0.47
2F	10.25	10.25	0.00	14.32	14.32	0.00
3F	10.67	10.67	0.00	14.99	14.99	0.00
4F	11.00	11.05	0.05	15.76	15.88	0.12
3OMe	12.17	12.17	0.00	15.83	15.83	0.00
2Me	11.12	11.12	0.00	15.13	15.13	0.00
3Me	11.25	11.25	0.00	15.42	15.42	0.00
4Me	11.28	11.28	0.00	15.42	15.42	0.00
2NO	12.74	12.79	0.06	16.04	16.17	0.13
3NO	13.86	13.86	0.00	17.28	17.28	0.00
4NO	14.17	14.22	0.05	17.78	17.90	0.12
2CF	10.37	10.37	0.00	14.98	14.98	0.00
3CF	11.28	11.28	0.00	16.37	16.37	0.00
4CF	11.63	11.72	0.09	17.16	17.39	0.23
24Cl	12.03	12.03	0.00	15.31	15.31	0.00
25Cl	11.99	11.99	0.00	15.10	15.10	0.00
34Cl	12.81	12.81	0.00	16.06	16.06	0.00

Table B4 (continued)

analyte	enthalpy term (kcal/mol)			entropy term (cal/mol·K)		
	$-\Delta H_1$	$-\Delta H_2$	$-\Delta\Delta H$	$-\Delta S_1$	$-\Delta S_2$	$-\Delta\Delta S$
24F	10.45	10.50	0.05	15.15	15.27	0.12
25F	10.42	10.42	0.00	14.83	14.83	0.00
26F	10.79	10.79	0.00	15.11	15.11	0.00
34F	11.40	11.53	0.13	16.55	16.87	0.32
24Me	11.67	11.67	0.00	15.37	15.37	0.00
25Me	11.64	11.64	0.00	15.39	15.39	0.00
34Me	11.95	11.95	0.00	15.68	15.68	0.00
triF	10.63	10.70	0.07	15.57	15.75	0.18
tetraF	10.68	10.84	0.15	15.74	16.14	0.39
pentaF	11.00	11.15	0.16	16.38	16.78	0.39
***cis*-2**	10.55	10.55	0.00	14.57	14.57	0.00
***trans*-2**	10.89	10.89	0.00	15.14	15.14	0.00
***cis*-3**	11.20	11.20	0.00	15.33	15.33	0.00
***trans*-3**	11.64	11.64	0.00	16.00	16.00	0.00
4	10.84	10.84	0.00	15.13	15.13	0.00
***cis*-5**	11.44	11.44	0.00	15.66	15.66	0.00
***trans*-5**	11.77	11.77	0.00	16.18	16.18	0.00
6	11.25	11.25	0.00	15.42	15.42	0.00
7	12.47	12.47	0.00	16.73	16.73	0.00
8	12.67	12.67	0.00	16.54	16.54	0.00
hexa	8.76	8.87	0.12	14.07	14.40	0.32
5hexe	8.86	9.05	0.20	14.33	14.87	0.54
octa	10.46	10.55	0.09	15.95	16.20	0.25
deca	11.64	11.64	0.00	16.57	16.57	0.00
9dece	12.02	12.08	0.06	17.45	17.60	0.16
dodec	13.15	13.15	0.00	18.14	18.14	0.00

Appendix C

Retention factor, selectivity and resolution

Table C1 Retention factor (k′), selectivity (α) and resolution (R_s) values of all epoxides on ASiMe and ASiAc columns

analyte	temp (°C)	ASiMe				ASiAc			
		k'_1	k'_2	α	R_s	k'_1	k'_2	α	R_s
1	100	6.174	6.603	1.070	3.57	3.515	3.515	1.00	-
2Br	120	8.855	9.232	1.043	2.35	5.850	5.850	1.000	-
3Br	180	1.545	1.612	1.044	1.55	1.192	1.192	1.000	-
	120	19.294	22.307	2.028	9.00	9.099	9.099	1.000	-
4Br	120	21.947	22.804	1.039	2.42	9.482	9.482	1.000	-
2Cl	120	5.405	5.608	1.038	1.94	3.615	3.615	1.000	-
3Cl	170	1.378	1.452	1.054	1.76	nd	nd	nd	nd
	120	10.736	12.301	1.146	7.64	5.334	5.334	1.000	-
4Cl	100	34.166	36.156	1.058	4.31	12.823	12.823	1.000	-
	80	nd	nd	nd	nd	33.350	33.787	1.013	1.01
3CN	200	1.420	1.508	1.062	1.99	1.164	1.164	1.000	-
	140	17.422	20.972	1.204	11.88	8.821	8.940	1.013	0.79
4CN	140	18.638	19.430	1.042	2.55	9.838	10.087	1.025	1.45
2F	120	2.122	2.181	1.028	1.13	1.486	1.486	1.000	-
	80	11.400	11.994	1.052	2.83	6.554	6.554	1.000	-
3F	120	2.974	3.275	1.101	4.36	1.809	1.809	1.000	-
	80	18.379	21.555	1.173	9.62	8.552	8.552	1.000	-
4F	120	3.202	3.331	1.041	1.83	1.880	1.880	1.000	-
	80	19.973	21.299	1.066	3.96	9.102	9.102	1.000	-
	70	nd	nd	nd	nd	14.504	14.581	1.005	0.34
3OMe	120	12.245	13.139	1.073	4.15	8.227	8.227	1.000	-

