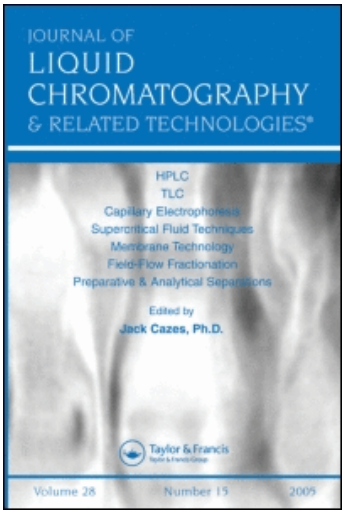

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Applications of Enantiomeric Gas Chromatography: A Review

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Abstract: Enantiomeric gas chromatography (GC) has demonstrated the potential for a broad array of applications in diverse industries; it remains a dynamic area for analytical chiral separations. This article reviews original research papers published in the period from 2001 to present, dealing with the applications of chiral GC for direct enantiomeric separation of optically active components in natural products, asymmetric synthesis, environmental contaminants and those important to space science, agricultural, food, flavor and fragrance industries. The applications are the grouped by chiral stationary phase (CSP) types and fields of interest.

Keywords: Gas chromatography, GC, Enantiomeric separation

INTRODUCTION

Chiral discrimination plays a central role in the activity of biosystems. Since the pioneer work of Gil-Av, Feibush and Charles-Sigler in 1966,[1] rapid advances in the development and understanding of enantiomeric interactions and separations have made many analyses, which were once thought to be impossible, now routine. Today, this science and technology has evolved to the point where there are often several different separation approaches from which to choose. Among them, high performance liquid chromatography (HPLC) and capillary gas chromatography (GC) are the most reliable and commonly adopted analytical techniques for the separation and quantitation of enantiomers, diastereomers, atropisomers and positional isomers. The choice of separation techniques is often governed by the properties of chiral

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molecules. GC is mainly used for the analysis of volatile and thermally stable samples. Compared to other chromatographic methods, chiral capillary GC combines the advantages of high efficiency, sensitivity and reproducibility. Ancillary techniques, such as mass spectrometer (MS), electron capture detector (ECD), head space extraction and comprehensive 2-dimensional GC (GC × GC), have made chiral GC the ideal choice for the analysis of enantiomers in complicated matrices including environmental, biological, agricultural, food, and essential oil specimens.

Enantiomers can be separated either by direct or indirect methods using capillary GC. The indirect approach involves pre-column derivatization by converting the enantiomers into diastereomers using a homochiral reagent, followed by separation on an achiral GC column. Various chiral derivatizating reagents available for GC analysis of enantiomers have been reviewed.[2,3] The success of direct GC separation of enantiomers relies on utilizing chiral stationary phases (CSPs), which can rapidly and reversibly form transient diastereomers with the targeted chiral molecules. Direct methods are straightforward and circumvent all the problems associated with chiral derivatization process in the indirect method. Except for very polar molecules, such as alcohols, amines, acids, amino alcohols and so forth, no pre-column derivatization is required to separate enantiomers. In this review article, only the direct method, i.e. using CSPs for the separation of enantiomers will be considered as this is deemed standard analytical practice.

At the center stage of direct enantiomeric GC separations is the design of broad based chiral selectors. As a result of the specific enantiomeric interactions with chiral molecules, chiral selectors are currently classified into three major categories: (A) amino acid derivatives and diamides which are capable of hydrogen-bonding with chiral analytes; (B) chiral metal complexes which can interact with analytes through coordination (or complexation); (C) cyclodextrin (CD) derivatives which separate enantiomers by forming an inclusion complex, dipole-dipole interactions, or other specific mechanisms dependent on the CD derivative employed. The chiral selectors have been used as nonvolatile neat liquids, or dissolved in achiral carriers (most commonly polysiloxanes), and chiral polysilaxoanes (Chirasil-type) which have chiral selectors chemically bonded to a polysiloxane backbone. General methodologies, separation mechanisms, scope, limitations, and applications, have been summarized in several excellent review articles.[4–7]

Among three chiral selector categories, the importance of chiral metal complex stationary phases has diminished dramatically with the advent of CD derivatives as CSPs in enantioselective GC. This trend is clearly revealed from a recent survey of publications dealing with separations of enantiomers using chiral capillary GC (Fig. 1). The use of chiral metal complex stationary phases has dropped to zero in the period of January, 2001 to July, 2004. On the other hand, derivatized cyclodextrin CSPs account for almost 90% of successful enantiomeric GC separations, while

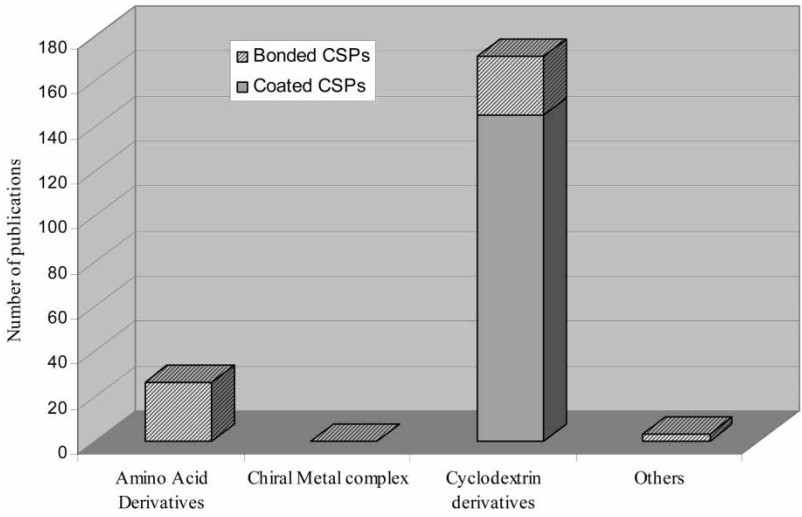

Figure 1. Statistical numbers of applications of different capillary GC chiral stationary phases in recent publications appeared in the period of January, 2001 to July, 2004. Several different types of chiral CSPs may be used in the same applications.

amino acid derivatives CSPs were restricted to specific applications. Therefore, the present review article will focus on the applications using amino acid derivatives and derivatized cyclodextrin GC CSPs. Readers who have interest in practice and theory of enantioselective complexation GC may refer to a recent review by Schurig.[6] Mechanistic studies of chiral separations will be excluded from this survey and detailed discussions can be found in above mentioned review articles.[4–7]

This article is divided into two sections based on the specific types of capillary GC CSP. Each section contains several subsections representing the most recent developments of the specific CSP type and the fields where the particular enantiomeric GC was applied.

CSPS BASED ON AMINO ACIDS AND DIAMIDES

CSP Descriptions

Since Gil-Av et al. introduced the first reproducible GC CSP based on N-trifluoroacetyl-L-isoleucine lauryl ester in 1966,[1] numerous hydrogen-bonding chiral phases have been developed.[4] Among them, Chirasil-Val, which is prepared by covalently anchoring L-valine-tert-butylamide units to a polydimethylsiloxane backbone with random distribution along the

backbone, is one of the most successful and versatile GC CSPs.[8] In an attempt to expand the usefulness of hydrogen-bonding GC CSPs, a few new phases have been reported recently.[10–14] A highly ordered Chirasil-type GC phase, namely Chiral-Calix, was synthesized by covalently linking resorcinarenes, which have pendant L-valine-*tert*-butylamide moieties, to a dimethylpolysiloxane.[10,11] Compared to Chirasil-Val, Chiral-Calix did not demonstrate any significant improvement in enantioselectivity.

Inspired by the success of *trans*-cyclohexylene bis-benzamide based CSP in LC and supercritical fluid chromatography (SFC), a copolymeric (1*R*-*trans*)-*N*,*N*′-1,2-cyclohexylene-bis-benzamide oligodimethylsiloxane (ChDA) was prepared and investigated as a new chiral stationary phase for capillary GC.[12] The ChDA phase demonstrates high enantioselectivity towards a broad spectrum of chiral molecules. However, this chiral stationary phase has a limited working temperature range of 110–260°C, and only shows high efficiency at the temperatures above 150°C.

