CHIRAL SEPARATION FOR ENANTIOMERIC DETERMINATION IN THE PHARMACEUTICAL INDUSTRY

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6.1. INTRODUCTION

Chirality plays a major role in biological processes. Enantiomers of a bioactive molecule often have different biological effects, as their pharmacological activity may reside in only one enantiomer of a racemic mixture. In some cases, enantiomers may have qualitatively similar pharmacological activity, but different quantitative potencies, while in others one enantiomer can be potentially toxic. Since drugs that are produced by chemical synthesis are usually a mixture of enantiomers, there is a need to quantify the level of enantiomeric impurity in an active pharmaceutical ingredient (API) [1].

The history of enantiomeric separation starts with the work of Pasteur. He discovered in 1848 that the spontaneous resolution of racemic ammonium sodium tartrate yielded two enantiomorphous crystals. Individual solutions of these enantiomorphous crystals led to *levo* and *dextro* rotation of polarised light. Because the difference in optical rotation was observed in solution, Pasteur suggested that, like two sets of crystals, the molecules are mirror images of each other and the phenomenon is due to molecular asymmetry [2].

While Pasteur made the historical discovery, subsequent advances in the resolution of enantiomers by crystallisation were based on empirical results. Several attempts to separate enantiomers using paper chromatography were met with unreliable results. In 1952, Dalgliesh postulated that three points of simultaneous interaction between the enantiomeric analyte and the stationary phase are required for the separation of enantiomers [3].

Developments in the field of life sciences and in the pharmaceutical industry brought enantiomeric separation to a new level. In the late 1950s/early 1960s, many drugs were synthesised and used in a racemic form. An example with tragic consequences is the use of thalidomide, a sedative and sleep-promoting drug used in the early 1960s which produced severe malformations in the newborn babies of women who took it in the early stage of pregnancy. Later, it was demonstrated that only the (*S*)-enantiomer possesses teratogenic properties [4].

The introduction of gas chromatography provided a stimulus to the field of enantiomeric separation. In 1966, a group from the Weizmann Institute of Science in Israel reported the first successful separation of enantiomers using gas chromatography (GC).

In a letter addressed to Emanuel Gil-Av after the publication of the first separation of enantiomers by a chiral GC stationary phase [5], A. J. P. Martin wrote: *"As you no doubt know, I had not expected such attempts to lead to much success, believing that the substrate-solvent association would normally be too loose to distinguish between the enantiomers."* At the time, there were only a few reports on the separation of enantiomers using chromatographic methods. Later developments in high performance liquid chromatography (HPLC) gave an additional boost to the field. Today, there are over 60 types of rugged, well-characterised columns capable of separating enantiomers. Unfortunately, there is a great deal of trial and error involved in choosing a particular column for chiral separation.

Chiral separation plays an important role in the determination of enantiomeric excess of API. The present chapter will present some of the rationale behind the interactions between enantiomeric solutes and a particular stationary phase along with some applications pertinent to each kind of interaction.

6.2. ENANTIOMERS, DIASTEREOMERS, RACEMATES

Chirality is due to the fact that the stereogenic centre, also called the chiral centre, has four different substitutions. These molecules are called asymmetrical. When a chiral compound is synthesised in an achiral environment, the compound is generated as a 50:50 equimolar mixture of the two enantiomers and is called a racemic mixture. This is because, in an achiral environment, enantiomers are energetically degenerate and interact in an identical way with the environment. Enantiomers can be differentiated from each other only in a chiral environment. Such conditions are provided during chromatographic enantiomeric separation offered by the asymmetric environment of the chiral column [6].

There are two approaches for achieving enantiomeric separation. The first approach involves a chiral mobile phase along with an achiral stationary phase, when a chiral additive is dissolved in the mobile phase and is constantly pumped through an achiral stationary phase. The second approach consists of chiral stationary phases where a chiral compound is immobilised to a solid matrix (*i.e.* silica gel, polymers, *etc.*). The separation of enantiomers using either chiral stationary or mobile phases involves the formation of transient diastereomeric complexes between the enantiomeric analytes and the chiral moiety present in the chromatographic column.

Diastereomers are chiral molecules containing two or more chiral centres with the same chemical composition and connectivity. They differ in stereochemistry about one or more chiral centres. If two stereoisomers are not enantiomers of one another, they can in principle be separated in an achiral environment *i.e.* using a non-chiral stationary phase [6].

6.3. REQUIREMENTS FOR CHIRAL SEPARATION

The chirality of the selector (chiral stationary phase) or the selectand (enantiomeric analytes) can arise from an asymmetric carbon, molecular asymmetry or the helicity of a polymer. Also, the bonds between substituents of the selectand and the selector can involve a single bond, but could also involve multiple bonds or surfaces. Such bonds represent the leading interactions between the selectand and selector. In chromatographic chiral separation, they control the retention on a certain column. Only when the leading interactions take place and the asymmetric moiety of the two bodies are brought in close proximity do the secondary interactions (*e.g.* van der Waals, steric hindrance, dipole-dipole) become effectively involved. Secondary interactions can affect the conformation and the formation energy of diastereomeric associates [7].

The interaction energy of one enantiomer in the active chiral phase can be described as the contribution of the interaction energies of all possible forms of chiral phase/solute associates. These associates are in equilibrium with fast interconversion rates. Each form contributes to the total free energy according to its particular formation energy and its particular molar fraction [7,8]. These complexes between the selector and selectand should also be as mutually exclusive as possible, to prevent a given interaction from occurring at multiple sites in the diastereomeric complex [6].

6.4. THE TYPES OF MOLECULAR INTERACTIONS

Chiral separations generally rely on the formation of transient diastereomeric complexes with differing stabilities. Complexes are defined as two or more compounds bound to one another in a definite structural relationship by forces such as hydrogen bonding, ion pairing, metal ion-to-ligand attraction, π -acid/ π -base interactions, van der Waals attraction and entropic component of desolvation. In the following sections, the most important types of molecular interactions in chiral separation are discussed.

6.4.1. Chiral separation through hydrogen bonding

Hydrogen bonding is a donor-acceptor interaction specifically involving hydrogen atoms [9]. When a covalently bonded hydrogen atom forms a second bond to another atom, the second bond is referred to as a hydrogen bond.

A hydrogen bond is formed by the interaction between the partners R-X-H and :Y-R' according to:

where R-X-H is the proton donor and :Y-R' makes an electron pair available for the bridging bond. The strength of hydrogen bonds depends on the solvent

conditions in which the complex occurs. For instance, in the presence of an ionic medium (which generates an electrical field), the H-bonds of the solvate become polarised and, consequently, their symmetry can change from a symmetrical to an asymmetrical H-bond. The change in symmetry leads to weakening of the H-bonds between solvate molecules [10].

Amide groups and peptide bonds are the most important functional groups involved in designing chiral phases that involve hydrogen bonding. Two configurations of the planar peptide bond are possible; they can be in either in a *trans* or *cis* configuration, which are in equilibrium (Figure 6.1). The *trans* form is energetically favoured, due to less repulsion between non-bonded atoms [11].

Figure 6.1. Configurational equilibrium of amide group

The amide group is also an integral functional group of the backbone of proteins and determines the secondary structure of α -helix and β -sheet. Preservation of the energy balance in the system necessitates that the backbone polypeptide groups form hydrogen bonded interactions between themselves in the protein folded state. Such requirement has important consequences for protein folding because the peptide carbonyl oxygen and N-H groups are regularly arranged along the polypeptide backbone. Extended arrangements having optimum hydrogen-bonded interactions among residues either within or between polypeptide chains reflect the periodic regularity and result in the formation of protein secondary structures [12]. In α -helix, the polypeptide backbone follows a path of a rigid right handed helical spring to form an arrangement in which each carbonyl group forms a hydrogen bond with the amide NH group.

β -sheets are formed when two or more almost fully extended polypeptide chains are brought together side by side, so that regular hydrogen bonds can form between the peptide amide NH and carbonyl oxygen groups of the adjacent chains. β -sheets can occur in two different arrangements: parallel β -sheet and antiparallel β -sheet (Figure 6.2).

In the parallel arrangement, the two adjacent polypeptide chains can close through hydrogen bonds a C5:C7 ring while in the antiparallel they can close both C5:C5 and a C7:C7 ring (*vide infra*).

Figure 6.2. Parallel **(a)** and antiparallel **(b)** β -sheets

The first successful chiral phases used under GC conditions were N-trifluoroacetyl (TFA)-L- α -amino acid esters. These phases separated racemates of the more volatile members of the same compounds [12]. The diamide stationary phase contained two hydrogen bonding sites, a C5 and a C7 site, where hydrogen bonding selector/selectand-associations could take place [7]:

The structure of the diamide phase appeared to be similar to an anti-parallel β -sheet of poly-L-alanine. X-ray diffraction of the D,L-leucyl derivative showed the C₅:C₅ association, while the C₇ site involved three molecules in the anti-parallel arrangement, closing a C₅:C₅ associate of the L-diamide selector with L- and D- α -amino acid derivatives [5].

Derivatised amino acids such as N-TFA- α -amino acid esters, which can form hydrogen bonds at these sites, can be separated successfully on such types of chiral stationary phases (CSP). Such a chiral phase is known under the trade name Chirasil-Val® and is used for the separation of enantiomers by gas chromatography [13,14]. Table 6.1 lists some chiral compounds successfully separated on Chirasil-Val® column.

Table 6.1. Names and structures of compounds separated on Chiralsil-Val® chiral stationary phase (CSP) consisting of embedded poly(dimethylsiloxane) with valine-*tert*-butylamide

Name	Structure	Conditions	Ref.
N,O-HFB-tranlycypromine		GC - 140°C	[18]
3-Dechloroethyl ifosfamide		GC - 195°C	[19]
N-Acetyl-4-chlorophenyl-alanine methyl ester		GC - 160°C	[20]
Di-N,O-ethoxycarbonyl serine ethyl ester		GC - 150°C	[21]
Di-N,O-PFP- <i>allo</i> -threonine isopropyl ester		GC - Temperature programming: 65°C, 4°C/min, 210°C.	[22]
N-TFA-2-Aminoheptane		GC - 100°C.	[23]

Name	Structure	Conditions	Ref.
N-TFA-Aspartic acid di-n-propyl ester		GC - Temperature program 80°C for 3 min, followed by 4°C/min to 200°C	[24]

Similar interactions occur in HPLC under normal phase chromatography conditions using hexane with polar modifiers such as alcohols [15]. Another type of chiral phase based on hydrogen bonding interactions is the poly(acrylamide)-type phase. Developed by Blaschke, the phase is comprised of poly(acrylamide) that incorporates phenylalanine ethyl ester. The phase has a helical structure, and the interactions are based on hydrogen bonding between the polar groups of the enantiomer and the CO-NH groups of the polymer [16,17]. The compounds separated on poly(acrylamide) type HPLC columns are listed in Table 6.2.