Table C1 (continued)

analyte	temp (°C)	ASiMe				ASiAc			
		k'_1	k'_2	α	R_s	k'_1	k'_2	α	R_s
2Me	120	4.562	4.623	1.013	0.71	2.998	2.998	1.000	-
3Me	120	5.338	5.879	1.101	5.11	3.073	3.073	1.000	-
4Me	120	5.425	5.553	1.024	1.23	3.165	3.165	1.000	-
2NO	120	22.434	23.406	1.043	2.74	14.865	15.017	1.010	0.65
	110	37.383	39.368	1.053	4.03	23.207	23.529	1.014	0.94
3NO	150	12.002	12.644	1.054	3.00	9.438	9.438	1.000	-
4NO	150	14.217	14.217	1.000	-	10.494	10.494	1.000	-
	120	nd	nd	nd	nd	41.038	41.675	1.016	1.24
2CF	80	8.398	9.083	1.082	4.15	5.589	5.589	1.000	-
3CF	80	19.371	20.854	1.077	4.28	1.962	1.962	1.000	-
4CF	80	23.705	23.705	1.000	-	10.960	11.032	1.007	0.43
	50	nd	nd	nd	nd	54.442	56.235	1.033	2.60
24Cl	140	8.091	8.277	1.023	1.24	4.105	4.105	1.000	-
25Cl	170	2.059	2.174	1.056	2.24	1.649	1.649	1.000	-
	140	6.331	7.155	1.130	6.63	4.388	4.388	1.000	-
34Cl	140	10.413	10.739	1.031	1.80	7.305	7.305	1.000	-
24F	70	22.185	23.225	1.047	2.89	8.792	8.854	1.007	0.45
25F	140	0.996	1.057	1.061	1.51	nd	nd	nd	nd
	70	18.483	22.936	1.241	12.86	10.122	10.122	1.000	-
26F	70	20.114	20.571	1.023	1.33	15.144	15.144	1.000	-
34F	130	2.085	2.174	1.043	1.73	1.491	1.491	1.000	-
	70	32.247	35.118	1.089	6.19	17.461	17.828	1.021	1.26
24Me	110	14.648	15.098	1.031	1.80	7.886	7.886	1.000	-
25Me	110	11.723	12.096	1.032	1.80	7.521	7.521	1.000	-
34Me	110	17.640	18.768	1.064	3.69	9.839	9.389	1.000	-
triF	80	9.494	9.494	1.000	-	5.908	5.953	1.008	0.46
tetraF	80	8.970	9.074	1.012	0.68	5.812	5.951	1.024	1.26
pentaF	80	7.624	7.780	1.020	1.10	6.642	6.814	1.026	1.40

Table C1 (continued)

analyte	temp (°C)	ASiMe				ASiAc			
		k'_1	k'_2	α	R_s	k'_1	k'_2	α	R_s
***cis*-2**	120	2.349	2.513	1.070	2.94	1.901	1.901	1.000	-
***trans*-2**	120	3.077	3.340	1.085	3.90	2.212	2.212	1.000	-
***cis*-3**	120	3.789	4.036	1.065	3.20	2.953	2.953	1.000	-
***trans*-3**	120	5.564	6.002	1.079	4.03	3.715	3.715	1.000	-
4	150	0.941	1.011	1.075	1.91	nd	nd	nd	nd
	120	2.589	2.968	1.147	6.20	2.096	2.096	1.000	-
***cis*-5**	120	5.111	5.392	1.055	2.80	3.409	3.409	1.000	-
***trans*-5**	120	6.657	7.049	1.059	3.11	4.039	4.039	1.000	-
6	120	4.426	4.426	1.000	-	3.032	3.032	1.000	-
	110	6.734	6.787	1.008	0.48	4.396	4.396	1.000	-
7	120	11.236	11.374	1.012	0.74	7.552	7.552	1.000	-
8	120	15.728	15.728	1.000	-	10.876	10.876	1.000	-
hexa	50	5.953	5.953	1.000	-	2.827	2.880	1.019	0.80
5hexe	50	5.634	5.634	1.000	-	2.910	2.998	1.030	1.29
octa	90	5.009	5.009	1.000	-	2.558	2.558	1.000	-
	50	39.614	40.159	1.014	-	15.733	16.049	1.020	1.15
deca	90	24.691	24.879	1.008	0.58	9.873	9.873	1.000	-
9dece	90	22.631	22.870	1.011	0.70	10.272	10.336	1.006	0.41
dodec	120	15.636	15.636	1.000	-	8.741	8.741	1.000	-

nd = not determined

VITA

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