To solve some problems surrounding Chirasil-Val, especially inadequate separation of Proline, a new diamide chiral polydimethylsiloxane phase based on (S)-(−)-*t*-leucine-(S)-(−)-1-(α-naphthyl)-ethylamide was synthesized, and also a new derivatization method was introduced converting amino acids into their N-pivaloyl derivatives by reacting with pivaloyl chloride under basic conditions.[13] The N-pivaloyl derivatives of most proteinogenic amino acids, especially Pro, have been easily base-line separated on this diamide phase. Unfortunately, the column was not so successful in the analysis of multi-functional amino acids of Asp, Glu, Orn, Lys, and Trp because of their low volatility. Most recently, a similar Chirasil-type CSP with (S)-(−)-*t*-leucine-(S)-(−)-1-phenylethylamide as chiral selector was introduced by the same research group. The enantiomers of warfarin, which is typically separated by an HPLC method, was successfully resolved on this chiral phase after conversion into *O*-perfluoroacyl derivative.[14]

Applications of CSPs Based on Amino Acids and Amides

CSPs based on H-bonding interaction have been used for a large variety of chiral molecules with different structures, including amino acids, amines, amino alcohols, hydroxyl acids, halo acids, alcohols, diols, carbohydrates and carbonyl containing compounds.[9] Generally, polar analytes need to be derivatized before subject to a chiral GC separation. For example, amino acids are usually derivatized to *N*(*O*)-perfluoroacyl isopropyl esters in order to increase their volatility and introduce function groups which enhance the enantiomeric interactions with the CSP.[15] In this methodology, carboxylic acids are transformed to amides and alcohols to urethanes.[7]

Chirasil-Val is a particular powerful alternative for the analysis of certain types of compounds such as α-amino acids because of its high efficiency and sensitivity. It is extremely useful in the detection of free or protein-bound amino acids in complex matrices, such as human urine and blood serum,[18] soils,[19] royal jelly,[20] plants (leaves of coniferous and decidious trees, fleshy fruits, leaf blades of fodder grasses, seeds and seedlings of edible legumes),[21] and coffee.[22] Mass spectrometry (MS) is commonly chosen as the detection method for most of these applications.

Selenomethionine, often called the wonder mineral, is a common constituent of food supplements. Chirasil-Val was used to determine both D- and L-enantiomers of selenomethionine in food supplements on the market and their presence in urine by capillary gas chromatography-inductively coupled plasma mass spectroscopy (CGC-ICPMS).[16] In this method, Selenomethionine was extracted from the pills with 0.1 N hydrochloric acid and then derivatized with ethylchloroformate (ECF) before analysis. A similar GC-ICPMS method was reported to determine selenomethionine enantiomers in selenized yeast.[17] A comprehensive overview concerning direct chiral GC separation of selenoaminoacids can be found in an earlier review article.[42] Most recently, a new method was proposed to perform the derivatization of chiral amino acids occurring in complex samples using supercritical carbon dioxide as both the reaction medium and the agent used to extract the obtained derivatives prior to enantiomeric chromatographic analysis.[41] A Chirasil-L-Val capillary column enabled the separation of the D- and L-forms of the amino acids as their *N*(*O*)-pentafluoropropionyl 1-propyl esters.

In an effort to investigate the origin of biomolecular chirality, Chirasil-Val was recently chosen by the European Space Agency (ESA) for the Cornerstone Mission ROSETTA, which will be launched in 2012 to probe for cometary amino acids. The experimental results of this Mission will shine light on all possible hypotheses.[23] To accelerate the analysis of chiral products generated by combinatorial chemistry in drug discovery process, an improved automated GC chiral analysis system was developed. The system, which incorporates a reactor, allows automated esterification and acylation of amino acids. Chirasil-Val column was used to test several non-natural amino acids with respect to their stereoisomeric configuration. In proteome research, acid hydrolysates of food proteins and tissues obtained by autopsy were analyzed with Chirasil-Val column.[24] Recently, several diamino acids, including D,L-2,3-diaminopropanoic acid, D,L-2,4-diaminobutanoic acid, 4,4′-diaminoisopentanoic acid, 3,3′-diaminoisobutanoic acid, and 2,3-diaminobutanoic acid were identified from Murchison meteorite samples using chiral GC-MS. Their concentrations were determined in parts per billion range after chemical transformation into *N*,*N*-diethoxycarbonyl ethyl ester derivatives.[25] The results obtained in this study favor the assumption that not only amino acids (as the required monomers of

proteins) form in interstellar circumstellar environments, but also the family of diamino monocarboxylic acids, which might have been relevant in prebiotic chemistry. A GC-MS method based on Chirasil-Val to check enantiomeric purities of synthesized chiral peptide nucleic acids (PNAs) was reported.[34] This method was used to evaluate the effect of synthetic parameters (coupling agent, base, preactivation time) on epimerization.

Chiral GC with amino acid based CSPs is a useful tool in the elucidation of the stereochemistry of natural products. Recently, several new bioactive peptides, tunichrome *Sp*-1,[26] lokisin,[27] leucamide A,[28] subtilosin A,[29] and cyclodecapeptide designated phakellistatin 12 (a new cancer cell growth inhibitory),[35] were isolated and characterized. Their structures were identified by hydrolysis and conversion to constituent amino acids by GC on a Chirasil-Val column. The absolute stereochemistry of novel amino acid derived natural products from the Ascidian *Atriolum robustu*m,[30] cytotoxic pyrroloiminoquinones from four new species of South African Latrunculid sponges,[31] semiplenamides A-G, fatty acid amides from a Papua, New Guinea Collection of the Marine Cyanobacterium *Lyngbya semiplena*[32] were established in similar ways. The absolute configuration of nobiloside, a neuraminidase inhibitor which contains a trisaccharide moiety, was also determined on a Chirasil-Val column.[33]

Moreover, Chirasil-Val was used in the separation of enantiomers with structures other than amino acids. Soman (O-1,2,2-trimethylpropyl methylphosphonofluoridate) is an extremely toxic organophosphorus agent with two chiral centers of carbon and phosphorus. Its four steroisomers, designated as C(+)P(+), C(+)P(−), C(−)P(+), C(−)P(−), were baseline separated on a Chiral-Val column.[36,37] Studies showed that 3-(2V-phenyl-2V-cyclopentyl-2V-hydroxyl-ethoxy) quinuclidine (8018)[36] and verapamil[37] were effective on eliminating soman in rat. A sensitive, specific and reproducible chiral GC-MS using Chirasil-Val was developed for the stereoselective determination of mephenytoin (MP) in human urine.[38] This method is suitable for the phenotypic evaluation of CYP2C19 activity using mephenytoin.

CSPS BASED ON CD DERIVATIVES

CSP Descriptions

It is clearly shown that CD derivatives are the most popular chiral selectors in the direct enantiomeric GC separation of volatile recemates in the most recent years (Fig. 1). Their applications cover almost all of fields where other CSPs are applied. For example, direct chiral GC separation of *N*(*O*)-trifluoroacetylalkyl ester derivatives of amino acids can be done on both modified cyclodextrins and Chirasil-Val CSPs.[24,39,40,50,68] A large number of GC CSPs based on cyclodextrins differing in size and type and site of

substitution have been synthesized and proved to be useful in separating a large variety of chiral molecules. The structures of CD derivatives employed as GC CSPs and their most recent applications are summarized in Table 1.

The enantiomeric selectivities of CD derivatives CSPs are greatly influenced by the cavity size and percentage of cyclodextrins (α, β, or γ), type and the percentage and the degree of substitution on positions (2-, 3-, and 6-position of glucose units of CD) of the substituents.[4,7] In some cases, the elution order of a chiral molecule can be reversed by simply changing the size of the CD.[7] It is believed that the type and site of substitution is at least of equal importance.[43,48] For these reasons, small changes in the cyclodextrin composition can significantly influence the enantioselective properties of the CSP. Incomplete substitution reaction often yields a mixture of CD derivatives. Therefore, the synthesis of CD derivatives must be carefully controlled to give unambiguous structures.[49] The obtained products must be completely characterized so as to avoid reproducibility problems.[47]

For complicated samples containing chiral molecules with different polarities or function groups, more than one CD derivative CSPs with different enantiomeric selectivities are often needed to separate all desired enantiomers. In recent years, several strategies have been proposed to combine the advantageous properties of two or more CD derivatives.[43–46] The simplest way is to coat the capillary with a mixture of two CSPs with complementary enantiomeric selectivity. Recently, Chiramix, a new chiral GC column coated with a mixture of heptakis-(2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin (2,6-Me-3-Pe-β-CD) and octakis-(2,6-di-*O*-methyl-3-*O*-trifluoroacetyl)-γ-cyclodextrin (2,6-Me-3-TFAc-γ-CD), was proved to be greatly superior to those with a single chiral phase for the separation of multicomponent samples, such as peach flavours, which contain chiral compounds with various functional groups. The enantiomeric purities of several components of monoterpene hydrocarbons, alcohols, ketones and lactones were determined simultaneously.[45]