Table 6.2. The HPLC conditions and mobile phase used for the separation of listed compounds on poly(acrylamide) chiral stationary phase: Chiraspher®

Name	Structure	Mobile Phase	Ref.
2-Phenyl-2,3-dihydro-benzofuran-3-carboxylic acid methyl ester		Chiraspher-NT 100 % Heptane	[25]
[1,1']Binaphthalenyl-2,2'-diol		90:10 CO ₂ / 2-propanol (SFC*)	[26]
4-Hydroxy-2,5-dimethyl-furan-3-one		7:3 pentane / (C ₂ H ₅) ₂ O	[27]

Name	Structure	Mobile Phase	Ref.
8-Chloro-2-(2,6-difluoro-benzyl)-3-methyl-1,1-dioxo-1,2,3,5-tetrahydro-1lambda*6*-benzo[f][1,2,5]thiadiazepin-4-one		50:50:2 hexane / CHCl ₃ / 2-propanol	[28]
8-Chloro-3-methyl-2-(2-methyl-allyl)-1,1-dioxo-1,2,3,5-tetrahydro-1lambda*6*-benzo[f][1,2,5]thiadiazepin-4-thione		80:20 hexane / 2-propanol	[29]
5-(2-Dimethylamino-ethoxy)-3,9-dimethoxy-7H-benzo[c]fluoren-7-ol		75:25 hexane / ethanol	[30]
Bunitrolol		60:20:20:0.05 hexane / ethanol / methanol / (25%aq) NH ₃	[31]
Cytosazone		95:5 hexane / 2-propanol	[32]
3-Methyl-3,4-dihydro-2H-benzo[1,2,4]thiadiazine 1,1-dioxide		70:30 hexane / tetrahydrofuran	[33]
2,3,3a,4-Tetrahydro-1H-pyrrolo[2,1-c][1,2,4]benzothiadiazine 5,5-dioxide		70:30 hexane / tetrahydrofuran	[34]
3-Methyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide		60:40 hexane / tetrahydrofuran	[35]
2,3,3a,4-Tetrahydro-1H-pyrrolo[2,1-c][1,2,4]benzothiadiazine 5,5-dioxide		70:30 hexane / tetrahydrofuran	[35]

*SFC – supercritical fluid chromatography;

6.4.2. Chiral separation through inclusion compounds

Inclusion complexing partners are classified as hosts and guests. Complexes are structured by contacts at multiple binding sites between hosts and guests. The binding energy at a single contact site is at most a few kilocalories per mole. Contacts at several sites between hosts and guests depends on the complementary placement of the binding sites; specifically, hosts must have binding sites which cooperatively contact and attract the binding sites of guests without generating non-bonded repulsion [36]. There are two types of hosts which have been successfully employed in the chromatographic separation of enantiomers: hosts which have a hydrophobic interior and hosts with a hydrophilic interior. The hydrophilic interior means that the cavity contains heteroatoms such as oxygen, where lone pair electrons are able to participate in bonding to electron acceptors such as an organic cation (e.g., chiral crown ethers). In contrast, a host with a hydrophobic interior cavity is able to include hydrocarbon-rich parts of a molecule [37]. This type of host is found in the cyclodextrins.

6.4.2.1. Cyclodextrins

The most popular are α -, β - and γ -cyclodextrin (α -CD, β -CD and γ -CD, respectively) with six, seven and eight glucose rings respectively, also called cyclohexa-, cyclohepta- and cyclooctaamylose (or CA6, CA7 and CA8). Structures, such as CA6, CA7 and CA8 have a doughnut shape and are able to host small molecules inside the cavity. Similar to amylose, the glucose units in the CAs are linked by $\alpha(1\rightarrow4)$ bonds that adopt a 4C_1 chair conformation (Figure 6.3). They may be considered as rigid building blocks giving fairly limited conformational freedom of the macrocycle in rotation of the C6-O6 groups and limited rotational movements about the glycosidic link C1(n)-O4(n-1)-C4(n-1). All glucose groups are aligned in *cis* configuration with the secondary O2 and O3 hydroxyls on one side and the primary O6 hydroxyls on the other side. They have the overall shape of a hollow, truncated cone with the wide side occupied by O2 and O3 and the narrow side by O6 [38].

Empirical rules for successful chiral recognition candidates using cyclodextrin selectors have evolved based on extensive chromatographic data. For instance, in the guest molecule, the presence of at least one aromatic ring enhances chiral recognition with β -CD, although two rings appear to be more beneficial, particularly if the chiral centre is positioned between the two rings or between a single aromatic ring and a carbonyl [39]. The enhanced chiral recognition is attributed to increased molecular rigidity [40].

The chromatographic separation of enantiomers using CDs is usually performed using aqueous-organic mobile phases. The apparent pH of these mobile phases must be carefully controlled in order to handle the charge of the enantiomeric analytes. For example, separation of basic enantiomeric analytes [41] cannot be achieved at a pH lower than 5. This is a consequence of the protonation of

nitrogens in the analyte molecules. At higher pH, complete separation can be achieved, indicating that enantiomeric separation requires the nitrogens to be partially deprotonated. Simultaneously, the hydrogen bonding between the β -CD and the analytes occurs through O-H to N.

Figure 6.3. Chemical structure of CA7 (β -CD) where the numbering of glucose unit (1-7) is performed counterclockwise (left). Atom numbering scheme for a glucose unit (right) (Adapted from [38])

The concentration of an organic modifier in a hydroorganic mobile phase also influences retention. For instance, the retention of analytes decreases as the amount of acetonitrile in the hydroorganic mobile phase increases up to a point, after which the retention starts increasing again. Such behaviour may indicate a change in retention interactions with an increased amount of acetonitrile in the mobile phase. No reversal of elution order was observed, indicating that no change in the enantioselective interactions occurred [41].

Polar organic mobile phases, such as mixtures of methanol and acetonitrile with small amounts of acetic acid, as well as triethylamine, can also be effective for the separation of enantiomers mediated by CDs. Under these conditions, the interior of the CD cavity is occupied by acetonitrile. The overwhelming concentration of acetonitrile renders its displacement by enantiomeric analytes basically impossible. Acetonitrile is a polar aprotic solvent, with limited capacity for hydrogen bond formation. As a consequence, analytes are thought to undergo hydrogen bonding under these conditions, with the secondary hydroxyl groups located at the rim of the CDs. The addition of methanol and traces of acetic acid and triethylamine allow solute retention to be modulated through solvent mediation of the hydrogen bond strength [42].

Derivatised CDs have also been used successfully in HPLC. Armstrong et al. [43, 44] synthesised several derivatised β -CDs and used them as chiral stationary phases under normal phase conditions. Under these conditions, inclusion is unlikely. A number of substituted derivatives were prepared including acetic anhydride, (*R*) and (*S*)-1-(1-naphthyl)ethyl isocyanate, 2,6-dimethylphenyl iso-

cyanate and *p*-toluoyl chloride. The presence of aromatic substitution provides possibilities for π - π interaction with the aromatic substituents of the enantiomeric analytes [43,44]. For example, in (*R*)-(-)- or (*S*)-(+)-1-(1-naphthyl)ethyl carbamate of β -CD, the naphthyl ethyl moiety has some π donor character. Incorporation of 3,5-dinitro phenyl substituents on chiral analytes promotes the formation of a π - π complex. At the same time, the carbamate functionality which links the aromatic group to the β -CD produces sites which are able to undergo hydrogen bonding as well as dipole stacking with the enantiomeric analytes.

Table 6.3 gives HPLC conditions for the enantiometric separation of selected substances using cyclodextrins CSP.

6.4.2.2. Crown ethers

Crown ethers can be described as heteroatomic macrocycles with repeating units of $(-X-C_2H_4-)$ where the heteroatom X is usually oxygen, but may also be sulphur or nitrogen. They can also incorporate aromatic moieties which enhance their lipophilicity. Each oxygen atom possesses two unshared electron pairs. All six oxygens of the cyclic ether are turned inward to provide dipole-to-ion attractive interactions between the host and guest. The main source of interaction is ion-dipole attraction between $+NH\cdots O$ and $+N\cdots O$. Three hydrogen bonds can be formed between the protonated amine hydrogens and the crown ether oxygens. The ethylene units of the crown ether are turned outward and form a lipophilic barrier around the hydrogens of the hydrophilic protonated amine ion. While the host molecule is roughly planar, and the nitrogen of the guest is situated slightly out of the plane at the apex of a shallow tripod, it may be argued that the association between the crown ether and the ammonium is not really an inclusion complex. The alkyl group attached to the nitrogen extends along the axis perpendicular to the plane of the cyclic ether. The protonated amine can complex at either of the two faces of the cyclic polyether. The counterion, X^- , in a non-polar environment, ion pairs with positive nitrogen atom from the face opposite that occupied by the protonated amine [45]. Cram used this principle to design chiral crown ethers. To achieve enantiomeric separation, Cram introduced additional units such as naphthalene rings into the crown ether structure, which provided additional interactions capable of discriminating between enantiomers. The host containing two chiral elements provided the highest chiral selectivity [46]. Shimbo *et al.* used a chiral 18-crown-6 dynamically coated on a reversed phase stationary phase [47,48]. This crown ether is commercially available under the trade name Crownpak®. This crown ether is able to resolve a large number of enantiomeric amines, amino alcohols and amino acids using reversed phase conditions.

It was found that additives such as perchlorate ion play an important role in chiral separation. In a series of anions such as ClO_4^- , CF_3COO^- , NO_3^- and $H_2PO_4^-$, the retention factor of amino alcohols such as *cis* and *trans* amino indanol (at a constant pH of 2) increases in the order $ClO_4^- > CF_3COO^- > NO_3^- > H_2PO_4^-$. The selectivity factor, however, is not influenced by the nature of the anion [49]. For

more hydrophobic analytes, retention can be modulated by the addition of organic modifiers such as methanol in the mobile phase. However, there is not a linear relationship between the amount of the organic modifier in the mobile phase and the retention factor of the enantiomeric analytes, indicating multiple types of retention interactions [50]. A different type of crown ether used to separate enantiomers is derived from 18-crown-6 tetracarboxylic acid, covalently immobilised on silica gel via the reaction between 18-crown-6 tetracarboxylic acid and amino propyl silica gel [51,52]. NMR spectroscopy of the complex between the 18-crown-6 tetracarboxylic acid and phenylglycine or phenylglycine methyl ester showed for the chiral recognition of the more stable complex the following interactions: 1) three $\text{-NH}\cdots\text{O}$ hydrogen bonds in a tripod arrangement between the polyether oxygens of 18-crown-6-tetra carboxylic acid and the ammonium moiety of the enantiomer; 2) a hydrophobic interaction between the polyether ring of 18-crown-6-crown ether and the phenyl ring of the enantiomer; 3) hydrogen bonding between the carboxylic acid of the crown ether and the carbonyl oxygen of the enantiomer [53]; 4) if the analyte contains an aromatic moiety, in some instances $\text{CH} - \pi$ interactions are possible from the carbon adjacent to the carboxyl group and the aromatic moiety.

Table 6.4 gives the HPLC mobile phase composition for the enantiomeric separation of selected compounds on the CSP containing (+/-)-18-crown-6 ether.

Table 6.3. Compositions of mobile and stationary phases for cyclodextrins-based HPLC enantiomeric separations of selected substances

Name/Structure	Stationary phase	Mobile Phase	Ref.
<p>Isoproterenol</p>	Perphenylcarbamate- β -cyclodextrin covalently bonded to aminopropyl silica gel (Kieselgel 100) via a mono-6-urea linkage (Staudinger reaction)	80:20 1% triethylammonium acetate (pH 4.65) / CH_3CN	[54]

Name/Structure	Stationary phase	Mobile Phase	Ref.
<p>OPA-2-ME-tyrosine</p>	Amino- β -cyclodextrin bonded to silica (unknown spacer)	20:80 methanol / aqueous 1% triethylammonium acetate buffer pH 7.0	[55]
<p>Taxifolin</p>	Permethyated- β -cyclodextrin cross-linked and bonded to aminopropyl silicagel via urea	40:60 methanol / triethylammonium acetate buffer pH 5.0 (prepared with Et ₃ N 1%, pH adjusted with glacial acetic acid)	[56]
<p>Mandelic acid</p>	β -cyclodextrin bonded to silica (Nucleodex beta-OH)	86.4:9.1:4.5 H ₂ O / CH ₃ COOH / CH ₃ CN 0.05 M ammonium acetate (pH 3.0)	[57]
<p>2-(1H-Indol-3-yl)-succinic acid</p>	β -cyclodextrin (<i>S</i>) and (<i>R,S</i>)-hydroxypropyl derivative bonded to silica (Cyclobond RSP)	40:60:2 methanol / H ₂ O / acetic acid	[58]
<p>Oxazepam</p>	β -cyclodextrin (<i>S</i>) and (<i>R,S</i>)-hydroxypropyl derivative bonded to silica (Beta-RSP-2000)	19:8:73 CH ₃ CN / 1% triethylamine acetate buffer (pH 4.5) / H ₂ O	[59]

Name/Structure	Stationary phase	Mobile Phase	Ref.
Propranolol	Perphenylcarbamate-heptakis(6-azido-6-deoxy) β -cyclodextrin cross-linked and immobilised to aminopropyl silicagel via multiple urea linkages (CHIDEX-MKP)	80:20 hexane / 2-propanol	[60]
(2-Nonyloxy-phenyl)-carbamic acid 1-methyl-2-piperidin-1-yl-ethyl ester	γ -cyclodextrin bonded to LiChrospher (ChiraDex-Gamma)	95:5 100 mM (pH 5) triethylammonium acetate / acetonitrile	[61]
Ephedrine	β -cyclodextrin phenylcarbamate bonded silica (undisclosed spacer) (Ultron ES-PhCD)	4:1 20 mM KH_2PO_4 (pH 4.6) / acetonitrile	[62]
N-[2-(7-Fluoro-1,2,3,4-tetrahydro-naphthalen-1-yl)-ethyl]-acetamide	β -cyclodextrin covalently bonded to glycidoxypropyl silica (Cyclobond I 2000)	methanol	[63]

