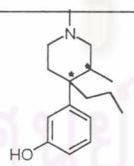
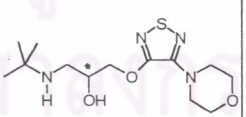
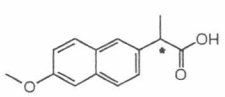
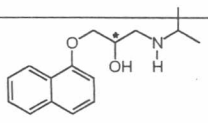
CHAPTER I

INTRODUCTION

The presence of asymmetric center(s) or plane(s) in many compounds of pharmaceutical, agrochemical, and biochemical interest gives rise to optical activity that is usually responsible for the different biological, pharmacological and toxicological properties of the enantiomers. Since biological systems are homochiral environments composed of biopolymer (e.g. protein, glycolipid and polynucleotides) derived from the chiral precursors of L-amino acids and D-carbohydrates, the interaction of each enantiomeric compound with chiral macromolecule can be different [1].

There is a broad range of examples where the stereoisomers of drugs show difference in terms of their bioavailability, distribution, metabolic and excretion behavior and where stereochemical parameters have a fundamental significance in their action disposition in biological system. Examples of chiral drugs in which the individual enantiomer has opposite pharmacological effect are shown in table 1.1.

Table 1.1 Chiral drugs with different pharmacological effect for each enantiomer [2-4]

chiral drug	structure	enantiomer	effect
picenadol		(+)-(3*R*,4*R*) (-)-(3*S*,4*S*)	opioid receptor analgesic antagonist at opioid receptor
timolol		(*S*) (*R*)	treatment for cardiovascular disease treatment for glaucoma
naproxen		(*S*) (*R*)	anti-inflammatory drug no activity
propranolol		(*S*) (*R*)	cardiac β-adrenergic blocking activity 100 times more potent less activity

The increasing demand of chiral compounds in pharmaceutical industry has also stimulated the development of new and more specialized companies in asymmetric synthesis capable of providing enantiomerically pure substances. These pure materials are further used as synthetic intermediates and catalysts or even libraries of chiral compounds with application in combinatorial chemistry [5-7]. Although the development of new synthetic routes for enantiomerically pure compounds is quite important, the determination of enantiomer composition and absolute configuration is as well essential for activity testing or to control the enantiomeric purity of starting materials and products. Consequently, analytical methods providing high sensitivity, efficiency and reproducibility in short analysis time are required in the process of synthesis, characterization and use of these chiral compounds.

Gas chromatography (GC) is a reliable modern analytical method for separating enantiomers of compounds, which can be vaporized without decomposition. Its inherent advantages include simplicity, speed, reproducibility and sensitivity. Separation of enantiomers by gas chromatography can be performed in two ways. One is an indirect method, which involved a conversion of enantiomers into diastereomers by reacting with an enantiomerically pure agent and subsequently a separation of the diastereomers with nonchiral stationary phase. The other is a direct method, which based on a separation of the enantiomers on a system containing a selector of high enantiomeric purity either as a chiral stationary phase or a chiral mobile phase [8].

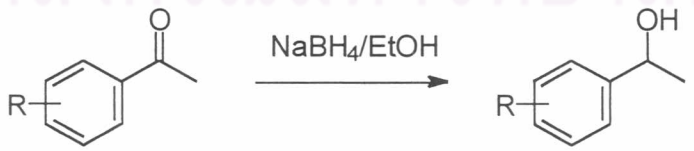
Enantiomer separation by gas chromatography can be performed on several types of chiral stationary phases, e.g. amino acid and peptide derivatives, transition metal complexes, or linear and cyclic carbohydrate derivatives [8,9]. Nonetheless, the most commonly used chiral GC stationary phases are based on cyclodextrin derivatives.

Derivatized cyclodextrin stationary phases have been applied for routine enantiomer separations by high-resolution capillary gas chromatography. It is generally perceived that the resolution of chiral analytes occurs through the intermediate formation of diastereomer between the chiral analyte and the

cyclodextrin molecule. Nevertheless, the mechanisms of chiral recognition involved are not yet well understood. In practical chiral analyses, the selection of the most suitable chiral stationary phase for certain enantiomer separation of a single or even a variety of chiral molecules of different chemical structures and molecular geometry is still sophisticated and required extensive experience. Thus systematic investigations of chiral separation of analytes in homologous series or compounds of similar structure but differ in their substituents and position on different types of cyclodextrin derivatives can lead to a general rule of proper selection of modified cyclodextrin for particular chiral analytes.

The objective of this study is to evaluate the effect of substituent type and position of aromatic alcohols on enantioselectivity when separated with modified cyclodextrin stationary phases using GC. Aromatic alcohols, 1-phenylethanol and its derivatives, with various substituent types at *ortho*, *meta* and *para* positions are used as chiral analytes. Two types of modified cyclodextrins, heptakis(2,3,6-tri-*O*-methyl) cyclomaltoheptaose (BMe) and heptakis(2,3-di-*O*-methy-6-*O*-*tert*-butyldimethylsilyl) cyclomaltoheptaose (BSiMe), diluted in polysiloxane are used as GC stationary phases.

Aromatic alcohols were selected as the analytes of interest owing to their importance as chiral intermediates in the asymmetric synthetic pathway of drugs, agrochemicals, and catalysts. For example, (*E*)-3-[2-(7-chloro-2-quinolinyl)ethenyl]-α-ethenylphenylmethanol was used as the chiral intermediate in the synthesis of LTD_4 antagonists [10]. In this experiment, chiral analytes, 1-phenylethanol derivatives, can be prepared according to a reaction below:



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

The enantioseparations of each aromatic alcohol by GC have been reported in terms of thermodynamic parameters, calculated by two different methods. In the first method (method A), thermodynamic parameters on each column are calculated from

retention and separation factors performed at various temperatures. The other method (method B) relies on the determination of the relative retention of the enantiomer with respect to an inert reference standard (normal alkanes) on a reference column (containing only polysiloxane) and on a chiral column (containing cyclodextrin derivative dissolved in polysiloxane). The thermodynamic parameters obtained from both methods are discussed with regard to substituent type and position that affect the enantioseparation. Base on the calculation of thermodynamic parameters responsible for diastereomeric complex formation between chiral alcohol and modified cyclodextrin selector, the significant factors related to enantioseparation can possibly be revealed and; subsequently, may lead to a better understanding of the interaction mechanism.