Another alternative method is to tune the properties of CD derivative by specific substitution. As an example, the enantiomeric separation properties of two parent CD derivatives, heptakis(6-*O*-*tert*-butyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrin and heptakis(2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin, were combined by exchanging a methyl group for an acetyl substituent in a single glucose unit of heptakis(6-*O*-tertbutyldimethylsilyl-2,3-di-*O*-methyl)-β-cyclodextrin.[43] Similarly, the properties of 2,3-di-*O*-methyl- and 2,3-di-*O*-acetyl-6-*tert*-hexyldimethylsilyl-γ-cyclodextrins was combined by introducing methyl and acetyl groups to the same 6-*tert*-hexyldimethylsilyl-γ-cyclodextrin (THDMS-γ-CDs), which afford 2-*O*-methyl-3-*O*-acetyl- and 2-*O*-acetyl-3-*O*-methyl-derivatives of (THDMS-γ-CDs) with 2-*O*-methyl-3-*O*-acetyl-6-*O*-THDMS-γ-CD showing higher enantioselectivity.[44] A new hybrid Chirasil-type CSP, named Chirasil-Calixval-Dex,

Table 1. Derivatized cyclodextrins stationary phases employed in most recent applications of chiral gas chromatography

GC chiral selector	Coated or bonded	Trademark	Vendor	Application	Reference
Hexakis (2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl)-α-cyclodextrin	Coated	Chiraldex A-TA	ASTEC	Nitroalkenes	[81]
Hexakis (2,3,6-tri-*O*-pentyl)-α-cyclodextrin	Coated	Lipodex-A	Macherey-Nagel	α-Ketoester hydrogenation	[79]
Heptakis (2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin	Coated	β-DEX325	SUPELCO	Lactone thio, thiono, dithioderivatives	[184]
		Chiraldex B-DM	ASTEC		
		Cyclosil-B	J&W Scientific	Bicyclic γ-lactone	[93]
		Hydrodex	Macherey-Nagel	γ-Butyrolactone derivatives	[62]
		β-6TBDM9		β-Irones	[150]
		Rt-βDEXsm	Restek	PCBs	[102,104,105,112]
		BGB-176	BGB Analytik	Diterpene	[141]
				Bicycloheptane	[94]
				α-HCHs	[113]
				CTTs	[107,110]
				Metolachlor	[118]
				Polychlorinated Bipyrrole	[111]
				Sesquiterpenes	[144,147,154]
				Essential oils	[165,166]
				Monoterpenes	[64,151,158,163]
				Sulfoxides and sulfinate esters	[57]
				1,2-*O*-isopropylidene-sn-glycerol	[77]
				Flovour	[161]

				Secondary alcohols	[73,74]
				Sex pheromone	[126,127]
				Positional isomers	[179]
				Pesticides	[116,117]
				Fragrances	[172]
				Methyl dihydrojasmonates	[170]
Heptakis (2,3-di-*O*-ethyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin	Coated	Rt-βDEXse EtTBS-β-CD	Restek MeGA	Monoterpene, Chiral alcohols 3-Hydroxy acids Positional isomers Essential oils	[86,87,160] [26,88] [142] [179] [168]
Heptakis (2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin	Coated	β-DEX225 Rt-βDEXsa	SUPELCO Restek	Lactone thio, thiono, dithioderivatives β, γ-Lactones Monoterpenes Sex pheromones 3-Hydroxy acids Aroma	[184] [132,139,178] [64,151,182] [26,128] [142] [172]
Heptakis (2,6-di-*O*-methyl-3-*O*-pentyl)-β-cyclodextrin	Coated			Isoprenoids Ring-bonded α-amino acids Chiral acids Amino acid derivatives Sex pheromone Terpenes	[152] [153] [76] [40] [33] [169]
Heptakis(2,6-di-*O*-nonyl-3-*O*-trifluoroacetyl)-β-CD	Coated			Mandelates and its analogs	[58]

(*continued*)

Table 1. Continued

GC chiral selector	Coated or bonded	Trademark	Vendor	Application	Reference
Heptakis (2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl)-β-cyclodextrin	Coated	Chira ldex B-TA	ASTEC	Carnitine derivative	[85]
Heptakis (2,3,6-tri-*O*-methyl)-β-cyclodextrin	Coated	CYDEX-B	SGE Ltd, UK	PCBs	[106]
		CP-Cyclodextrin-β-2,3,6-M-19	Varian/Chrom-Pack	Glucopyranosides	[180]
				Polychlorinated substances	[47,111]
		β-DEX 120	SUPELCO	Quinolizidine	[145]
		Cyclodex-B	J&W Scientific	Furan derivatives	[60]
		Hydrodex-β-PM	Macherey-Nagel	Odorants	[183]
		Rt-βDEXm	Restek	Ketones	[82]
				α-Ketoester hydrogenation	[79]
				Tartaric acid	[88]
				Sex pheromones	[123,129,130,135]
				Hydroxy acids	[91]
				Amino acid derivatives	[40]
				Curtisians	[148]
				Essential oil	[167]
				Positional isomers	[63,179]
				Monoterpenes (aroma)	[64,87,156]
				Fragrance	[157,162]
				α-Hydroxy fatty acids	[67]
	Bonded	Chirasil-DEX CB	Varian/ChromPack	PCBs	[100,102–105]
		Chirasil-β-Dex	Restek	CTTs	[107,110]

				Diterpenes	[140]
				Terpenes	[173,174]
				Aliphatic hydrocarbons	[59]
				Aryl- and heteroarylcarbinols	[61]
				Sex pheromones	[125]
Heptakis (2,3,6-tri-*O*-methyl)-β-cyclodextrin	Bonded	C11- Chirasil-β-Dex		Secondary alcohol	[71,72]
				Racemic-conglomerate crystallization	[98]
Heptakis (2,3,6-tri-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin	Coated	BGB-172	BGB Analytik	PCBs	[105]
				Pesticides	[108,109,116,119]
Heptakis (2,3,6-tri-*O*-ethyl)-β-cyclodextrin	Coated			Methyl-branched alcohol and acids sulfur-containing aroma	[149] [159]
(S)-Hydroxypropyl derivatized)-β-cyclodextrin	Coated	Chiraldex B-PH	ASTEC	Thiazolinecarboxylates	[89]
				PCBs	[102,103]
Octakis (bis-*tert*-butyldimethylsilyl)-γ-cyclodextrin	Coated			Metalaxyl	[120]
Octakis (2,3-di-*O*-acetyl-6-*O*-*tert*-butyldimethylsilyl)-γ-cyclodextrin	Coated	γ-DEX 225 Rt-γDEXsa	SUPELCO Restek	Branched hydrocarbons	[121]
Octakis (2,6-di-*O*-methyl-3-*O*-pentyl)-γ-cyclodextrin	Coated			Sesquiterpene	[144]
Octakis (2,6-di--pentyl-3-*O*-trifluoroacetyl)-γ-cyclodextrin	Coated	Chiraldex G-TA	ASTEC	Glucopyranosides (aroma)	[180]
				Sulfoxides and sulfinate esters	[157]
				Epoxides	[78,90]

(*continued*)

Table 1. Continued

GC chiral selector	Coated or bonded	Trademark	Vendor	Application	Reference
				Substituted carbocycles	[80]
Octakis (2,6-di-*O*-pentyl-3-*O*-propionyl)-γ-cyclodextrin	Coated	Chiraldex G-PN	ASTEC	Sulfoxides and sulfinate esters	[57]
Octakis (2,3,6-tri-*O*-methyl)-γ-cyclodextrin	Coated	γ-DEX 120	SUPELCO	Bicyclic γ-lactone	[93]
			SGE Ltd, UK	Alkaloids, hemiterpenoids	[96]
				Chlodane	[114,115]
Octakis (2,3,6-tri-*O*-ethyl)-γ-cyclodextrin	Coated			Pesticides	[134,157]
Octakis (3-*O*-butanoyl-2,6-di-*O*-pentyl)-?γ-cyclodextrin	Coated	Lipodex-E	Macherey-Nagel	Cyclic β-ketoesters	[84]
		Chiraldex G-BP	ASTEC	Amino acids	[68]
				Flavor compounds	[181]
				Sulfoxides and sulfinate esters	[57]
				Lactones	[97]
				Insecticides	[146]
				Essential oils	[168]
				Anesthetics	[66]
				Halodiether B	[161]
	Bonded	Chirasil-γ-DEX		Halogenomethanes	[65]
Octakis (2,3-di-*O*-pentyl-6-*O*-methyl)-γ-cyclodextrin	Coated			Isoprenoids	[152]
				Homoterpene esters	[133]
				Chiral alcohols	[85]
				Sex Pheromones	[124]

was synthesized by chemically bonding a resorcinarene with pendant permethylated β-cyclodextrin to poly(hydromethyl) dimethylsiloxane.[46] It is shown that Chirasil-Calixval-Dex retains the individual enantioselectivites of the known phases Chirasil-Calixval and Chirasil-Dex. The enantiomers of both apolar hydrocarbons and polar amino acid derivatives can be separated on this mixed CSP.