Name/Structure	Stationary phase	Mobile Phase	Ref.
1-(3-Amino-propyl)-1-(4-fluoro-phenyl)-1,3-dihydro-isobenzofuran-5-carbonitrile	Acetylated cyclodextrin bonded to glycidoxypropyl silica (Cyclobond I 2000 Ac)	55:45 methanol / 10mM citrate triethylamine buffer (pH 6.3)	[64]
Acetoxy-phenyl-acetic acid 2,2,2-trifluoro-ethyl ester	Permethylated- β -cyclodextrin covalently bonded to silicagel undisclosed spacer (Sumichiral OA 7500)	80:20 methanol / H ₂ O	[65]
3-Hydroxy-1-[4-(7-nitro-benzo[1,2,5]oxadiazol-4-yl)-piperazin-1-yl]-butan-1-one	β -cyclodextrin phenylcarbamate bonded silica (undisclosed spacer) (Ultron ES-PhCD)	80:20 methanol / H ₂ O	[66]
Tyrosine phenylisocyanate	β -cyclodextrin covalently bonded to glycidoxypropyl silica (Cyclobond I)	490:10:1:3 acetonitrile / methanol / acetic acid / triethylamine	[67]

Name/Structure	Stationary phase	Mobile Phase	Ref.
<p>4-Bromo-phenylethanol</p>	Perphenylcarbamate-heptakis(6-azido-6-deoxy) β -cyclodextrin cross-linked and immobilised to aminopropyl silicagel via multiple urea linkages (CHIDEX-MKP)	2-propanol	[68]
<p>Methadone</p>	β -cyclodextrin (<i>S</i>) and (<i>R,S</i>)-hydroxypropyl derivative bonded to silica (β -RSP-2000)	90:10 1% triethylamine / acetonitrile (pH 3.2 with H_3PO_4)	[69]
<p>N-(3-Chloro-benzoyl)-alanylglycine</p>	(<i>R</i>)-Naphthylethyl-isocyanate derivatised β -cyclodextrin bonded to silica (Cyclobond I 2000 RN)	490:10:1:2 acetonitrile / methanol / acetic acid / triethylamine	[70]
<p>Phenylalanine phenylisocyanate</p>	(<i>R</i>)-Naphthyl-ethylisocyanate derivatised β -cyclodextrin bonded to silica (480:20:1:2 CH_3CN / methanol / $\text{CH}_3\text{CO}_2\text{H}$ / Et_3N)	480:20:1:2 acetonitrile / methanol / acetic acid / triethylamine	[67]
<p>Ala-Phe phenylisocyanate</p>	β -cyclodextrin-(<i>S</i>)-naphthylethyl carbamate derivative (Cyclobond I SN)	475:25:1:3 acetonitrile / methanol / acetic acid / triethylamine	[67]
<p>Baclofen</p>	γ -cyclodextrin bonded to silica (CYCLOBOND II)	90:10 10 mM Ammonium acetate (pH 6.8)	[71]

Name/Structure	Stationary phase	Mobile Phase	Ref.
Benzoic acid 2-(6-amino- purin-9-ylmethoxy)-2- phenyl-ethyl ester	β -cyclodextrin (<i>S</i>) and (<i>R,S</i>)- hydroxypropyl derivative bonded to silica (Cyclobond RSP)	98:2 CH ₃ CN / methanol	[72]
3-Methoxy-6a,11a-dihydro- 6H-benzo[4,5]furo[3,2- c]chromene	α -cyclodextrin bonded to silica (CYCLOBOND III)	80:20 H ₂ O / methanol	[73]
Dimethyl-[4-(2-phenyl- 4,5,6,7-tetrahydro-benzo- furan-4-yl)-phenyl]-amine	β -cyclodextrin (<i>S</i>) and (<i>R,S</i>)- hydroxypropyl derivative bonded to silica (Cyclobond RSP)	60:40:0.1:0.1 CH ₃ OH / H ₂ O / triethylamine / CH ₃ CO ₂ H (pH 8)	[74]
2-Styryl-2,3-dihydro-benzo- furan-5-carboxylic acid methyl ester	Heptakis-2,3-O-dimethyl β - Cyclodextrin covalently bonded to glycidox isopropyl silica (Cyclobond I DM)	40:60 methanol / H ₂ O	[75]
2-Ethylidene-1,5-dimethyl- 3,3-diphenyl-pyrrolidine	β -cyclodextrin (<i>S</i>) and (<i>R,S</i>)- hydroxypropyl derivative bonded to silica (β -RSP-2000)	19:9:72 CH ₃ CN / 1% triethylammonium acetate (pH 4.5) in H ₂ O / H ₂ O	[76]

Name/Structure	Stationary phase	Mobile Phase	Ref.
8-Iodo-5-methoxy-7-(4-methoxy-phenyl)-5H-pyrano[4,3-b]pyridine	β -cyclodextrin covalently bonded to glycidoxypropyl silica (Cyclobond I)	Not reported	[77]
4-[4-(2-Hydroxy-cyclohexylmethyl)-phenoxy]-3-methyl-but-2-enoic acid ethyl ester	β -cyclodextrin bonded to silica (Nucleodex beta-OH)	4:1 methanol / H ₂ O	[78]
2'-Hydroxyflavanone	Perphenylcarbamate- β -cyclodextrin covalently bonded to aminopropyl silicagel (Kromasil silica) via a mono-6-urea linkage (CHIDEX-SKP)	50:50 H ₂ O / methanol	[79]
Thioridazine	β -cyclodextrin bonded to LiChrospher (ChiraDex)	50:50 Phosphate buffer 0.05M, pH 6.5 / acetonitrile	[80]
Bis(alpha-methylbenzyl)amine	Acetylated cyclodextrin bonded to glycidoxypropyl silica (Cyclobond I 2000 Ac)	100:0.1 H ₂ O / triethylammonium acetate (pH 4.1)	[81]

Name/Structure	Stationary phase	Mobile Phase	Ref.
1,2,5,6,9,10-Hexabromo- cyclododecane	Permethylated-beta- cyclodextrin covalently bonded to silicagel (Nucleodex beta-PM)	Gradient acetonitrile / H ₂ O	[82]
4-[(2-Hydroxymethyl-4- oxo-4,6,7,8-tetrahydro-3H- cyclopenta[g]quinazolin-6- yl)-prop-2-ynyl-amino]- benzoic acid	β -cyclodextrin covalently bonded to glycidoxypropyl silica (Cyclobond I)	25 mM Na ₂ HPO ₄ / 25mM NaH ₂ PO ₄ / acetonitrile	[83]
6-(Azetidin-1-ylcarbonyl)- 5-[(3R)-3-hydroxy-3-(2-me- thylphenyl)propyl]-1,2-di- methyl-1H-benzimidazol-4- ol	β -cyclodextrin bonded to LiChrospher (ChiraDex)	20:80 methanol / H ₂ O	[84]

Name/Structure	Stationary phase	Mobile Phase	Ref.
2-Hydroxy-2-phenyl-acetamide	β -cyclodextrin bonded to silica (Nucleodex beta-OH)	50:50 methanol / H ₂ O	[85]
6-phenyl-1,2,3,4,5,6-hexahydro-2,6-methano-3-benzazocin-8-ol	2,3-O-((4-Trifluoromethyl-2,6-Dinitrophenyl)- β -cyclodextrin covalently bonded to glycidoxypopyl silica (Cyclobond I 2000 DNP)	90:10 hexane / 2-propanol / triethylamine 0.2%	[86]
8-hydroxy-6-phenyl-1,4,5,6-tetrahydro-2,6-methano-3-benzazocine-3(2H)-carboxamide	β -cyclodextrin-3,5-dimethylphenylcarbamate derivative (Cyclobond I 2000 DMP)	90:10 hexane / 2-propanol / triethylamine 0.2%	[86]
3-methyl-6-phenyl-1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine	β -cyclodextrin covalently bonded to glycidoxypopyl silica (Cyclobond I 2000)	65:35 ammonium acetate buffer pH 7 / acetonitrile	[86]

Name/Structure	Stationary phase	Mobile Phase	Ref.
1,3-Dibenzyl-tetrahydro- furo[3,4-d]imidazole-2,4- dione	β -cyclodextrin phenyl- carbamate bonded silica (carbamate spacer) (Chiral CD-Ph)	70:30 acetonitrile / H ₂ O	[87]
N-(2,4- Dinitrophenyl)tyrosinol	β -Cyclodextrin bonded to LiChrospher (ChiraDex)	40:60 CH ₃ CN / triethylammonium phosphate buffer 20 mM, pH 7	[88]
Clopidogrel	β -Cyclodextrin bonded to LiChrospher (ChiraDex)	15:5:80 CH ₃ CN / methanol / 0.01 M aqueous KH ₂ PO ₄	[89]
trans-Permethrin	β -Cyclodextrin bonded to LiChrospher (ChiraDex)	Gradient methanol / H ₂ O (56:44 0-16 min, then a linear gradient to 70:30 in 30 min, then 10 min at 56:44)	[90]

Table 6.4. Mobile phase compositions for the enantiomeric separation of selected substances on (+/-)-18-crown-6 ether coated on octadecylsilyl silica(ODS) stationary phase

Name	Structure	Mobile Phase	Ref.
Amino-phenyl-acetic acid methyl ester		Aqueous HClO ₄ (pH 2.0)	[91]
2-Amino-4-phenyl-butyramide		HClO ₄ Solution (pH 2)	[92]
3-Amino-3-cyclohex-3-enyl-propionic acid		Aqueous HClO ₄ (pH 2.0)	[93]
Amino-phenyl-acetic acid		Aqueous HClO ₄ (pH 1.5-2.0)	[94]
2-Amino-pentanedioic acid		Aqueous HClO ₄ (pH 2.0)	[95]
2-Amino-3-(4-hydroxy-[1,2,5]thiadiazol-3-yl)-propionic acid		Aqueous trifluoro acetic acid (pH 2)	[96]
2-Amino-cyclohexanol		95:5:2 H ₂ O / methanol / CF ₃ CO ₂ H	[97]

Name	Structure	Mobile Phase	Ref.
Alanine		Aqueous HClO ₄ (pH 1.5)	[98]
Leucine		Aqueous HClO ₄ (pH 2)	[99]
2-Amino-butyric acid methyl ester		Aqueous HClO ₄ (pH 1.3)	[100]
Baclofen		90:10 10 mM ammonium acetate (pH 6.8)	[71]
2-Amino-3-phenyl-propionitrile		90:10 10 mM H ₂ O HClO ₄ / methanol	[101]
(RR,SS)-1-(4-Hydroxy-phenyl)-2-amino-1-propanol		Aqueous HClO ₄ (pH 1.0)	[102]
7-Ethyl-1,2,3,4-tetrahydro-1-naphthylamine hydrochloride		90:10 H ₂ O + 0.1% trifluoroacetic acid / methanol	[103]
2-Amino-propionamide		60 mM HClO ₄	[104]
Phenylglycine		90:10 HClO ₄ H ₂ O (pH 1.2) / methanol	[105]

Name	Structure	Mobile Phase	Ref.
2-Amino-3-phenyl-propionic acid ethyl ester		90:10 HClO ₄ (pH 2) / methanol	[106]
2-Amino-succinamic acid		100 mM HClO ₄ (pH 1)	[107]
7-Methoxy-2-aminotetralin		15:85 methanol / aqueous 1% HClO ₄	[108]
2-Amino-3-[3-(2-fluoro-ethyl)-4-methoxy-phenyl]-propionic acid		95:5 Aqueous HClO ₄ (pH 2) / methanol	[109]
<i>p</i> -Borono-phenylalanine		0.4% Aqueous HClO ₄	[110]
Amino-(2-hydroxy-4-propyl-2H-pyrazol-3-yl)-acetic acid		HClO ₄	[111]
2-Amino-2-phenyl-acetamide		HClO ₄ (pH 1.3)	[85]

Name	Structure	Mobile Phase	Ref.
Phenylalanine		Aqueous HClO ₄ (pH 1.5)	[112]
2-Amino-cyclobutane-carboxylic acid		0.17 M HClO ₄ (pH 1)	[113]
2-Amino-propionic acid		30 mM HClO ₄ (pH 2)	[114]
2-Amino-4-[[<i>(E)</i> -2-carboxyethenyl](hydroxy)phosphoryl]butanoic acid		Aqueous HClO ₄ pH 1.0	[115]
2-Phenylpropan-1-amine		Aqueous 0.03 N HClO ₄ (pH 6) buffer	[116]

6.4.3. Charge transfer

Charge transfer complexes are an electron donor/electron acceptor associations for which an intermolecular electronic charge transfer is observed [117]. Sometimes, it is very difficult to discriminate between electronic charge transfer and donor-acceptor complexes. A donor-acceptor complex may also involve adduct formation by proton transfer. At the same time, there is no definite boundary between coordination complexes and charge transfer complexes. In charge transfer complexes, an electron may be transferred from a non-bonding orbital of the donor to an anti-bonding orbital of the acceptor. A coordination complex involves the donation of a lone pair of electrons from the donor to a vacant orbital of the acceptor molecule. In general, the acceptor is a metal atom of the transition series. The adducts are usually stabilised by other bonding contributions [118].

