CHAPTER I

INTRODUCTION

In living systems, a number of biological processes such as enzymatic reactions, messenger-receptor interactions, and metabolic processes proceed stereoselectively and consequently exhibit different responses to each individual enantiomer in pairs of biologically active compounds [1-2]. For instance, only L-forms of amino acids exist in natural protein while their D-forms are occasionally found in the free state. This indicates that the enzymatic conversions in amino acid metabolism can only occur specifically with L-forms of amino acids whereas D-forms possess toxicity [3]. For chiral drugs, often the main pharmacological activity resides in solely one enantiomer while several undesirable effects exist in the other: inactivity, qualitatively different effect, side effect, antagonistic effect, or fatal toxicity [1-2]. For example, (S)-penicillamine can be used as an antiarthritic drug whereas (R)-penicillamine is mutagenic [4]. (S)-Dopa (3,4-dihydroxyphenylalanine) exhibits an anti-Parkinson effect, but (R)-Dopa causes granulocytopenia (a severe eye disease) [4].

(S) : antiarthritic   (R) : mutagenic

penicillamine

(S) : anti-Parkinson   (R) : granulocytopenia
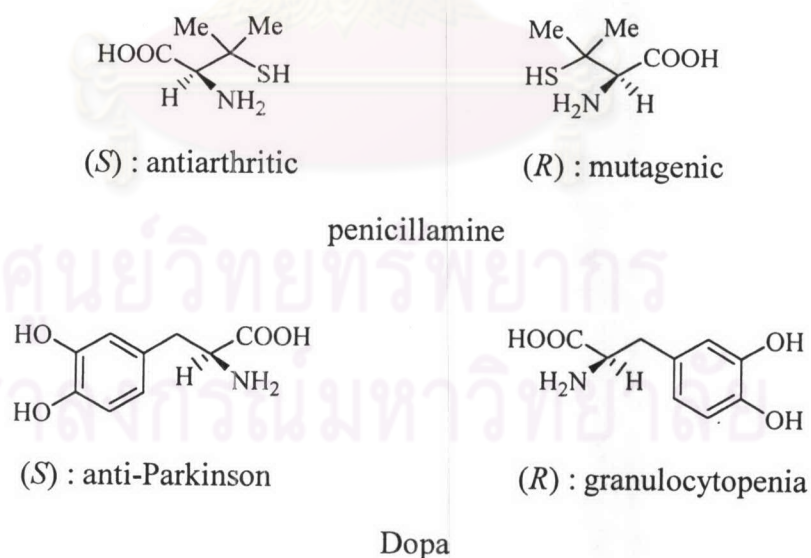
Dopa

Figure 1.1 Chemical structures of penicillamine and Dopa

All the aforementioned examples illustrate the great importance of chirality. Simply the differences in the spatial configuration of asymmetric molecules

are able to engender disastrous consequences. This results in a strong impulse for the development of techniques providing the desired pure enantiomer.

In order to obtain purely the single enantiomer of chiral compound, two basic methods are available: the asymmetric synthesis of the desirable enantiomer and the separation of prepared racemate [5]. Currently, asymmetric synthesis is a topic that arouses a lot of interest and is dynamically developing. As a consequence, enantiomeric separation techniques are highly required not only to resolve enantiomers but also to control and analyze enantiomeric purity of chiral reagents, auxiliaries, catalysts and products in the asymmetric syntheses. In general, chromatographic and electrophoretic methods are used for the analysis of enantiomers due to their simplicity and fast analysis.

Among chromatographic and electrophoretic techniques, direct gas chromatography (GC) is widely employed to analyze enantiomers of volatile and thermostable organic compounds owing to its high efficiency, sensitivity, and speed of analysis. Numerous types of cyclodextrin (CD) derivatives have been extensively synthesized and successfully used as chiral stationary phases (CSPs). Primarily, the applications of enantioselective GC involve the accurate determination of enantiomeric ratios of chiral research chemicals, intermediates, auxiliaries, metabolites, precursors, drugs, pesticides, fungicides, herbicides, pheromones, flavors, and fragrances [6].

Undoubtedly, knowledge about separation mechanisms is advantageous to designing and improving separation system. Indeed, the mechanistic aspects of enantioselective GC separation with CD derivatives as CSPs are extremely complicated and have not been entirely understood yet. In practical chiral separation, selecting the most appropriate CSP for the resolution of a group of chiral molecules with different chemical structure or even a single one is still an abstruse task which necessitates extensive experience. Typically, chiral separations have been performed through trial and error.

The enantioseparation can be influenced by many parameters such as the types and the concentration of CD derivatives, the polarity of polysiloxane, and the nature and structure of analytes. However, of all contributions to chiral

recognition, analyte structure seems to be one of the crucial factors and the easiest one to vary in chiral separation system. In fact, only a few studies into the relationships between enantioselectivities of CD derivatives and chiral analytes were previously carried out [7-14]. Therefore, this research aims at systematic investigation into the influence of analyte structure on the enantiomeric separation. Several esters and their corresponding acids examined in this study are important for the widespread use as chiral building blocks in asymmetric synthesis and as precursors in the synthesis of herbicides. Ester derivatives with different patterns of substituents, i.e. different ester chain length together with different type and position of substituent, were separated by gas chromatography using heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose (or BSiMe) and heptakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)cyclomaltoheptaose (or BSiAc), both of which were separately dissolved in polysiloxane OV-1701, as CSPs. These two phases have been used successfully for chiral separation in GC [15-20]. Thermodynamic investigation was also performed in order to acquire greater insight about the interaction between ester analytes and cyclodextrin derivatives. Hopefully, the interpretation of the data obtained from this work will provide some mechanistic knowledge about the influence of analyte structure on enantioselective selector-analyte binding interaction. This would enhance the possibility of selecting the most suitable chiral stationary phase and separation condition for the chiral recognition of these ester analytes including other esters having similar structure to the test compounds.