Applications

Since its introduction in the late 80s, derivatized CD CSPs have separated a broad spectrum of chiral molecules with different geometries and functionalities. These chiral compounds are of great importance to the pharmaceutical,[9] agricultural,[122] food,[54] flavor and fragrance[55,56] industries, and environmental protection.[51–54] Separations of new classes of chiral compounds continue to be reported in scientific journals.[57–66] Chiral sulfoxides, as an example, are important bioactive compounds and intermediates for synthetic reactions. Volatile chiral sulfoxides have been separated with great facility on several CD derivative CSPs, among which heptakis (2,6-di-*O*-pentyl-3-trifluoroacetyl)-γ-cyclodextrin (DPTFA-GCD) phase exhibited superior enantioselectivity for most sulfoxides and sulfinate esters. DPTFA-GCD and heptakis (2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin phase (DMTBDS-BCD) generally gave opposite elution orders for most of the compounds studied.[57]

Mandelates and their analogs, which are important intermediates in asymmetric synthesis and pharmaceutical chemistry, were separated on both heptakis (2,3,6-tri-*O*-methyl)-β-cyclodextrin (PMBCD) and heptakis(2,6-di-O-nonyl-3-*O*-trifluoroacetyl)-β-CD (DNTBCD).[58] Either coated or bonded PMBCD phase is suitable for the separation of saturated chiral aliphatic hydrocarbons,[59] enantiomers and geometrical isomers of furan derivatives,[60] position isomers of xylenes and dimethylnaphthalenes,[63] aryl- and heteroarylcarbinols,[61] and α-hydroxyl fattic acid esters.[67] DIMET-BCD phase was found useful in the separation of γ-butyrolactones and analogous alcohols (62), geometric isomers of terpene derivatives.[64] Octakis(3-*O*-butanoyl-2,6-di-*n*-pentyl)-γ-cyclodextrin phase is extremely successful in the separation of chiral halogenomethanes, such as CHFBrI and CHFClI,[65] and various chlorinated/fluorinated ethers (inhalation anesthetics).[4,66]

In the following context, the applications of derivatized CD CSPs are classified into several groups according to the fields where they are applied.

Asymmetric Synthesis

The development of high enantioselective and efficient GC CSPs has been one of the driving forces for the popularity of asymmetric synthesis. Enantiomeric

purity and stereochemistry of chiral products are important issues in asymmetric synthesis. It is a common practice to seek the answers for these questions by the analysis of products using enantiomeric GC technologies. (R)-3-hydroxyalkanoic acids is a group of biological significant compounds with antimicrobial, insecticidal and antiviral activities. Recently, it was demonstrated that one of the efficient approaches to prepare enantiomerically pure (R)-3-hydroxyalkanoic acids and (R)-3-hydroxyalkanoic acid methylesters was based on hydrolysis of poly(hydroxyalkanoate) copolymers synthesized by Pseudomonas putida (91). Chiral GC analysis proved that the (R)-enatiomers of both 3-hydroxyoctanoic acid and 3-hydroxyoctanoic acid methylester were present in products at a very high enantiomeric excess (>99.9%). Similarly, the structures and absolute configurations of many synthesized chiral products, including some bicyclic γ-lactones,[93] brominated (+)-methylenefenchone,[94] several o-dibenzylic diols,[95] a range of alkaloid and coumarin hemiterpenoids,[96] and 5-hydroxydecano-4-lactones[97] were confirmed with chiral GC methods. In a study of temperature-dependent racemic compound-conglomerate crystallization, enantiomeric GC was proposed as a simple method to detect conglomerate formation of 2,3:6,7-dibenzobicyclo[3.3.1]nona-2,6-diene-4,8-dione.[98]

Chiral GC is a convenient approach to monitor reactions and screen enantioselective catalysts. Modified β-CD CSPs were commonly used to determine the enantiomeric purity of both substrates and products, and DMTBDS-BCD was found to be the most popular GC CSP in all these applications.

Enzyme-mediated transformation is an important strategy to access enantiomerically pure secondary alcohols. One type of most often used enzymes are lipases, whose natural function is to catalyze the hydrolysis of triacylglycerol ester bonds and/or the synthesis of the same triacylglycerol ester bonds. Depending on the organic medium employed, these enzymes are able to catalyze hydrolysis, esterification, transesterification and interesterification reactions.[69] Lipases from different strains of *Pseudomonas* have been used to kinetically resolve racemates of secondary alcohols through transestification.[70–75] Racemic acids were resolved by using lipases from *Candida* through esterification, however, different acids require different combination of lipases and organic solvents.[76] 1,2-*O*-isopropylidene-sn-glycerol (IPG) ester was kinetically resolved in the presence of lipase A of *Bacillus subtilis*.[77] The result from a recent study showed that 4-hydroxyacetophenone monooxygenase (HAPMO), an enzyme from *Pseudomonas fluorescens* ACB, has a remarkably broad substrate range and is capable of enantioselective formation of lactones from ketones and stereoselective sulfoxidation.[92] Given the importance of sulfur-containing compounds in flavor chemistry, enzyme-catalyzed reactions have been proposed as strategies to obtain flavoring-type sulfur-compounds. Lipase B from *Candida antarctica* was proved to be effective in the enantioselective hydrolysis of 3-acetylthiohexanal resulting in (S)-configured thiol products.[159]

Another important class of catalysts for asymmetric synthesis is chiral transition metal complexes. A wide range of reactions have been successfully promoted by the use of a single enantiomer of a transition metal complex, affording an enantio-enriched product.[78–84] A dimeric homochiral Mn(III) Salen complex was found to be an excellent catalyst for the enantioselective epoxidation of non-functionalised alkenes using oxone as oxidant. High chiral induction (>99%) was obtained in case of nitro and cyano chromene determined by chiral GC with an octakis (2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl)-γ-cyclodextrin (DPTFA-GCD) column.[78] Cinchona-modified Platinum gave excellent ee values of products in sono-chemical hydrogenation.[79] A cationic rhodium bis(phosphine) complex was identified as an effective catalyst for enantioselective cyclizatio/hydrosilylation of 1,6-enynes.[80] Chiral titanium complexes was proved to be effective catalysts for dehalogenation of alkyl halides, however, there was no detectable difference in the rate of reduction between the two enantiomers of alkyl halides, which implies a radical reaction mechanism.[83] In a study of enantioselective Michael additions of cyclic β-ketoesters to methyl vinyl ketone catalyzed by cinchona alkaloids, chiral GC results revealed that the induced enantioselectivity was significantly influenced by both the structure of the catalyst and that of the substrate.[84]

The dependence of chiral catalysts and the structure of the substrate require a high-throughput screening methodology to quickly identify efficient catalysts and optimize reaction conditions. For this purpose, a multi-substrate screening methodology using chiral GC-MS analysis was demonstrated by enantioselective alkylation of prochiral aldehydes catalyzed by norephedrine-derived β-amino alcohols.[85] Chiral GC analysis of the crude product mixture using octakis(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin as the CSP avoids time-consuming workup procedures. This protocol can determine the chemical yield, enantioselectivity, substrate specificity, and catalytic activity of the chiral catalysts as well as the induced absolute configuration in a single screening experiment. In another high-throughput procedure, copper-phosphoramidites were evaluated as catalysts for conjugate addition of diethylzinc to nitroalkenes; up to 9 different substrates were used in one-pot reaction. The crude product containing 9 pairs of enantiomers was analyzed simultaneously in a single run by chiral GC with hexakis (2,6-di-*O*-pentyl-3-*O*-trifluoroacetyl)-α-cyclodextrin (DPTFA-ACD) as CSP (Fig. 2).[81]

Chiral GC also helped to validate a high-throughput NMR technique, using isotopically chiral probes, for the analysis of amino alcohol-ruthenium arene-catalyzed asymmetric transfer hydrogenation.[82] This method allowed fast identification of simple catalysts for reduction of dialkyl ketones.