Charge transfer complexes can be classified according to the type of orbitals interacting:

1. π donors and π acceptors in which it is a π orbital which donates or accepts the bonding electron, which is delocalized over the orbital of the adduct. This type of charge transfer complexes are usually strong complexes.
2. σ donors and σ acceptors in which the bonding involves the s orbital of the reactants.
3. n donors where the bonding orbital is localized within the reactant molecules. An example of this effect is of tertiary nitrogen [118].

In the following we will focus on the aromatic interactions which occur between a π donor molecule and a π acceptor counterpart. They provide stability to duplex DNA and are believed to contribute to the unique properties of thermophilic proteins. They may play a role in amyloid aggregation in Alzheimer's disease, being a common motif in biomolecular recognition. They are integral part in enantiomeric recognition when the stationary phase consists of a π donor/acceptor and the analyte contains a π donor/acceptore moiety

Aromatic interactions have been suggested to consist of van der Waals, hydrophobic and electrostatic forces. The relative contribution and magnitude of each of these components is still a matter of debate. The controversy arises from the fact that aromatic groups interact in one of several geometries, depending on the nature of the rings involved [119]. The electrostatic component has been suggested to arise from interactions of the quadrupole moments of the aromatic rings. The edge-face geometry can be considered as a CH- π interaction found in benzene in the solid and liquid state, and is commonly observed between aromatic residues in proteins [120]. Aromatic rings can also act as hydrogen bond acceptors. The presence of a solvent affects the complexation constant describing the equilibrium between the individual components of the complex. This is due to the competition of solvent molecules toward each component of the complex. The solvent does not have to be a charge-transfer competitor. Competitive interactions such as hydrogen bonds can also affect the equilibrium. When the equilibrium constant of complexation is quite low, the influence of the solvent is very significant, due to its overwhelming concentration compared to the concentration of the complex.

6.4.4. Chiral separation through a combination of charge transfer, hydrogen bonding and electrostatic interactions

In 1966, Pirckle first reported that (*S*)-1-phenylmethylaniline caused ^{19}F -NMR non-equivalency of 2,2,2-trifluoro-1-phenylethanol in a carbon tetrachloride solution [121]. In later studies, 2,2,2-trifluoro-1-(9-anthryl)ethanol, an NMR shift reagent, was used as a mobile phase additive to separate racemates of 2,4-dinitrophenyl methyl sulfoxide on a silica gel column [122]. Later, one enantiomer of this fluoroalcohol was covalently attached to silica gel and used for the resolution of a large number of solutes, including sulfoxides, lactones,

derivatives of alcohols, amines, amino acids, hydroxy acids and mercaptans [123]. The model used to describe complex formation between the selectand and the selector consists of three simultaneous points of interaction first described by Dalglish [3,124]. The Pirkle-type phases are based on amino acids bound on one side to the silica gel matrix and on the other side derivatised with an aromatic moiety which can be either a π donor or a π acceptor. This chiral stationary phase (CSP) undergoes π - π interactions with enantiomeric analytes which have an aromatic moiety. The complex is stabilised through additional interactions such as hydrogen bonding, dipole-dipole interactions or steric repulsion [125]. An improved chiral stationary phase synthesised by Pirkle's group possesses both dinitrobenzoyl and naphthyl moieties, allowing for simultaneous face-to-face π - π interactions and phase-to-edge interactions [126]. The elution order is controlled through the configuration of the CSP. These phases were used under normal phase conditions, with mixtures of solvents such as hexane-isopropyl alcohol. They were also used under supercritical and reversed phase conditions [125]. Table 6.5 lists some enantiomeric compounds and the compositions of CSP and mobile phase for the separation of their racemic mixture based on simultaneous charge transfer and hydrogen bonding interactions.

Another type of CSP capable of undergoing charge transfer interactions is the one developed by Lindner's group [127], based on cinchona alkaloids. They can operate under both normal phase and reversed phase. Under reversed phase conditions, they operate through an ion pairing interaction with acidic enantiomeric analytes. Under normal phase conditions, they operate through π - π interactions as well as ion pairing [128,129].

The basis of the interactions in the complex consists of electrostatic interactions between the quinuclidine of the amine ion and the carboxylate of the selectand, the π - π interactions between the quinoline ring of the selector and the dinitrobenzoyl of the selectand and the steric repulsion between the leucine side chain and the carbamate moiety [129]. Table 6.6 lists some successful separation on the commercial Chiral AX[®] column based on quinine CSP.

Table 6.5. Selected compounds and the conditions for the separation of their racemic mixture on CSP working through charge transfer and H-bonding

Name/Structure	Stationary phase	Mobile Phase	Ref.
3- <i>tert</i> -Butyl-3H-naphtho[1,2- <i>c</i>]furan-1-one	(3 <i>R</i> ,4 <i>S</i>)-4-(3,5-Dinitrobenz-amido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>S,S</i>)-Whelk-O1)	10:90 hexane / 2-propanol	[130]

Name/Structure	Stationary phase	Mobile Phase	Ref.
3-Methyl-2-phenyl-2,3-dihydro-benzofuran	(3 <i>R</i> ,4 <i>S</i>)-4-(3,5-Dinitrobenzamido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>S,S</i>)-Whelk-01)	Heptane	[25]
1-Trimethylsilylanyl-2-azabicyclo[3.1.0]hexane-2-carboxylic acid <i>tert</i> -butyl ester	(3 <i>R</i> ,4 <i>S</i>)-4-(3,5-Dinitrobenzamido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>S,S</i>)-Whelk-01)	95:5 hexane / 2-propanol	[131]
4-Bromo-benzoic acid 1-(6-oxocyclohex-1-enyl)- <i>hept</i> -4-enyl ester	(3 <i>S</i> ,4 <i>R</i>)-4-(3,5-Dinitrobenzamido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>R,R</i>) Whelk-01)	95:5 hexane / 2-propanol	[132]
4-Cyano-3-(4-fluoro-phenyl)-butyric acid methyl ester	(3 <i>S</i> ,4 <i>R</i>)-4-(3,5-Dinitrobenzamido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>R,R</i>) Whelk-01)	90:10 hexanes / ethanol	[133]

Name/Structure	Stationary phase	Mobile Phase	Ref.
<p>Butyric acid 1-(4-methoxy-phenyl)-ethyl ester</p>	(3 <i>R</i> ,4 <i>S</i>)-4-(3,5-Dinitrobenzamido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>S,S</i>)-Whelk-O1)	90:10 hexane / 2-propanol	[134]
<p>((<i>E</i>)-1-Hydroxy-5-methyl-hex-2-enyl)-phosphonic acid dimethyl ester</p>	(3 <i>R</i> ,4 <i>S</i>)-4-(3,5-Dinitrobenzamido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>S,S</i>)-Whelk-O1)	80:20 hexane / ethanol	[135]
<p>Tiropamide</p>	(3 <i>S</i> ,4 <i>R</i>)-4-(3,5-Dinitrobenzamido)-3-[3-(trioxysilyl)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>R,R</i>) Whelk-O2)	700:300:2:1 methanol / H ₂ O / acetic acid / triethylamine	[136]
<p>N-[2-Methoxymethoxy-1-(2-methoxy-5-methyl-phenyl)-ethyl]-acetamide</p>	4-(3,5-Dinitrobenzamido)-3-tetrahydrophenanthrene derivative incorporated into polymethylhydrosiloxane (coated on silicagel 300A) ((<i>S,S</i>)-polyWhelk-O1)	30:20 hexanes / 2-propanol	[137]

Name/Structure	Stationary phase	Mobile Phase	Ref.
2-(Benzhydrylidene-amino)-4-(2,2-dimethyl-propylidene)-pentanedioic acid 1- <i>tert</i> -butyl ester 5-methyl ester	(3 <i>R</i> ,4 <i>S</i>)-4-(3,5-Dinitrobenz-amido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>S,S</i>)-Whelk-01)	99:1 hexane / 2-propanol	[138]
2-Phenyl-cyclopropanecarboxylic acid	(3 <i>S</i> ,4 <i>R</i>)-4-(3,5-Dinitrobenz-amido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>R,R</i>) Whelk-01)	98:1.5:0.5 phexane / ethyl acetate / acetic acid	[139]
6,6'-Dibromo-1,1'-bi-2-naphthol	(3 <i>S</i> ,4 <i>R</i>)-4-(3,5-Dinitrobenz-amido)-3-[3-(trioxysilyl)-propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>R,R</i>) Whelk-02)	98:2 hexane / 2-propanol	[140]
[(<i>S</i>)-(<i>S</i>)-(1-Acetyl-2-oxo-cyclopentyl)- <i>m</i> -tolyl-methyl]-carbamic acid allyl ester	(3 <i>S</i> ,4 <i>R</i>)-4-(3,5-Dinitrobenz-amido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>R,R</i>) Whelk-01)	90:10 hexane / 2-propanol	[141]

Name/Structure	Stationary phase	Mobile Phase	Ref.
3-(Indan-1-ylamino)-indan-1-one	(3 <i>S</i> ,4 <i>R</i>)-4-(3,5-Dinitrobenz-amido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>R,R</i>)-Whelk-O1)	0.95:0.95:8:3:87.1 triethylamine / H ₃ PO ₄ / 2-propanol / acetonitrile / H ₂ O	[142]
1-[2-(3,3-Dimethyl-but-1-ynyl)-pyrimidin-5-yl]-2-methylpropan-1-ol	(3 <i>R</i> ,4 <i>S</i>)-4-(3,5-Dinitrobenz-amido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>S,S</i>)-Whelk-O1)	Gradient 4-40 % methanol (SFC)*	[143]
4a,7-Dimethyl-1,4,4a,8a-tetrahydro-1,4-methanonaphthalene-5,8-dione	(3 <i>R</i> ,4 <i>S</i>)-4-(3,5-Dinitrobenz-amido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>S,S</i>)-Whelk-O1)	99:1 hexane / 2-propanol	[144]
2-[(4-Methoxy-phenylamino)-phenyl-methyl]-hexanoic acid ethyl ester	(3 <i>R</i> ,4 <i>S</i>)-4-(3,5-Dinitrobenz-amido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>S,S</i>)-Whelk-O1)	99:1 hexane / 2-propanol	[145]

Name/Structure	Stationary phase	Mobile Phase	Ref.
(3-Oxo-1-phenyl-butyl)- carbamic acid tert-butyl ester	(3 <i>R</i> ,4 <i>S</i>)-4-(3,5-Dinitrobenz-amido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>S,S</i>)-Whelk-01)	85:15 hexane / 2-propanol	[146]
2,2,6,6-Tetramethyl-1-[2,4,4-trimethyl-1-(toluene-4-sulphonyl)-pyrrolidin-2-ylmethoxy]-piperidine	(3 <i>R</i> ,4 <i>S</i>)-4-(3,5-Dinitrobenz-amido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>S,S</i>)-Whelk-01)	97:3 hexane / 2-propanol	[147]
2-(Hydroxy-phenyl-methyl)-5-oxo-2,5-dihydro-pyrrole-1-carboxylic acid tert-butyl ester	(3 <i>R</i> ,4 <i>S</i>)-4-(3,5-Dinitrobenz-amido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>S,S</i>)-Whelk-01)	85:15 hexane / ethanol	[148]

