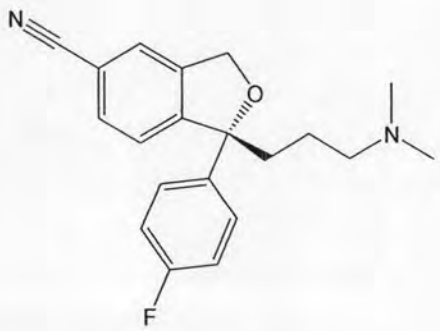
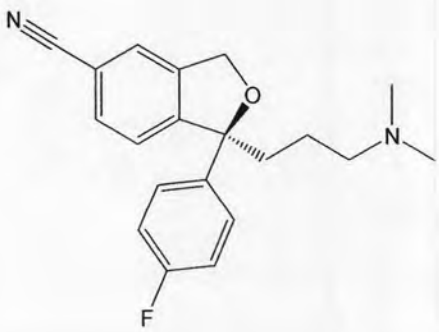
CHAPTER I

INTRODUCTION

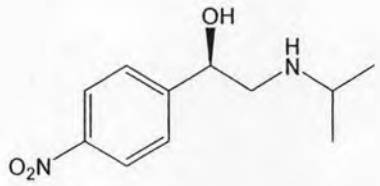
Nowadays, many chiral organic compounds are used in pharmaceutical and agrochemical industries. Two molecular forms of the chiral compounds which differ from each other as non-superimposable mirror image are called enantiomers. Enantiomers have identical physical and chemical properties in an achiral environment. In a chiral environment, one enantiomer may display different biological behavior from the other. In many cases, only one enantiomer is responsible for the desired activity, whereas the other one may cause unexpected side effects or no biological activity [1]. For example, (*S*)-citalopram is primarily responsible for treatment of depression, whereas (*R*)-citalopram is 30-fold less potent [1]. Another example is nifenalol; (*R*)-enantiomer acts as an β-adrenergic blocker, which is effective in the treatment of cardiovascular disease while (*S*)-enantiomer is inactive [2].



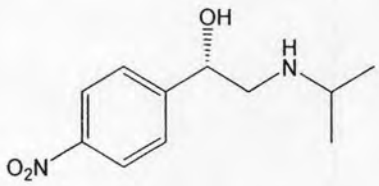
(*R*)-citalopram



(*S*)-citalopram



(*R*)-nifenalol



(*S*)-nifenalol

Figure 1.1 Structures of (*R*)- and (*S*)-enantiomers of citalopram and nifenalol.

Considering these differences in biological activity between each enantiomer, there are several advantages in using purely single enantiomers, such as a reduction in the consumption of chemical reagent, less unwanted effect, and enhancement of the therapeutic ability. These factors have led to the production of single enantiomers, especially in pharmaceutical market. Survey of worldwide pharmaceutical data through the last decades indicates that the use of single enantiomer drugs has been increased from 25% to 58% while the use of racemic drugs has been decreased from 32% to 8% [3].

There are two basic methods to obtain purely single enantiomers: asymmetric synthesis and separation of enantiomers. Although the asymmetric syntheses are favorable method but the development of enantioseparation technique is still needed to determine the enantiomeric purity of the synthesized products. The separation of enantiomers can be achieved in two approaches [4,5]. One approach, sometimes referred to as indirect method, involves the coupling of both enantiomers with a pure auxiliary chiral reagent to convert them into diastereomers. Diastereomers can then be separated by any achiral separation techniques. While the direct method resolves an enantiomeric pair via a chiral selector, acting as a mobile phase additive or a stationary phase, capable of forming a diastereomeric complex with one enantiomer stronger than the other. Direct enantiomeric separations are feasible in most chromatographic or electrophoretic systems which contain appropriate chiral selector.

Among many chromatographic techniques, gas chromatography (GC) is a versatile tool for the determination of enantiomeric purity of volatile and thermally stable organic compounds because of its high efficiency, sensitivity and short analysis time [6, 7]. Cyclodextrins (CDs) and their derivatives are frequently used as chiral stationary phases because they can form inclusion complexes with many substances. Generally, it is perceived that the resolution of chiral analytes occurs through the reversible diasteromeric association between each enantiomer and CD molecule [8,9]. However, the mechanism of chiral recognition is complicate and still not fully understood. Thus, more investigations of chiral separation are still needed.

There are various parameters that affect enantiomeric separations using CD derivatives such as size, shape, and concentration of CD derivatives; type and position of substituents on CD rings; and analyte structure. Nonetheless, there are only a few studies on the relationship between enantioselectivity of CD derivatives and structure of chiral analytes [10−17]. In this research, the influence of analyte structure on the enantiomeric separation was systematically examined by GC and the chiral recognition was studied by molecular modeling.

In this study, aromatic and aliphatic epoxides were selected as the analytes of interest owing to their importance as building blocks for pharmaceutically active compounds, such as setraline, nifenalol and salmeterol [18]. Previously, heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose (abbreviated as BSiMe) and heptakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose (abbreviated as BSiAc) have been used as chiral selectors in GC for the separation of chiral aromatic epoxides [16], whereas the γ-CD derivatives have not yet been explored. The present study covers the styrene oxide and their derivatives with different types, positions, and number of substitutions on aromatic ring, different types of side chain, and different positions of chiral center, as well as aliphatic epoxides of different chain lengths. The systematic investigation includes

i) the separation of epoxide derivatives by GC,
ii) the quantification of the interaction between analyte and stationary phase by the thermodynamic parameters (ΔH, ΔS, ΔG, ΔΔH, ΔΔS, and ΔΔG), and
iii) the theoretical study on the chiral recognition by molecular docking and semi-empirical calculation.

Hopefully, the results obtained from this study enable us to explain the influence of analyte structure on the enantioselectivity. This would enhance the possibility of selecting the most suitable chiral stationary phase and separation condition for the enantioresolution of these epoxide analytes, including other epoxides having similar structure to the test compounds.