Chiral GC can even provide evidence to elucidate reaction mechanism.[86–90] Recently, chiral GC shed light into the mechanism of

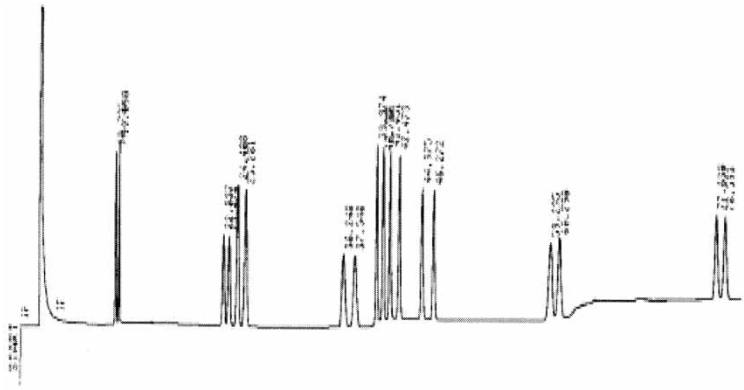

Figure 2. GC chromatogram for one-pot multi-substrate conjugate addition of diethylzinc to nitroalkenes. 9 chiral nitroalkenes were separated in a single run with CHIRALDEX A-TA column.[81]

monoterpene cylclization catalyzed by monoterpene synthases (cyclases). Chiral GC and mass spectrometry analysis revealed that normal cyclization of geranyl diphosphate by (−)-4S-limonene synthase and by (−)-pinene synthase proceeds via preliminary isomerization to the bound tertiary intermediate 3S-linalyl diphosphate, whereas the cyclization catalyzed by (+)-bornyl diphosphate synthase proceeds via the intermediate 3R-linalyl diphosphate. In another investigation of the nitroxide-mediated oxidation of D-glucose to D-glucaric acid, the degradation pathway of glucose was proposed and side products were determined based on chiral GC analysis.[88] Recently, the mechanism of MnO_2-mediated asymmetric oxidation of thiazolidines[89] and amine catalyzed epoxidation[90] were also proposed.

Essential Oils, Aromas, and Flavors

Characterization of volatile oils, such as essential oils, is extremely difficult and laborious task since these volatile oils are chemically diverse mixtures. GC is an indispensable technique used to identify unknown constituents of volatile oils. Methods, based on various retention ratios which can be calculated using standard solutes, were proposed to chemically characterize unknown solutes in volatile oils. In one such method involving dipentyl (DA) cyclodextrin phases, γ-DA/α-DA ratios indicated a bicyclic or monocyclic monoterpenoid. The applications and state-of-the-art of this methodology has been reviewed by Betts and the methodology is illustrated in Fig. 3.[56] More often the identification of the components of volatile oils is

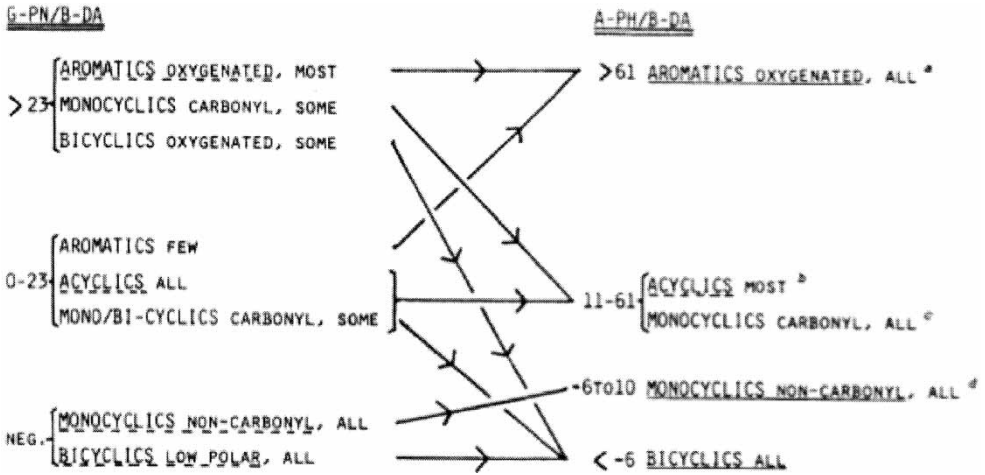

Figure 3. Solute groupings found for various relative retention time (n-undecane = 1.00) percentage increases on changing from Chiraldex B-DA to the other phase indicated (G-PN or A-PH). (a) Together with acyclic geraniol; (b) together with aromatic hydrocarbon p-cymene. Acyclic alcohols give over 35% increase A-PH/G-PN. (c) Some carbonyl monocyclics have been in a different group before. (d) Monocyclic alcohols can be detected using Chiraldex B-PH/A-PH, where they give 40–50% increase.[56]

completed by GC-MS analysis or by comparison with authentic standards. In addition to the identification of unknown components, the determination of enantiomeric composition is of great importance in fields of essential oils, aroma and flavors, since the enantiomeric information of these matrices will help to characterize a vegetable matrix or extract, evaluate the biosynthetic pathway of one or more of their components, and establish the origin and/or to identify possible adulterations.

The major constituents found in essential oils, such as α-pinene, β-pinene, myrcene, β-ocimene, α-phellandrene, *p*-cymene, *cis*-ascaridol, *(E)*-caryophyllene, germacrene D, limonene and linalool, belong to terpenes, an important class of natural products. CD derivative CSPs have played a crucial role in identifying major terpene constituents in various samples of essential oils. A comprehensive review of using CD derivative CSP for enantiomeric separation of enantiomers in essential oils, aroma, and flavor can be found in a recent article.[55] Heptakis (2,3-di-*O*-methyl or ethyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin and octakis (3-*O*-butyryl-2,6-di-*O*-pentyl)-γ-cyclodextrin are probably the most popular CSPs used for this purpose.[164–169] In recent applications, both CSPs were applied to determine enantiomeric compositions or profiles of essential oils of *Erechtites hieracifolia* from Bolivia,[164] two Mandarin cultivars from southern Brazil,[165] aromatic Verbenaceae species *Lippia albaMill.* N. E. Br. from southeastern Brazil,[166] long-time stored Dill (*Anethum graveolens* L.) seeds from Bulgaria,[167] a Uruguayan biotype of *Salvia sclarea* L.,[168] and some *Salvia* species.[169]

In addition to essential oils, aroma and flavor from various sources were analyzed with chiral GC. 1-octen-3-ol is the main odorant of mushroom aroma and only (R)-(−)-enantiomer gives desired fruity mushroom-like characteristic. In a recent study, the optical purity of (R)-(−)-octen-3-ol in various species of edible mushrooms was found to be in the range of 98.5% to 82.1%.[175] Very high quantities of monoterpenes, such as 3-carene, (Z)-β-ocimene, β-phellandrene, and terpinolene and the sesquiterpenoids (E)-β-caryophyllene and caryophyllene oxide were detected in black currant aroma obtained from leaves, buds, and berries of *Ribes nigrum* L.[176]

The characteristic flavor of wines is linked to the many different types of compounds. Monoterpenes are the most important flavor compounds of several white wines and also precursors for other flavoring compounds of wines, such as linalool, nerol and geraniol, several highly odiferous cyclic ethers and lactones. In an effort to understand the oxidative metabolism of monoterpenes in grapes, enantiomeric analysis of various free and glycosidically bound monoterpene polyols in musts of two aromatic grapes were achieved simultaneously with multidimensional chiral GC-MS.[151] A typical chiral GC chromatogram is shown in Fig. 4. Esters represent another group of wine flavor. Several chiral 2- and 3-methyl substituted isomers of butanol, butyl acetate, and butanoic acid and its ethyl ester, were

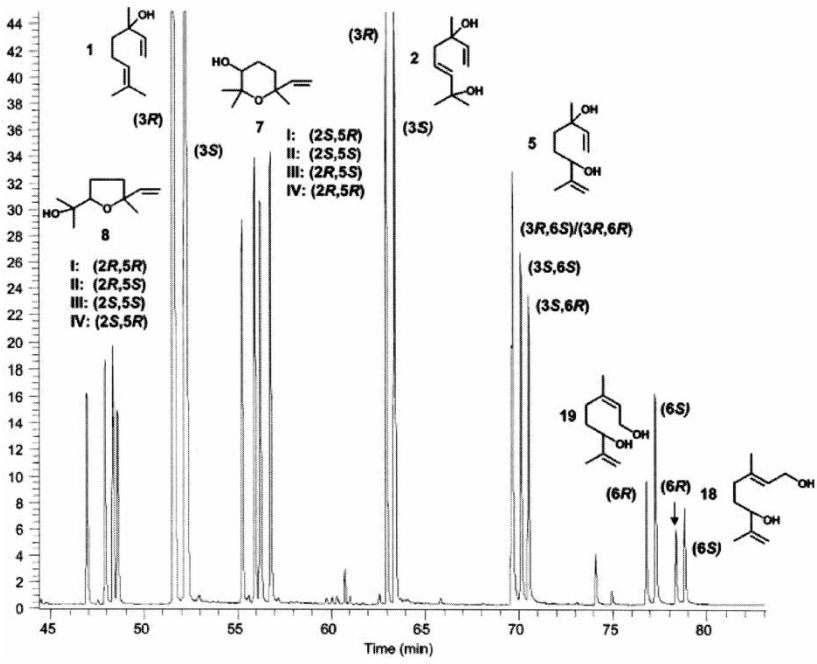

Figure 4. Chromatogram of racemic standard compounds 8, 1, 7, 2, 5, 19, and 18 on heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodexrin CSP. The elution order of linalool oxide stereoisomers is indicated by Roman numerals.[151]

simultaneously resolved with cryogenic modulated comprehensive two-dimensional chiral GC.[179]