Name/Structure	Stationary phase	Mobile Phase	Ref.
4-Oxo-3-phenyl-3-((<i>E</i>)-3-phenyl-allyl)-3,4-dihydro-2H-quinoline-1-carboxylic acid allyl ester	(3 <i>R</i> ,4 <i>S</i>)-4-(3,5-Dinitrobenzamido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>S,S</i>)-Whelk-O1)	80:20 hexanes / 2-propanol	[149]
1-Phenyl-2-propanol	(3 <i>S</i> ,4 <i>R</i>)-4-(3,5-Dinitrobenzamido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>R,R</i>)-Whelk-O1)	90:10 hexane / 2-propanol + acetic acid (apparent pH: 3.6)	[150]
Methyl -phenyl(prop-2-en-1-yloxy)ethanoate	(3 <i>S</i> ,4 <i>R</i>)-4-(3,5-Dinitrobenzamido)-3-[3-(dimethylsilyloxy)propyl]-1,2,3,4-tetrahydrophenanthrene ((<i>R,R</i>)-Whelk-O1)	99:1 hexane / 2-propanol	[151]

*SFC – supercritical fluid chromatography

Table 6.6. Selected compounds and the conditions for their HPLC separation on Chiral AX[®] CSP containing quinine

Name/Structure	Stationary phase	Mobile Phase	Ref.
<p>N-(2,4-Dinitro-phenyl)-alpha-naphthalen-1-ylmethyl-proline</p>	(2,6-Diisopropyl-phenyl)-carbamoyl-Quinine bonded to mercaptopropylsilica (Chiral AX QN-2)	30:70 Aqueous ammonium acetate 0.05 M / methanol (pH 6.5)	[152]
<p>2-Benzyloxycarbonylamino-3-phenyl-propionic acid</p>	<i>tert</i> -Butylcarbamoyl-Quinine bonded to mercaptopropyl silica (Chiral AX QN-1)	80:20 methanol / 50 mM sodium phosphate buffer (pH 5.6)	[153]
<p><i>cis</i>-Chrysanthemic acid</p>	<i>tert</i> -Butylcarbamoyl-quinine bonded to mercaptopropyl silica (Chiral AX QN-1)	80:20 methanol / H ₂ O, 10 mM ammonium acetate buffer (pH 6.0)	[154]

Name/Structure	Stationary phase	Mobile Phase	Ref.
1-Furan-2-yl-1,2-dihydro-imidazo[5,1-b]quinazoline-3,9-dione	<i>tert</i> -Butylcarbamoyl-quinine bonded to mercaptopropyl silica (Chiral AX QN-1)	90:10 0.1 M Ammonium acetate buffer (pH 6.0) / acetonitrile	[155]
1-(4-Chloro-phenyl)-1,2-dihydro-imidazo[5,1-b]quinazoline-3,9-dione	(2,6-Diisopropyl-phenyl)-carbamoyl-quinine bonded to mercaptopropyl silica (Chiral AX QN-2)	60:40 0.1 M Ammonium acetate buffer (pH 6.0) / methanol	[155]
Ala-OPA (Alanine ortho-phthalaldehyde derivative)	<i>tert</i> -Butylcarbamoyl-quinine bonded to mercaptopropyl silica (Chiral AX QN-1)	80:20 methanol / aqueous 0.1 M ammonium acetate buffer (pH 6.0)	[156]
2-Methoxy-2-(1-naphthyl)propionic acid	<i>tert</i> -Butylcarbamoyl-quinine bonded to mercaptopropyl silica (Chiral AX QN-1)	96:4 methanol / acetic acid	[157]

Name/Structure	Stationary phase	Mobile Phase	Ref.
<p>Fmoc-Glu</p>	<p><i>tert</i>-Butylcarbamoyl-quinine bonded to mercaptopropyl silica (Chiral AX-QN)</p>	<p>methanol / 0.25% acetic acid (44 mM)</p>	[158]
<p>NBD-<i>trans</i>-Hydroxyproline*</p>	<p><i>tert</i>-Butylcarbamoyl-quinine bonded to mercaptopropyl silica (Chiral AX QN-1)</p>	<p>50:50 methanol / acetonitrile / 10 mM citric acid</p>	[159]
<p>NBD-Proline*</p>	<p>(2,6-Diisopropyl-phenyl)-carbamoyl-quinine bonded to mercaptopropyl silica (Chiral AX QN-2)</p>	<p>50:50 methanol / acetonitrile / 10 mM citric acid</p>	[159]

* NBD - 4-nitrobenzo-2-oxa-1,3-diazole

6.4.5. Ligand exchange

Ligand exchange chromatography (LEC) is a typical example of complexation chromatography. Complexes formed during LEC encompass a metal cation associated with ligands (anions or neutral molecules) able to donate electron pairs to a vacant orbital of the metal [160]. The term ligand exchange was introduced Helfferich in 1961 when he described the substitution of organic diamine molecules with metal ion-coordinated molecules containing amine groups in a polymeric phase [161]. The technique was further developed by Davankov and Rogozin for the separation of enantiomers [162]. This technique is applicable to those enantiomers which are able to form metal complexes with the moiety bound onto the stationary phase. Enantiomeric analytes such as amino acids and hydroxy acids were successfully separated into enantiomers using LEC.

In their paper, the authors described the model of interaction during the enantiomeric separation with LEC [162]:

"In such a process, one ligand (the optically active one) should be rigidly attached to a stationary phase, while the other (racemic) ligand should be able to move with the mobile phase. The metal atom forming the complex may be combined with either ligand. The important point is that the complex generated should be kinetically labile, i.e. readily decomposed and reformed."

Based on the model, the chiral phase is usually an amino acid anchored to a silica matrix through a spacer. Table 6.7 shows several examples of enantiomeric separations through LEC. The mobile phase used in conjunction with these chiral phases is a buffer containing millimolar amounts of copper. At a constant pH, the retention increases with an increase in the length of the spacer. The pH of the mobile phase influences the stability constant of the complexes and, consequently, the retention as well as the enantioselectivity. The retention of hydrophobic analytes can be controlled by the amount of an organic modifier such as acetonitrile or methanol. The flow rate of the mobile phase has major role on the resolution; the slower the flow rate, the higher the resolution [163].

Table 6.7. Conditions for LEC enantiomeric separation of selected compounds

Name/Structure	Stationary Phase	Mobile Phase	Ref.
5,5-Dimethylthiazolidine-4-carboxylic acid	(S)-Leucinol monosodium salt covalently bonded to aminoundecyl silica	80:20 aqueous CuSO ₄ / 0.2 mM / methanol	[164]
2R,3R-2S,3S-2-Hydroxy-3-methyl-pentanoic acid	N,N-Dioctyl-L-alanine coated octadecyl silica (Chiralpak MA(+))	85:15 2 mM CuSO ₄ / acetonitrile	[165]
N-Methyl glutamic acid	N,S-Dioctyl-(D)-penicillamine coated on octadecylsilanised silica (Chirex 3126)	90:10 2 mM CuSO ₄ / acetonitrile	[166]

Name/Structure	Stationary Phase	Mobile Phase	Ref.
Proline	N,S-Dioctyl-(<i>D</i>)-penicillamine coated on octadecylsilanised silica (Chirex D-penicillamine)	95:5 2 mM CuSO ₄ / acetonitrile	[167]
2-(1-Amino-1-carboxy-ethyl)-cyclopropanecarboxylic acid	N,S-Dioctyl-(<i>D</i>)-penicillamine coated on octadecylsilanised silica (Chirex D-penicillamine)	1 mM CuSO ₄	[168]
2-Amino-4-methylselanylbutyric acid	Isoleucine reacted on (3,4-epoxycyclohexyl)ethyltrimethoxy-silane reacted on silica	50 mM KH ₂ PO ₄ , 0.1 mM CuSO ₄ (pH 5.5)	[169]
3-(4-Hydroxyphenyl)lactic acid	Chitosan (95% deacetylated) bonded to aminopropylsilica with glutaraldehyde	Aqueous 3 mM CuSO ₄	[170]
Alanine	S-Trityl-(<i>R</i>)-cysteine coated on Lichrospher 100 RP18 silica.	0.5 mM CuSO ₄ (pH 4.5)	[171]
Amino-(3-hydroxyadamantan-1-yl)-acetic Acid	(<i>L</i>)-Proline bonded to silica gel (Chiralpak (WH))	Aqueous 0.3 mM CuSO ₄	[172]

6.4.6. Mixed types of interactions

The previous sections described the main types of interactions occurring between the enantiomeric analytes and the stationary phase (hydrogen bonding, inclusion complexes, charge transfer and ligand exchange). In the following section, we will present enantiomeric separation based on combinations of these interactions. These types of stationary phases include polysaccharides, antibiotic phases (macrocytic antibiotics) and protein phases.

6.4.6.1. Polysaccharide phases

Many polysaccharides serve as extracellular elements in the cell walls of unicellular microorganisms and higher plants and on the outer surfaces of animal cells. There are many different structural polysaccharides. Cellulose is the most abundant extracellular structural polysaccharide of all biomolecules, plant or animal. Structurally, cellulose is a polysaccharide composed of several thousand molecules of D-glucose joined by $\beta(1\rightarrow4)$ glycosidic linkages. Complete hydrolysis of all glycosidic bonds of cellulose yields D-glucose.

Starch is a mixture of a water-dispersible fraction called amylose and a second component, amylopectin. Amylose is a polysaccharide made up of about 100 to several thousand D-glucose units joined together by $\alpha(1\rightarrow4)$ glycosidic bonds [173]. This difference in the structure of cellulose and amylose results in polymeric structures with very different properties. Because of their β linkages, the D-glucose chains in cellulose assume an extended conformation and undergo side-by-side aggregation due to hydrogen bonding between the hydroxyl groups of adjacent cellulose chains. Due to the geometry of their $\alpha(1\rightarrow4)$ linkages, the main chains of D-glucose units in amylose tend to assume a coiled, helical conformation [174].

Cellulose has been used in thin layer chromatography to separate enantiomers of tryptophan and tryptophan derivatives using aqueous mobile phases [175-177], while amylose has been used to separate biphenyl atropisomers and other optical isomers [178]. The interactions between the enantiomeric analytes and these chiral stationary phases occur only through H-bonding as well as inclusion between the polymeric chains of these biomolecules. The chiral discrimination of these native biopolymers is thereby reduced. Modification of hydroxy groups through esters or carbamate formation greatly enhances the enantioselective properties of these polysaccharides due to multiple possibilities of H-bonds and π - π interactions as well as through inclusion complex formations. Phenyl esters and phenyl carbamates of amylose and cellulose are the most popular CSPs today. For example, the major chiral adsorption site in cellulose tris-methylbenzoate is considered to be the polar carbonyl groups of the esters, which can interact with the racemate through hydrogen bonding and dipole-dipole interactions for discrimination between enantiomers [179]. The cellulose and amylose carbamate assume a left-handed three-fold helical conformation, while the corresponding amylose has a left-handed four-fold helix. A chiral helical

channel is formed along the backbone. Aromatic moieties are located at the surface of the chain while the polar groups are located in the interior [180]. The shape of the chiral cavities varies depending on the nature of the substitution on the polysaccharide [125]. Chiral recognition is attributed to shape-selective inclusion along with π - π interactions, hydrogen bonding and van der Waals interactions [181]. These stationary phases operate under normal phase as well as under reversed phase mobile phase conditions. Under normal phase conditions, combinations of hexane/alcohols are used. Under reversed phase conditions, it is assumed that the interaction between the CSP and the enantiomeric analytes occurs through shape-specific interactions into the chiral cavities [182].

Tables 6.8 – 6.19 give some selected examples of enantiomeric separation using cellulose derivatised and amylase derivatised CSPs.