The coupling of chiral GC and olfactometry allows the study of the odoriferous property of individual enantiomers. One application of chiral GC/olfactometry is aroma extract dilution analysis (AEDA). This method has been used to investigate the characteristic odor components of Kabosu cold-pressed oil, flavor dilution factors, and relative flavor activities. The result showed that (R)-(+)-citronellal is a characteristic element of Kabosu peel oil odor while (S)-(−)-citronellal was described as sweet and turpentine-like.[182] In a recent study of Chinese jasmine green tea scented with jasmine flowers (Jasminum sambac), 66 odorants, including linalool, methyl anthranilate, 4-hexanolide, 4-nonanolide, (E)-2-hexenyl hexanoate, and 4-hydroxy-2,5-dimethyl-3(2 H)-furanone, were identified from the extract. (R)-(−)-linalool and methyl anthranilate were found to be the key odorants of the jasmine tea flavor.[183] Sulfur-containing volatiles are potent flavor compounds and play critical roles in the aroma patterns of several fruits. Recently, thio-, thiono- and dithio- derivatives of s (*Cis*- and *trans*-3-methyl-4-octanolide) were synthesized. GC/olfactometry analysis

showed that *cis*-thio-whiskey lactone is a sweet coconut-like odor, while the *cis*-thiono- and *trans*-dithio-derivatives are pleasant mushroom-like flavors.[184]

Enantioselective sensor can be an alternative tool for the determination of enantiomeric composition of chiral flavoring gas mixture. Quartz-crystal microbalance (QCM) sensors coated with three β-CDs derivatives were used to analyze a limonene sample. Heptakis(2,3-di-*O*-methyl-6-*O*-*ter*t-butyldimethylsilyl)-β-CD and heptakis(2,3-di-*O*-ethyl-6-*O*-*ter*t-butyldimethylsilyl)-β-CD gave better response than heptakis(2,3–di-*O*-acetyl-6-*O*-*ter*t-butyldimethylsilyl)-β-CD.

In the past few years, coupling achiral and chiral GC (usually CD derivative CSPs as the secondary column) has been an integral part of this complex analysis which has been further enhanced with the use of Mass Spectrometry. This multidimensional approach has allowed for rapid component and chiral analysis. The powerfulness of 2-dimensional GC has been demonstrated by the measurement of enantiomeric distribution of several monoterpene compounds in bergamot essential oil. Total analysis time of the target components was only 8.5 min.[160] Most recent applications of 2-dimensional GC technique include studying wine aroma pattern changes during malolactic fermentation,[161] monitoring the biosynthesis of lilac aldehyde and lilac alcohol by feeding *Syringa vulgaris* L. inflorescences with their deuterium-labeled precursors.[162] Enantioselective analysis of all four stereoisomers of methyl dihydrojasmonates in numerous natural products.[170] flavour constituents of Cactus pear (*Opuntia ficus indica*),[171] and analysis of monoterpene compounds in tea tree oil, eucalypus oil and thyme oil[163] have also been reported.

The determination of volatile components emitted from plant is usually done by first isolation by steam distillation or solvent extraction, and then analyses by GC or GC-MS.[176] Recently, several novel sample extraction techniques were introduced. For example, an attractive solventless extraction technique, stir bar sorptive extraction, coupled with multidimensional GC-MS, was applied to establish characteristic authenticity profiles of the essential oils.[163] Solid-phase microextration (SPME), an accurate and efficient technique for collecting head space volatiles, was coupled with chiral GC-MS and used to characterize fragrances of lemon,[172] establish the authenticity of fruit beverages based on their enantiomeric compositions of chiral terpenes,[173] and study the variations in terpene composition between different berries.[174]

Pheromones and Other Natural Products

Pheromones are a group of important natural products. Naturally occurred pheromones are complex mixtures of thermally stable and volatile

compounds. For the reasons of high resolution, sensitivity and simplicity, GC has become the central to the analysis of pheromones and other volatile natural products. Very often chiral GC is employed to elucidate the structures and evaluate the enantiomeric compositions of chiral components of pheromones. The applications of chiral GC in pheromone chemistry were included in an earlier general review of GC, which also highlighted related sampling and detection techniques.[122]

An unambiguous assignment of the structure and absolute configuration of a chiral pheromone is usually established by organic synthesis and comparison of the natural and synthetic stereoisomers using chiral GC. In recent years, the number of new chiral pheromones identified from different spices of insects and animals continues growing. Several novel chiral terpene hydrocarbons in secretions from the paracloacal glands of crocodilians, a putative source of pheromones, were identified and proved to contain an unusual trisubstituted conjugated diene system. Chiral GC with a heptakis(2,6-dimethyl-3-*O*-pentyl)-β-CD phase was utilized to determine the structures and absolute configurations of a monoterpene and a sesquiterpene in this application.[123] Similarly, many bioactive compounds from insects were characterized, such as sex-attracting compounds from European oak bark beetle *Scolytus intricatus*,[124] ponerine ant *Gnamptogenys striatula*,[133] dung beetle *Kheper nigroaeneus*,[135] and *Limnephilid caddis* flies;[143] sex pheromones from scarab beetle *Phyllophaga elenans*,[125] Israel vine mealybug *Planococcus ficus*,[126] *Lambdina* species,[127] bumblebees and cuckoo bumblebees,[128] *Pseudococcus cryptus*,[129] female Douglas-fir cone gall midge *Contarinia oregonensis*,[130] pine sawfly *Diprion nipponica*,[131] giant white butterfly *Idea leuconoe*,[132] European spider *Linyphia triangularis*;[134] gender-specified volatile chiral compounds from sugarcane weevil *Sphenophorus levis*,[136] currant stem girdler *Janus integer* Norton,[137] flea beetles *Phyllotreta* and *Aphthona*,[138] and African butterfly *Amauris niavius*.[155]

In addition to pheromones, a great deal of novel natural products were isolated and identified from a wide range of matrices. Microorganisms are often a productive source of new natural products with pharmaceutical importance. Recently, Two new caprolactones, (*R*)-10-methyl-6-undecanolide and (6*R*,10*S*)-10-methyl-6-dodecanolide, were identified in the lipid extract of a marine streptomycete. These caprolactones were proved to be potential drugs attacking cancer cells with moderate phytotoxicity and concomitant low general cytotoxicity.[139] The presence of five phyllocladene-related tri- and teteracyclic diterpene hydrocarbons produced by fusicoccin-producing fungus *Phomopsis amygdale* F6 was demonstrated by GC-MS and NMR. Among them, (+)-Kaurene was confirmed by chiral GC.[140] Eight diterpene hydrocarbons produced by the fungus *Phoma betae* were isolated and the absolute configurations of the diterpenes were established by capillary GC with a heptakis(2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin

CSP.[141] Soil bacterium *Stenotrophomonas maltophilia* was found to be able to biotransform various long-chain fatty acids to 3-hydroxy fatty acids of shorter chain length. A multidimensional GC (MDGC) method based on a modified cyclodextrin phase was developed to determine the enantiomeric composition and absolute configuration of 3-hydroxy fatty acids and evaluate the enantiodistribution of 1,3-diols formed in the bacterial products.[142]

The sesquiterpenes, which often present biological activity, including antimicrobial, antitumour, and cytotoxic properties, are a large family of C_{15}-isoprenoid natural products of many microbes and some marine organisms and plants. For instance, helminthogermacrene, an esquiterpene hydrocarbon, was found in fungus, termite and the essential oil of the liverwort *Scapania undulat.* Recently, the stereochemistry of helminthogermacrene was deduced from enantioselective GC analysis using authentic standards.[144] In the course of searching biologically relevant plant volatiles, progress has been made by coupling chiral GC with electrophysiology. Recently, esquiterpene germacrene D was demonstrated to be an effective odorant for the moth *Helicoverpa armigera*, and the (−)-enantiomer had approximately 10 times stronger effect than (+)-enantiomer. The separation, identification and coupling to a single cell recording were performed with a heptakis (2,3-di-*O*-methyl-6-*O*-*tert*-butyldimethylsilyl)-β-cyclodextrin CSP.[154] By chiral GC-MS analysis, an enzyme cDNA from goldenrod *Solidago canadensis* was identified as a sesquiterpene (+)-(10R)-germacrene A synthase.[147]

Plants are another abundant source of chiral natural products. Recently, many new chiral compounds from plants, such as curtisians from inedible mushroom *Paxillus curtisii*,[148] methyl-branched alcohols and acids in Rhubarb (*Rheum rhabarbarum* L.) stalks,[149] a β-irone precursor named hoogianal from Iris *hoogiana* Dykes,[150] highly branched isoprenoid alkenes from Diatoms,[152] cyclopeptides from the bark of *Discaria Americana*,[153] a new lactone (i.e., 4,8-dimethylnon-7-en-4-olide) in apple juice of *Malus. domestica* var.,[178] γ-sultines in yellow passion fruit (*Passiflora edulis* f. *flavicarpa*),[181] and glycosides (aroma precursors) from young leaves of a Japanese pepper[177] and the rhizomes of greater galangal (*Alpinia galanga* W.),[180] were identified and their structures were established. An interesting study of the volatile emissions from the hemlock showed that α-pinene, myrcene, and camphene comprised greater than 75% by mass of the total release, and the rest emission compositions included tricyclene, α-phellandrene, β-pinene, limonene, β-phellandrene, terpinolene, and bornyl acetate. Infestation by hemlock woolly adelgid resulted in an increased release rate on monoterpenes (α-pinene $>$ 57% of totals) from branch tips.[156]

In an effort to understand the ecophysiological and chemotaxomic roles of chiral monoterpenes released from plant, a head-space sampling (HS) method combined with enantioselective GC was developed to study these chiral compounds present in the cortical tissues of five

different Norway spruce clones. It was found that (1*S*)-(−)-α-pinene, (1*S*,5*S*)-(−)-sabinene, (1*S*)-(−)-β-pinene, and (4*S*)-(−)-limonene dominated over (1*R*)-(+)-α-pinene, (1*R*,5*R*)-(+)-sabinene, (1*R*)-(+)-β-pinene, and (4*R*)-(+)-limonene (Fig. 5). A large variation existed in the enantiomeric composition of cortical tissues between different clones. These results clearly showed that it is possible to distinguish Norway spruce clones based on the head-space/chiral GC analysis of cortical chiral monoterpenes.[158]

Linalool is a widespread natural product and its (S)-enantiomer is an attractant to males of the vernal solitary bee species. Most recently, sila-linalool, a synthetic chiral linalool analogue, was prepared and tested as a pheromone with chiral GC coupled with electroantennographic detection (EAD). Distinct bioisosteric relationships were correlated between the C/Si analogues linalool and sila-linalool in this study.[157]

Natural products from insects and animals are also under extensive investigation. Recently, the absolute stereochemistry of a natural 1,4-substituted quinolizidines found in amphibian skin was determined to be 1*S*,4*S*,10*S* by an enantioselective synthesis and GC analysis by co-injection with racemate on a heptakis (2,3,6-tri-*O*-methyl)-β-cyclodextrin column.[145] The presence of a terpenoid cantharidin-related plant toxin, (*R*)-(+)-palasonin, in insect *Hemolymph*, was also confirmed.[146]

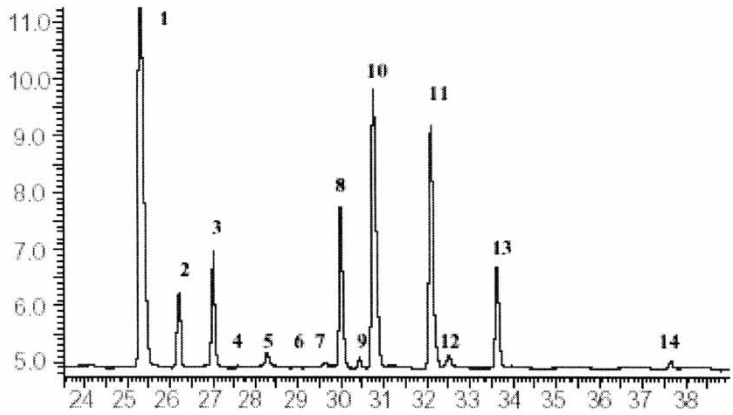

Figure 5. Typical chromatogram showing the complete separation of chiral and non-chiral monoterpene compounds present in liquid extracts of cortical tissues collected from Norway spruce trees. **1** (1*S*)-(−)-α-pinene; **2** (1*R*)-(+)-α-pinene; **3** myrcene; **4** (1*R*,5*R*)-(+)-sabinene; **5** (1*R*)-(+)-camphene; **6** (1*S*,5*S*)-(−)-sabinene; **7** (1*S*)-(−)-camphene; **8** (1*S*)-(+)-δ-3-carene; **9** (1*R*)-(+)-β-pinene; **10** (1*S*)-(−)-β-pinene; **11** (4*S*)-(−)-limonene; **12** (4*R*) (+)-limonene; **13** (4*R*)-(−)-β-phellandrene; and **14** 1,8-cineol.[158]

Environmental and Agricultural Analysis

Many synthetic chemicals are important to both agriculture and the evaluation of the environment. For example, organochlorines represent a wide range of agrochemicals, including α-hexachlorocyclohexanes (α-HCH), *cis*- and *trans*-chlordanes, heptachlors, heptachlorepoxides, oxyxhlordane, *o,p′*-DDT, technical toxaphene, and polychlorinated biphenyls (PCBs). These synthetic chemicals are widely applied as pesticides, herbicides, insecticides or for other uses. Meanwhile, they are ubiquitous environmental contaminants because of their extremely persistent degradation property. Their potential health impacts on a wide variety of biota, including humans and wildlife have caught extensive attention, since the presence of PCBs has been detected in insects, frogs, fishes, birds, marine mammals, human tissues, and breast milk.[52] A large number of agriculturally and environmentally important chemicals are chiral molecules, and may exhibit different biological effects in a chiral environment. Only bioprocesses (e.g., enzymatic biotransformation, uptake, and depuration) can affect the enantiomeric composition of a chiral compound. Thus, enantiomeric ratio (ER: (+)-enantiomer/(−)-enantiomer) and enantiomeric fraction (EF: ER/1 + ER) are important markers of biological activity and are often used to interpret the environmental fate of chiral agrochemicals and persistent organic pollutants. After the introduction of proper derivatized CD GC CSPs, it is routine to monitor and determine ER of trace chiral agrochemicals and environmental pollutants in a variety of matrices. The applications of high-resolution chiral GC in analysis and separation of organochlorines,[51] and PCBs[52,54] have been comprehensively reviewed. A brief summery of chiral analysis for environmental field was reported recently.[53]

Polychlorinated biphenyls (PCBs), which have 209 possible congeners, represent one of the most prevalent pollutants in ecosystems. Among 78 PCBs axially chiral congeners, only 19 tri- and tetra-*ortho* chlorinated congeners can exist as stable atropisomers at ambient temperatures due to asymmetric chlorine substitution about the long axis of the molecule and restricted rotation around the central C-C biphenyl bond.[99] Separation of 19 atropisomers has been done with chiral GC, however, at least 3 to 4 different columns are required to get all chiral PCBs separated.[52,100] Currently, bonded permethylated-β-cyclodextrin column (Chirasil-type) is the most commonly used chiral GC column. Nine of the 19 atropisomeric PCBs, namely PCBs 84, 91, 95, 132, 135,136, 149, 174, and 176, can be enantiomerically separated on this column.[101] To better understand the fate and distribution of individual PCBs' atropisomers in the environment, the ER measurements of trace PCBs in aquatic and riparian biota,[102] sediment,[103,104] standard and certified materials,[105] and animal[100] were conducted recently. Due to the complexity and similarity of PCBs' composition, two-dimensional GC (GC × GC) is adopted as a powerful tool to

study PCBs in complex samples.[100,106] Recently, two classes of axially chiral synthetic chemicals, i.e., polychlorinated bipyrroles[111] and polybrominated biphenyls,[112] with structures close to PCBs, were investigated with enantioselective GC.

Organochlorines other than PCBs, such as technical toxaphenes, *cis*- and *trans*-chlordanes, α-HCH, are also subject to intensive investigation in environmental chemistry around the world. Components of technical toxaphene (CTTs) were once the most heavily used organochlorine pesticides in the United Sates. In its unmodified form, toxaphene consists of several hundred chlorinated bicyclic compounds. Recently, the structure of a persistent heptachlorobornane in toxaphene (B7–1000) was elucidated by chiral GC/MS and NMR (107). The ERs of toxaphene in human milk,[108] animal tissues,[109] and anaerobically mediated media such as sediment, soil, and sewage sludge[110] were also determined. The information revealed from these studies enriched the knowledge of the biotransformation of toxaphene in environment, and distribution and metabolism in biota.