Table 6.8. Conditions for chiral separations of selected compounds using cellulose tris(3,5-dimethylphenylcarbamate)/macroporous silica gel (Chiralcel OD®) stationary phase

Name	Structure	Mobile Phase	Ref.
1-[[4-(4-Chloro-phenyl)-1-methyl-1H-pyrrol-3-yl]-phenyl-methyl]-1H-imidazole		90:10 hexane / ethanol / 0.1% diethylamine	[183]
Indapamide		50:50 hexane / ethanol	[184]
Dia-(1 <i>S</i> 3 <i>R</i> ,1 <i>R</i> 3 <i>R</i>)-3-benzyl-oxyethyl-1,3-dihydro-isobenzofuran-1-thymine		80:20 hexane / ethanol	[185]
Dia-(1 <i>R</i> 3 <i>R</i> ,1 <i>S</i> 3 <i>R</i>)-3-benzyl-oxyethyl-1,3-dihydro-isobenzofuran-1-uracil		80:20 hexane / ethanol	[185]

Name	Structure	Mobile Phase	Ref.
5,7-Dimethyl-1,4-dioxo-1,5,8,8a-tetrahydro-4H-naphthalene-4a-carboxylic acid methyl ester		95:5 hexane / 2-propanol	[186]
5-(N,N'-Bisbenzyloxy-carbonyl-hydrazino)-4-hydroxy-heptan-2-one		60:40:0.1 H ₂ O / acetonitrile / tri-fluoro acetic acid	[187]
3-Methyl-1,3,4-triphenyl-butan-1-one		85:15 hexane / methyl- <i>t</i> -butyl ether	[188]
5-(3,5-Dinitro-benzoyloxy)-3-aza-tricyclo[2.2.1.0*2,6*]heptane-3-carboxylic acid <i>tert</i> -butyl ester		50:50 hexane / ethanol	[189]
Diniconazole		85:15 hexane / ethyl acetate	[190]
Phosphinamide derivative		90:10 hexane / 2-propanol	[191]

Name	Structure	Mobile Phase	Ref.
(5-Methyl-4,5-dihydro-pyrazol-1-yl)-pyridin-3-yl-methanone		90:10 hexane / 2-propanol	[192]
1-(4-Chloro-phenyl)-3-phenyl-propane-1,3-diol		95:5 hexane / 2-propanol	[193]
6-Chloro-2,2-dimethyl-1a,7b-dihydro-2H-1,3-dioxa-cyclopropa[a]naphthalene		99:1 hexane / 2-propanol	[194]
1-(1-Methyl-1H-imidazol-2-yl)-2-(2,3,4,9-tetrahydro-1H-carbazol-1-yl)-ethanone		90:10 hexanes / 2-propanol	[195]
Nadolol		100% acetonitrile	[196]
(1-Isobutyl-pyrrolidin-2-yl)-phenyl-methanol		99.5:0.5 hexane / 2-propanol	[197]
Acetic acid 2-benzyl-3-(tert-butyl-dimethyl-silanyloxy)-propyl ester		95:5 hexane / 2-propanol	[198]
3-Furan-2-yl-2,3-dihydro-benzofuran-3-ol		90:10 hexane / 2-propanol	[199]

Name	Structure	Mobile Phase	Ref.
4-Acetyl-5-ethyl-3-hydroxy-2,3-dihydro-furan-3-carboxylic acid ethyl ester		95:5 hexane / 2-propanol	[200]
Indan-1-yl-carbamic acid 2,2,2-trichloro-ethyl ester		9:1 hexane / 2-propanol	[201]
3-Phenethyl-decanoic acid methyl ester		99.2:0.8 hexane / 2-propanol	[202]
(3,5-Dimethyl-phenyl)-(1-phenyl-ethyl)-amine		99:1 hexane / 2-propanol	[203]
3-[4-Methyl-3-[methyl-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-amino]-piperidin-1-yl]-3-oxo-propionitrile		methanol	[204]
2,2,4-Trimethyl-4-(2-phenyl-allyl)-[1,3]dioxan-5-one		99:1 hexanes / ethanol	[205]
2-(Benzoyl-methyl-amino)-3-methyl-butyrac acid methyl ester		50:1 hexane / 2-propanol	[206]

Name	Structure	Mobile Phase	Ref.
3-Ethyl-4-oxo-3-phenyl-[1,2]diazetidine-1,2-dicarboxylic acid dimethyl ester		95:5 hexane / 2-propanol	[207]
4-(4-Fluorophenylsulphonyl)-2-phenylmorpholine		95:5 hexane / 2-propanol	[208]
[1-(4-Fluoro-phenyl)-ethyl]-(3-methoxy-phenyl)-amine		95:5 hexane / 2-propanol	[209]
Methyl 4-bromo-alpha-methyl-N-[(propan-2-yloxy)carbonyl]-L-phenylalaninate		80:20 hexane / ethanol	[210]
2-Amino-4-(4-methylphenyl)-8-oxo-5,6,7,8-tetrahydro-4H-chromene-3-carbonitrile		15:85 2-propanol / hexane	[211]
5-Bromo-N-hydroxy-6-methyl-N-[3-methylbut-3-en-2-yl]pyridin-2-amine		95:5 hexanes / 2-propanol	[212]
1-Chloro-2-but-3-enyl benzoate		1000:1 hexane / 2-propanol	[213]

Table 6.9. Conditions for chiral separations of selected compounds using amylose tris(3,5-dimethylphenylcarbamate) coated on silica (Chiralpak AD[®]) stationary phase

Name	Structure	Mobile Phase	Ref.
1-[[4-(4-Chloro-phenyl)-1-methyl-1H-pyrrol-3-yl]-phenyl-methyl]-1H-imidazole		90:10 hexane / ethanol / 0.1% diethylamine	[183]
5-[2-[1-(3,5-Bis-trifluoromethyl-phenyl)-ethoxy]-3-phenyl-morpholin-4-ylmethyl]-2,4-dihydro-[1,2,4]triazol-3-one		93:7 hexane / propanol	[214]
2-Amino-3-[4-((E)-styryl)-phenyl]-propionic acid methyl ester		90:10 hexane / 2-propanol	[215]
Omeprazole		20 mM phosphate buffer (pH 4.65) / acetonitrile (Chiralpak AD-RH)	[216]
2-Phenyl-2-(N-phenyl-aminoxy)-ethanol		90:10 hexane / ethanol	[217]
5-Methyl-2-thioxo-oxazolidine-4-carboxylic acid tert-butyl ester		10:1 hexane / 2-propanol	[218]
3-Phenyl-propane-1,2-diol		98:2 hexane / 2-propanol	[219]
1,2-Di-furan-2-yl-2-hydroxy-ethanone		90:10 hexane / 2-propanol	[220]

Name	Structure	Mobile Phase	Ref.
4-Ethoxy-6-(4-nitro-phenyl)-5,6-dihydro-pyran-2-one		85:15 hexane / 2-propanol	[221]
3-Naphthalen-1-yl-pentan-1-ol		50:1 hexane / 2-propanol (Chiralpak AD-H)	[222]
N-(1-Phenyl-ethyl)-acetamide		95:5 hexane / 2-propanol	[223]
3-Methyl-2-phenyl-pent-4-en-2-ol		999:1 hexane / 2-propanol (Chiralpak AD-H)	[224]
[2-(2-Bromo-phenyl)-3-((E)-styryl)-cyclopropyl]-phenyl-methanone		100:4 hexane / 2-propanol	[225]
(6- <i>tert</i> -Butoxycarbonyl-amino-5-oxo-cyclohex-3-enyl)-carbamic acid <i>tert</i> -butyl ester		20:1 hexane / 2-propanol	[226]
2-(Hydroxy-pyridin-4-yl-methyl)-cyclohexanone		90:10 hexane / 2-propanol	[227]

Name	Structure	Mobile Phase	Ref.
5-(N-Phenyl-aminooxy)-hept-1-en-4-ol		97:3 hexanes / 2-propanol	[228]
Efaroxan 2-(2-Ethyl-2,3-dihydro-benzofuran-2-yl)-4,5-dihydro-1H-imidazole		98:2:0.05 hexane / 2-propanol / diethylamine	[229]
Diarylphosphinamide derivative		50:1 hexane / 2-propanol	[230]
1-Methyl-2,4,5-triphenyl-4,5-dihydro-1H-imidazole		90:10 heptane / 2-propanol	[231]
2-[(1H-Indol-3-yl)-phenyl-methyl]-3-methyl-butyraldehyde		85:15 hexane / 2-propanol	[232]
2-[Hydroxy-(4-nitro-phenyl)-methyl]-cyclopentanone		95:5 hexane / 2-propanol	[233]
2-Ethyl-3-methyl-5-phenyl-pyrrolidine-2,4-dicarboxylic acid dimethyl ester		40:1 hexane / 2-propanol	[234]

Name	Structure	Mobile Phase	Ref.
2-[1-(4-Chloro-phenyl)-2-nitro-ethyl]-malonic acid diethyl ester		65:35 hexane / 2-propanol	[235]
4-Hydroxy-4-m-tolyl-butan-2-one		90:10 hexane / 2-propanol	[236]
Methyl 4-bromo-alpha-methyl-N-[(propan-2-yloxy)carbonyl]-L-phenyl-alaninate		80:20 hexanes / ethanol (AD-H)	[210]
Ethyl 3-(4-methoxy-1H-indol-3-yl)butanoate		95:5 hexane / 2-propanol	[237]
Koga base		95:5 Isobutanol / methanol / 0.03% triethylamine	[238]

Table 6.10. Conditions for chiral separations of selected compounds using cellulose tris(3,5-dimethylphenylcarbamate) immobilised on silica (Chiralpak IB®) stationary phase

Name	Structure	Mobile Phase	Ref.
5-Ethyl-1-methyl-5-propyl-pyrimidine-2,4,6-trione		90:10 hexane / 2-propanol	[239]
N- <i>p</i> -Methoxy-1,α-dihydroaristoyagonine		80:20 hexane / ethanol + 0.5% trifluoroacetic acid	[240]
Monastrol		60:40 ethylacetate / hexane	[241]
7b-Phenyl-1a,2,3,7b-tetrahydro-1-oxa-cyclopropa[a]naphthalene		95:5 hexane / 2-propanol	[242]
2-(3-Ethyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione		80:20 methyl- <i>t</i> -butyl ether / tetrahydrofuran	[243]
N-Phthaloyl-valine		95:5 hexane / 2-propanol / 0.1% CF ₃ CO ₂ H	[244]
3-(4-Methoxy-phenylamino)-2-methyl-3-phenyl-propan-1-ol		90:10 hexane / 2-propanol	[145]

Name	Structure	Mobile Phase	Ref.
4-[[Carboxy-(3,4-dimethoxy-phenyl)-methyl]-carbamoyl]-butyric acid		66:30:4:0.1 hexane / CHCl ₃ / ethanol / trifluoroacetic acid	[245]
Metanephrene		65:35:0.1 hexane / ethanol / diethylamine	[246]
BOC-Phg-Oet		40:60 methyl-t-butyl ether / hexane / 0.1% trifluoroacetic acid	[247]
3-(4-Methoxy-phenyl)-1,4-diphenyl-azetidin-2-one		hexane / 2-propanol	[248]
(Cyclobutyl-phenyl-methyl)-(4-methoxy-phenyl)-amine		99:1 hexane / 2-propanol	[249]
Flurbiprofen <i>n</i> -butyl ester		85:15:0.4:0.1 hexane / <i>tert</i> -butyl methyl ether / 2-propanol / trifluoroacetic acid	[250]
(7 <i>E</i>)-6-Hydroxytetradec-7-ene-2,4-diyn-1-yl acetate		90:10 heptane / ethyl acetate	[251]

Table 6.11. Conditions for chiral separations of selected compounds using amylose tris(3,5-dimethylphenylcarbamate) immobilised on silica (Chiralpak IA®) stationary phase

Name	Structure	Mobile Phase	Ref.
3,5-Dinitro-benzoic acid 2-phenyl-1-trifluoromethyl-cyclopropylmethyl ester		90:10 hexane / 2-propanol	[252]
Pirprofen		80:20:0.1 hexane / 2-propanol / trifluoroacetic acid	[253]
Propafenone		60:40:0.1 hexane / tetrahydrofuran / diethylamine	[254]
[1]Benzothieno[5',4':2,3][1]benzothieno[5,4-b]thieno[3,2-e][1]benzothiophene		19:1 hexane / dichloromethane	[255]
3-[[7-Ethyl-5-methoxy-9-oxo-6,7,8,9-tetrahydro-5H-5,8-epoxybenzo[7]annulen-6-yl]carbonyl]-1,3-oxazolidin-2-one		80:20 hexane / 2-propanol	[256]
3-p-Tolyl-cyclohexanone		98:2 hexane / 2-propanol	[257]

Name	Structure	Mobile Phase	Ref.
Rabeprazole		80:20:0.1 heptane / 2-propanol / triethylamine	[258]
2-(3-Ethyl-2,6-dioxo-piperidin-3-yl)-isoindole-1,3-dione		80:20 CH ₂ Cl ₂ / tetrahydrofuran	[259]
[(4-Isopropoxy-phenylamino)-phenyl-methyl]-phosphonic acid dimethyl ester		9:1 hexane / 2-propanol	[260]
Flavanone		90:10 methanol / 10 mM sodium phosphate (Na ₂ HPO ₄ + NaH ₂ PO ₄) buffer pH 3.0 (pH adjusted with 0.1 N NaOH or 10% H ₃ PO ₄)	[261]
1-Phenylethanol		95:5 hexane / 2-propanol	[262]
4-Cyclohexyl-4-hydroxy-butan-2-one		90:10 heptane / 2-propanol	[263]
2,4,5-Triphenyl-1-(toluene-4-sulphonyl)-4,5-dihydro-1H-imidazole		75:25 heptane / 2-propanol	[231]
BOC-Val-Oet		40:60 methyl-t-butyl ether / hexane / 0.1% trifluoroacetic acid	[247]

Name	Structure	Mobile Phase	Ref.
3-(Phenylthio)cyclopentanone		90:10 hexane / 2-propanol	[264]
2-(N-Phenyl-aminooxy)-hexan-1-ol		95:5 hexane / 2-propanol	[265]
Protohypericin		90:10:0.25 methanol / acetonitrile / N,N-diisopropylammonium acetate	[266]
(E)-1-(Triisopropylsilyl)tetradeca-6-en-1,3-diyn-5-ol		99:1 heptane / 2-propanol	[251]
[(endo)-1-(Hydroxymethyl)-1,5,6,10b-tetrahydropyrazolo[5,1-a]isoquinolin-3(2H)-yl](phenyl)methanone		4:1 hexane / ethanol	[267]

Table 6.12. Conditions for chiral separations of selected compounds using cellulose tris(4-methyl-benzoate) coated on silica gel (Chiralcel OJ®) stationary phase

Name	Structure	Mobile Phase	Ref.
cis-1,2-Indanediol		Various mobile phases (OJ-R)	[268]
Dia-(1S3R,1R3R)-3-benzyl-oxymethyl-1,3-dihydroisobenzofuran-1-thymine		80:20 hexane / ethanol	[185]

Name	Structure	Mobile Phase	Ref.
2-Benzyl-indan-1-one		90:10 hexane / 2-propanol	[269]
Disopyramide		73:27 CO ₂ / ethanol (SFC*)	[270]
Mepivacaine		85:15:0.1 isohexane / ethanol or 2-propanol / diethylamine	[271]
2,2-Dimethyl-3-(2-methyl-propenyl)-cyclopropane-carboxylic acid		90:10 hexane / 2-propanol	[272]
4-Hydroxy-4-(3-nitro-phenyl)-butan-2-one		80:20 hexane / 2-propanol	[273]
2-Hydroxy-4-phenyl-pent-4-enoic acid ethyl ester		97:3 hexane / 2-propanol	[274]
3-(tert-Butyl-dimethyl-silyloxy)-2-(3-trimethyl-silanyl-prop-2-ynylidene)-cyclopentanol		75:25 methanol / H ₂ O (OJ-R)	[275]
6-Biphenyl-4-yl-4-ethoxy-5,6-dihydro-pyran-2-one		80:20 hexane / 2-propanol	[276]
1-(4-Chloro-phenyl)-3-methyl-but-3-en-1-ol		50:1 hexane / 2-propanol	[277]

Name	Structure	Mobile Phase	Ref.
3-Benzylsulphanyl-pentan-1-ol		96:4 hexane / 2-propanol	[278]
4-Methyl-N-(1-phenyl-ethyl)-benzenesulphonamide		70:30 hexane / 2-propanol	[279]
3-[Hydroxy-(4-nitro-phenyl)-methyl]-but-3-en-2-one		96:4 hexane / 2-propanol	[280]
2-(3-Oxo-1,3-diphenyl-propyl)-malonic acid dibenzyl ester		90:10 hexane / 2-propanol	[281]
1-(4-Chloro-phenyl)-3-methyl-but-3-en-1-ol		50:1 hexane / 2-propanol	[282]
1-Ethynyl-4-methyl-2-oxo-cyclohex-3-enecarboxylic acid tert-butyl ester		90:10 hexane / 2-propanol	[283]
1,2,3,4-Tetrahydro-2,2,4,7-tetramethylquinoline		70:30 CO ₂ / ethanol (SFC*)	[284]

Name	Structure	Mobile Phase	Ref.
3-(4-Nitro-phenyl)-5-phenyl-4,5-dihydro-isoxazole		100 methanol	[285]
10-Hydroxycamptothecin		100 methanol	[286]
Acetic acid 3-tert-butoxycarbonylamino-7,9-dichloro-8-oxo-1-oxa-spiro[4.5]deca-6,9-dien-2-yl ester		90:10 hexane / ethanol	[287]
Anti-bicyclo[3.3.1]nonane-3,7-dione dioxime		99:1 hexane / 2-propanol	[288]
3-(4-Chloro-phenyl)-1-phenyl-pent-4-yn-1-one		85:15 hexane / 2-propanol	[289]
2-Ethylhexyl 3-[(2-[[2-phenylpropanoyl]amino]phenyl)sulphonyl]propanoate		H ₂ O / acetonitrile (gradient 40:60 to 0:90 in 30min)	[290]
2-[2-Hydroxypropyl]-1H-isoindole-1,3(2H)-dione		Not reported	[291]
(RR,SS)-2-(4-Benzylpiperazin-1-yl)-1-(5-chloro-6-methoxynaphthalen-2-yl)propan-1-ol		80:20:0.1 hexane / 2-propanol / diethylamine	[292]

* SFC – supercritical fluid chromatography

Table 6.13. Conditions for chiral separations of selected compounds using cellulose triphenylcarbamate coated on silica (Chiralcel OC®) stationary phase

Name	Structure	Mobile Phase	Ref.
3-(3-Hydroxy-1-isopropyl-2,2-dimethyl-4-oxo-azetidin-3-yl)-benzoic acid methyl ester		90:10 hexane / 2-propanol	[293]
4-(3-Methyl-2-oxo-tetrahydro-furan-3-yl)-benzoic acid ethyl ester		90:10 hexane / ethanol	[294]
3-Hydroxy-1,3,4,5-tetrahydro-benzo[b]azepin-2-one		97:3 hexane / 2-propanol	[295]
4-Methyl-3,6-dioxabicyclo[3.1.0]hexan-2-one		10:1 hexane / 2-propanol	[296]
3-Allyl-2-butyl-4-methyl-1-[(4-methylphenyl)sulphonyl]-2,5-dihydro-1H-pyrrole		97:3 hexane / 2-propanol	[297]
2-tert-Butoxycarbonylamino-3-thiazol-4-yl-propionic acid		65:35 hexane / 2-propanol	[298]
5-[2-[2-(2-Ethoxy-phenoxy)-ethylamino]-propyl]-2-methoxy-benzenesulphonamide, Tamsulosin		Not reported	[299]
3-Methyl-4-oxo-4-pyridin-2-yl-butyraldehyde		90:10 heptane / 2-propanol	[300]
Metaproterenol		90:10 hexane / ethanol / 0.2% butylamine	[301]

Name	Structure	Mobile Phase	Ref.
di-O,O-(p-ToluyI)-D-tartaric acid		90:10 hexane / 2-propanol	[302]
[3a,4-Dimethyl-hexahydro-benzofuran-(2E)-ylidene]-acetic acid isopropyl ester		30:1 hexane / ethanol	[303]
2,6-Diethoxy-1,5-dimethyl-2,6-diphenyl-3,7-dioxabicyclo[3.3.1]nonane		100 % hexane	[304]
2-(tert-Butyl-dimethyl-silanyloxy)-2-(2-nitro-phenyl)-pent-4-enal		99:1 heptane / 2-propanol	[305]
1-Cyclohexenyl-1-oxopent-4-en-2-yl acetate		99:1 heptane / 2-propanol	[306]
Pilocarpine, 3-Ethyl-4-(3-methyl-3H-imidazol-4-ylmethyl)-dihydro-furan-2-one		30:70 hexanes / ethanol	[307]

Name	Structure	Mobile Phase	Ref.
Imino thiazoline derivative		90:10 hexane / 2-propanol	[308]
2,2,2-Trifluoro-N-[2-hydroxy-1-phenylethyl]acetamide		70:30 hexane / 2-propanol	[309]

Table 6.14. Conditions for chiral separations of selected compounds using cellulose tris(4-Methyl-phenylcarbamate)coated on silica (Chiralcel OG®) stationary phase

Name	Structure	Mobile Phase	Ref.
N-(2-Hydroxy-1-phenylethyl)-4-methyl-benzenesulphonamide		70:30 hexane / 2-propanol	[310]
3-Phenyl-cyclopentanol		90:10 hexane / 2-propanol	[311]
2-Acetylamino-2-(5-trimethylsilanyl-penta-2,3-dienyl)-malonic acid diethyl ester		98:2 hexane / 2-propanol	[312]
2-Methyl-1,2,3,4,9,13b-hexahydro-2,4a,5-triaza-tribenzo[a,c,e]cycloheptene		98:2:0.1 hexane / ethanol / diethylamine	[313]
Z-ketoxime derivative		50:1 hexane / 2-propanol	[314]

Name	Structure	Mobile Phase	Ref.
Ethaboxam		70:30 hexane / ethanol	[315]
4-Phenyl-tetrahydro-pyran-2-one		90:10 hexane / 2-propanol	[316]
Metaproterenol		90:10 hexane / ethanol / 0.2% butylamine	[301]
Butyric acid 2'-hydroxy-[1,1']binaphthalenyl-2-yl ester		15:1 hexane / 2-propanol	[317]
19-Methyl-6,7,9,10-tetrahydro-dibenzo[b,g][1,3]thiazolo[3,2-d][1,9,12,4,6]trioxadiazacyclo tetradecine		60:40 hexane / 2-propanol	[308]
Diisopropyl 1-(3-benzyl-5-chloro-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate		90:10 hexane / 2-propanol	[318]
2,6-Dimethylphenyl 3-(1,3-benzodioxol-5-yl)-3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoate		90:10 hexane / 2-propanol	[319]
2,6-Dimethylphenyl (3R)-3-(3,5-dimethylphenyl)-3-(1,3-dioxo-1,3-dihydro-2H-isoindol-2-yl)propanoate		90:10 hexane / 2-propanol	[319]

Table 6.15. Conditions for chiral separations of selected compounds using cellulose tris(4-Chloro-phenylcarbamate) coated on silica (Chiralcel OF®) stationary phase

Name	Structure	Mobile Phase	Ref.
Econazole		425:74:1 hexane / 2-propanol / diethylamine	[320]
3-Methyl-1-(2-oxo-3-phenyl-tetrahydro-pyran-4-ylmethyl)-piperidine-3-carboxylic acid ethyl ester		Gradient 96:4 CO ₂ / methanol to 60:40 CO ₂ / methanol (SFC*)	[321]
2-Acetyl-4,4-dimethyl-2-(3-phenyl-allyl)-cyclohexanone		96:4 hexane / 2-propanol	[322]
6-Bromo-7,8-dihydro-benzo[def]chrysene-7,8-diol		50:50 hexane / 2-propanol	[323]
3-Benzyloxymethyl-5-hydroxy-2-phenyl-1-pyrrolidin-1-yl-pentan-1-one		Gradient 96:4 CO ₂ / methanol to 60:40 CO ₂ / methanol (SFC*)	[324]
2-(1-Methyl-1H-indol-3-yl)-1,2-diphenyl-ethanol		91:9 hexane / 2-propanol	[325]
3-(2-Nitro-1-p-tolyl-ethyl)-2-phenyl-1H-indole		85:15 hexane / 2-propanol	[326]