The main toxic action of α-HCH is central nervous system damage, and previous studies have shown that these compounds accumulate in the brain of mammals where this toxic action occurs. Very high ER values of α-HCH have been found in the brains of wildlife by enantioselective GC.[113] Recently, a study using laboratory rat as a model pointed out that the enantioselective metabolism of α-HCH by the brain is not the mechanism responsible for high ERs in the tissue.[113]

In order to provide details of the fate and transport of chlordane, its compositional and chiral profiles in soil and vegetation were investigated. It was found that abiotic processes dominated the transport of the chlordane components through the soil to the plant.[114] Later, two distinct plant uptake routes for chlordane, namely air-to-plant and soil-to-plant pathways, and its subsequent translocation within plant tissues were comprehensively compared.[115] No remarkable difference in the enantiomer fractions of *trans*-chlordane and *cis*-chlordane in plant tissues was observed between the two routes.

Besides organochlorines, synthetic pyrethroid (SP) insecticides are also of environmental significance because of their high aquatic toxicity. Enantiomeric separation of SP insecticides can be chanllenging since they contain 2 or 3 stereogenic centers, making them a pesticide group with one of the highest number of chiral components. Recently, a GC method was developed to separate the diastereomers and enantiomers of SP compounds using cypermethrin and cyfluthrin as models. The structures of both pesticides are shown in Fig. 6. In this GC method, an achiral column (HP-5) was used to separate the diastereomers and a derivatived β-cyclodextrin chiral column for the separation of the cypermethrin and cyfluthrin enantiomers. All diastereomers of both cypermethrin and cyfluthrin were separated on the achiral column. On

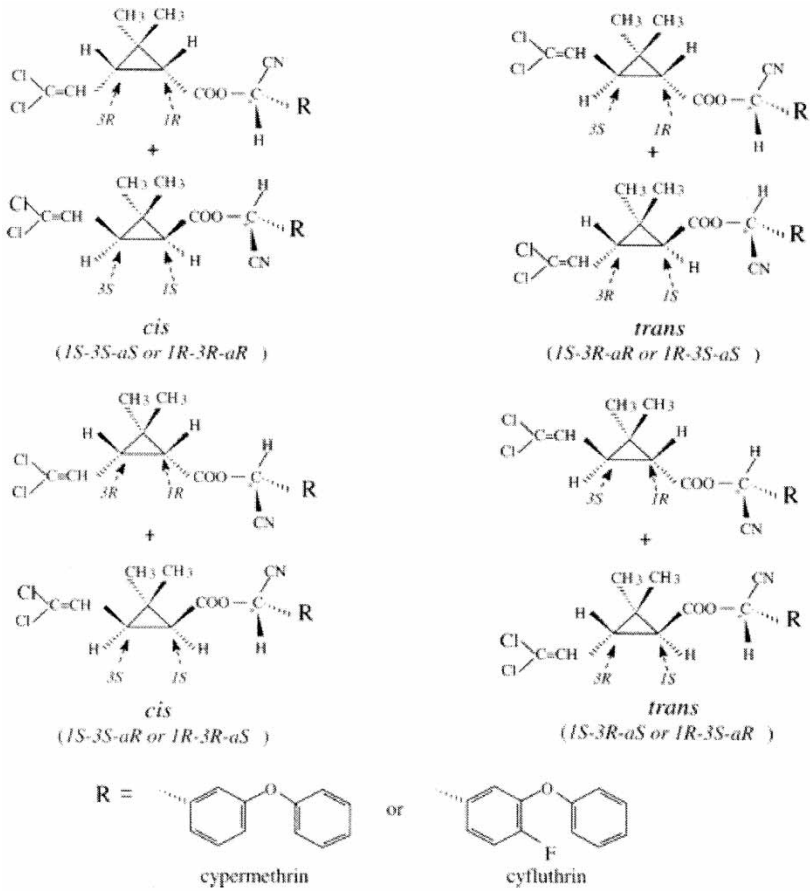

Figure 6. Structures of stereoisomers of cypermethrin and cyfluthrin.[116]

the chiral[116] column, enantiomers of all *cis*-diastereomers were resolved, while those of *trans*-diastereomers were not separated as exemplified by the GC chromatogram of cyfluthrin in Fig. 7.[116] The chiral GC analysis of two other pesticides in this group, i.e. (Z)-*cis*-bifenthrin and *cis*-permethrin, was also reported recently.[117] An solid phase microextraction(SPME) method was used to quantitatively extract (Z)-*cis*-bifenthrin and *cis*-permethrin in aqueous samples. However, the concentrations determined by this method only reflect the dissolved fraction of SPs in water.

Metolachlor is an important selective herbicide with 2 chiral centers. Four stereoisomers of metolachlor are stable at ambient temperature with *aS*S-, *aR*S-, *aS*R-, and *aR*R-configurations *(aS*S, the isomer with *a*S,1'S-configuration, etc.). Due to the lack of individual enantiomers, it is challenging to

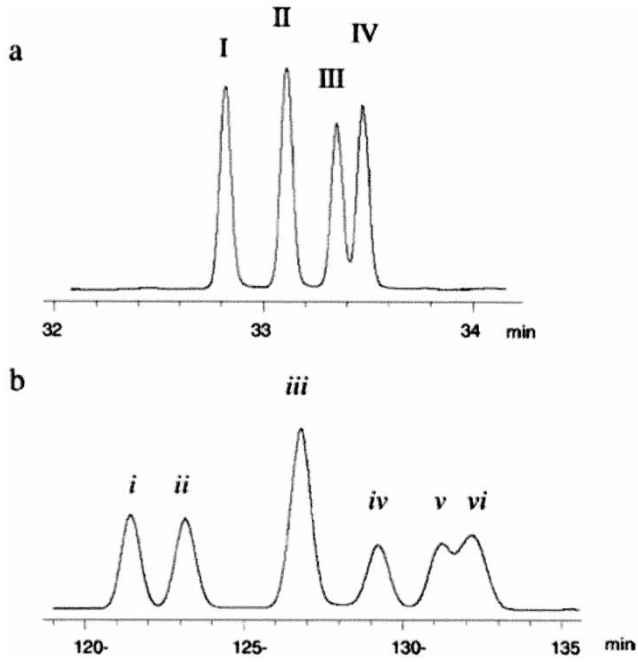

Figure 7. Achiral (a) and chiral (b) GC chromatograms of cyfluthrin.[116]

determine the exact enantiomeric composition of metolachlor in technical products, and in environmental residues. In a recent study, four stereoisomers of metolchlor were obtained with a method involving HPLC purification and thermally induced interconversion of the atropisomers. The kinetic study of interconversion indicated that chiral GC is not suitable for the accurate isomer analysis of metolachlor.[118]

Racemic metalaxyl, a chiral acetamide fungicide, is currently being replaced in many countries by metalaxyl-M, enantiomerically enriched with the biologically active R-enantiomer. A study was carried out to investigate the enantioselective degradation and chiral stability in soil. Metalaxyl and its primary carboxylic acid metabolite (MX-acid) in soil were analyzed using enantioselective GC-MS. The degradation of racemic metalaxyl in soil was proved to be enantioselective with the R-enantiomer degrading faster than the S-enantiomer due to biological process.[119] A later study showed that the biodegradation of metalaxyl in soils depended on the soil pH.[120]

Petroleum contamination is another source of environmental pollution. Due to the complexity of petroleum components, the broad peak of "unresolved complex mixture" (UCM) imposes a problem for petroleum analysis with conventional GC techniques. Recently, a comprehensive

two-dimensional GC (GC × GC) was developed to resolve the UCM hydrocarbons from petroleum-contaminated marine sediments. A γ-CD derivative CSP was used as the second GC × GC dimension to separate individual branched alkanes and cycloalkanes of the UCM based on shape selectivity. The data provided by the GC × GC method helped to understand the sources, weathering, and toxicity of UCM hydrocarbons.[121]

CONCLUSIONS

Chiral GC has been an essential and ever expanding applied analytical tool in understanding the origins of the universe and the complexities of our environment. The multidimensional GC technique, coupled with modern analytical technologies such as MS, ISCP and Head Space, SPME have tackled some of the most complex matrices ever attempted with a great deal of success. The Chirasil-Val column and the most of derivatized cyclodextrin CSP's have produced a wide variety of applications and methodologies that will be the bases for new and better consumer products and advances in natural pharmaceuticals.

In addition, with the current emphasis on diversity-oriented synthesis, chiral GC will be a valuable tool for this new approach to combinatorial chemistry. Due to the high resolving power and sensitivity of these new analytical tools, environmental analysis has been enhanced and the impacts of prevalent pollutants in a variety of ecosystems have been more clearly understood. The issue of environmental pollutants alone may have promoted the advance of these new techniques.

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