Name	Structure	Mobile Phase	Ref.
3-Hydroxy-pyrrolidine-1-carboxylic acid tert-butyl ester		4:1 hexane / 2-propanol	[327]
3,5-Dinitro-benzoic acid 4-(tert-butyl-dimethyl-silanyloxy)-1,3,3-trimethyl-butyl ester		Gradient 99:1 to 97:3 hexane : 2-propanol	[328]
1-[2-(3,3-Dimethyl-but-1-ynyl)-pyrimidin-5-yl]-2-methyl-propan-1-ol		70:30 CO ₂ / methanol	[143]
<i>sn</i> -1/3-Monocaproylglycerol (sn-1/3-6:0)		95:5 hexane / 2-propanol	[329]
anti-1-(2- <i>tert</i> -Butylphenyl)-3-(<i>tert</i> -butylthiomethyl)pyrrolidine-2,5-dione		90:10 hexane / 2-propanol	[330]
<i>tert</i> -Butyl 3-(4-aminophenylthio)-2-phthalimidopropionate-2-d1		50:50 hexane / 2-propanol	[330]

* SFC - supercritical fluid chromatography

Table 6.16. Conditions for chiral separations of selected compounds using cellulose tribenzoate coated on macroporous silica(Chiralcel OB/OB-H®) stationary phase

Name	Structure	Mobile Phase	Ref.
5-Methyl-3-phenyl-cyclopent-2-enone		90:10 hexane / 2-propanol	[331]
2-Furan-2-yl-3-(2-trimethylsilanyl-vinyl)-cyclopropane-carboxylic acid methyl ester		200:1 hexane / 2-propanol	[332]
4-Dimethylamino-2-(6-methoxy-naphthalen-2-yl)-butan-2-ol		98:2:0.1 hexane / ethanol / diethylamine	[333]
Acetic acid 1-methyl-3-phenyl-allyl ester		80:20 hexane / 2-propanol	[334]
3-(1-Methyl-1-nitro-ethyl)-cyclohexanone		80:20 hexane / ethanol	[335]
Phenyl-o-tolyl-methanol		9:1 hexane / 2-propanol	[336]

Name	Structure	Mobile Phase	Ref.
2-Methanesulphinyl-pyridine		85:15 hexane / 2-propanol	[337]
1,2-Di-thiophen-2-yl-ethane-1,2-diol		85:15 hexane / 2-propanol	[338]
2-Methyl-1-phenyl-propan-1-ol		95:5 hexane / 2-propanol	[339]
Benzoic acid 1-methyl-butyl ester		49:1 hexane / 2-propanol	[327]
(4-Methoxy-phenyl)-(1-phenyl-ethyl)-amine		85:15 CO ₂ / methanol (SFC*)	[340]
<i>E</i> -1,3-Di(2-methylphenyl)-but-1-ene		98:2 heptane / 2-propanol	[341]
(2-Chloro-phenyl)-thiophen-2-yl-methanol		98:2 hexane / 2-propanol	[342]

Name	Structure	Mobile Phase	Ref.
<i>tert</i> -Butyl(dimethylamino)phenyl phosphine-borane complex		99:1 hexane / 2-propanol	[343]
(3-Chloro-phenyl)-trimethylsilyloxy-acetonitrile		99.75:0.25 hexane / 2-propanol	[344]
1-(4-Chloro-phenyl)-propan-1-ol		98:2 hexanes / ethanol	[345]
2-Hydroxy-1,4-diphenyl-pent-4-en-1-one		97:3 hexane / 2-propanol	[346]
1-[2-(3,3-Dimethyl-but-1-ynyl)-pyrimidin-5-yl]-2-methyl-propan-1-ol		Gradient 96-60:4-40 CO ₂ / methanol	[143]
1-(Methanesulphinyl)-2-methyl-benzene		80:20 hexane / 2-propanol	[347]
4-(2-Methyl-1-oxo-1,2,3,4-tetrahydro-naphthalen-2-yl)-benzonitrile		80:20 hexane / 2-propanol	[348]
2-(Cyclopentyl-hydroxy-methyl)-cyclohex-2-enone		99:1 hexane / 2-propanol	[349]

Name	Structure	Mobile Phase	Ref.
3-Phenylcyclopentanone		99.75:0.25 hexane / 2-propanol	[350]
4-[1-Hydroxypropyl]phenol		90:10 hexane / 2-propanol	[351]
1-(Pyridin-2-yl)ethyl acetate		95:5 hexane / 2-propanol	[352]
2-But-3-enyl benzoate		1000:1 hexane / 2-propanol	[213]
(<i>SR,RS</i>)-2-Ethenyl-1-phenylpropane-1,3-diol	(<i>SR,RS</i>)-2-ethenyl-1-phenylpropane-1,3-diol	93:7 hexane / 2-propanol	[353]
5-(Benzyloxymethyl)-2,2,5-trimethylheptan-3-one		0.05:99.95 2-propanol / hexane	[354]

* SFC – supercritical fluid chromatography

Table 6.17. Conditions for chiral separations of selected compounds using cellulose tricinamate coated on silica gel (Chiralcel OK®) stationary phase

Name	Structure	Mobile Phase	Ref.
Econazole		425:74:1 hexane / 2-propanol / diethylamine	[320]
Miconazole		425:74:1 hexane / 2-propanol / diethylamine	[320]
Sulconazole		425:74:1 hexane / 2-propanol / diethylamine	[320]
2-Phenyl-4,5-dihydro-oxazole-4-carboxylic acid methyl ester		90:10 hexane / 2-propanol	[355]
2-Phenoxy-propionic acid butyl ester		Not reported	[356]
Phosphine borane derivative		80:20 hexane / ethanol	[357]

Name	Structure	Mobile Phase	Ref.
2-[(3-Chloro-phenyl)-hydroxy-methyl]-acrylic acid		90:10 hexane / 2-propanol	[358]
2-(4-Ethyl-phenoxy)-propionic acid		98:2:0.1 hexane / 2-propanol / trifluoroacetic acid	[359]
2-Phenoxy-propionic acid		98:2:0.1 hexane / 2-propanol / trifluoroacetic acid	[359]

Table 6.18. Conditions for chiral separations of selected compounds using cellulose tris(3,5-dichlorophenylcarbamate) photochemically immobilised on silica (Chiralpak IC®) stationary phase

Name	Structure	Mobile Phase	Ref.
Benzoin		60:20:20 hexane / dimethoxymethane / tetrahydrofuran	[360]
1-Naphthalen-2-yl-propane-1,3-diol		10:1 hexane / 2-propanol	[361]
3-(Dimethoxymethyl)-6-methoxy-2-(4-nitrophenyl)tetrahydro-2H-pyran		50:1 hexane / 2-propanol	[362]

Name	Structure	Mobile Phase	Ref.
7a-Benzyl-2,3,7,7a-tetrahydro-6H-indene-1,5-dione		60:40 hexane / 2-propanol	[363]
3-Formyl-2-nitromethyl-hexanoic acid methyl ester		90:10 hexane / ethanol	[364]
3-(4-Chloro-phenyl)-4-nitro-butan-1-ol		10:1 hexane / 2-propanol	[361]
2-Phenylglutaric anhydride		90:10 CO ₂ / tetrahydrofuran (SFC)	[284]
Terazosin		90:10:0.1 methanol / H ₂ O / diethylamine	[365]
[4-(4-Amino-6-hydroxy-7-methoxyquinazolin-2-yl)piperazin-1-yl][(5S)-5-methyltetrahydrofuran-2-yl]methanone		95:5:0.1 methanol / H ₂ O / diethylamine	[365]
1,1,1,2,3,3,4,4,5,5,6,6,7,7,8,8,8-Heptafluoro-N-(4-methoxybenzyl)octane-2-sulphonamide		40:60 0.1% Aqueous acetic acid / methanol + 0.1% acetic acid	[366]

Name	Structure	Mobile Phase	Ref.
[3-(6-Benzoyloxy-hexyl)-oxiranyl]-methanol		95:5 hexane / 2-propanol	[367]
5,5-Diphenyl-4-methyl-2-oxazolidinone		40:60 acetonitrile / H ₂ O	[368]
(<i>SS,RR</i>)-2-[1-(2-Chlorophenyl)-2-nitroethyl]pentanal		85:15 hexane / 2-propanol	[369]
Methyl 2-(2-formylphenyl)-2-phenylpropanoate		5:95 2-propanol / hexane	[370]
<i>tert</i> -Butyl 2-methylidene-3-[[[4-methylphenyl]sulphonyl]amino]hexanoate		80:20 hexane / 2-propanol	[371]
<i>tert</i> -Butyl (<i>RR</i>),(<i>SS</i>)-3-methyl-5-nitro-2-oxo-4-phenylpentanoate		98:2 hexane / ethanol	[372]

Table 6.19. Conditions for chiral separations of selected compounds using amylose tris[(S)alpha-phenethyl]carbamate coated on silica gel (Chiralpak AS®) stationary phase

Name	Structure	Mobile Phase	Ref.
Dia-(1 <i>S</i> 3 <i>R</i> ,1 <i>R</i> 3 <i>R</i>)-3-benzyl-oxymethyl-1,3-dihydro-iso-benzofuran-1-thymine		80:20 hexane / ethanol	[185]
Dia-(1 <i>R</i> 3 <i>R</i> ,1 <i>S</i> 3 <i>R</i>)-3-benzyl-oxymethyl-1,3-dihydro-iso-benzofuran-1-uracil		80:20 hexane / 2-propanol	[185]
Bromo- <i>p</i> -tolyl-acetic acid benzyl ester		99.8:0.2 hexane / 2-propanol	[373]
2-(3-Bromo-phenyl)-oxirane		90:10 hexane / 2-propanol	[374]
6-Methyl-5-(<i>N</i> -phenyl-aminoxy)-hept-3-en-2-one		98:2 hexane / 2-propanol	[375]
3-(4-Cyanophenyl)-2,3-epoxy-1-phenylpropanone		9:1 hexane / 2-propanol	[376]
2-(1-Hydroxy-propyl)-cyclohex-2-enone		Not reported	[377]
Ethaboxam		80:20 hexane / 2-propanol	[315]

Name	Structure	Mobile Phase	Ref.
1-(2'-Hydroxymethyl-[1,1']binaphthalenyl-2-ylmethyl)-cyclohexanol		hexane / 2-propanol	[378]
Atenolol		90:10 hexane / ethanol / 0.2% butylamine	[301]
Chlorthalidone		100 methanol	[196]
5-Benzyl-3-(4-chlorophenyl)-4,6-dioxo-octahydro-pyrrolo[3,4-c]pyrrole-1-carboxylic acid methyl ester		50:50 hexane / 2-propanol	[379]
Pantoprazole		50:50:0.1 Heptane / ethanol / triethylamine	[258]

Name	Structure	Mobile Phase	Ref.
N-Allyl-N-[1-(2-chloro-phenyl)-ethyl]-2,2,2-trifluoroacetamide		99:1 hexane / 2-propanol	[380]
<i>tert</i> -Butyl (benzyloxy)[6-oxodecan-4-yl]carbamate		99.5:0.5 hexane / 2-propanol	[146]
6-[2-[4-(3-Fluorophenyl)pi-perazin-1-yl]propanoyl]-1,3-benzoxazol-2(3H)-one		90:10 hexane / ethanol	[381]
Methanesulphonic acid 1-(6-chloro-pyridin-3-yl)-ethyl ester		70:30 Isohexane / 2-propanol	[382]
3-(2-Nitro-1-p-tolyl-ethyl)-pentane-2,4-dione		85:15 hexane / 2-propanol	[383]
Triadimenol-(1 <i>RS</i> ,2 <i>SR</i>)-1-(4-chlorophenoxy)-3,3-dimethyl-1-(1 <i>H</i> -1,2,4-triazol-1-yl)butan-2-ol		2:98 ethanol / hhexane	[384]
2-Ethylhexyl 3-[(2-[[2-phenylpropanoyl]amino]phenyl)sulphanil]propanoate		H ₂ O / acetonitrile (gradient 40:60 (0 min), 10:90 (30 min)) to (gradient 40:60 to 10:90 in 30 min)	[290]
(<i>Z</i>)-5-Hydroxy-5-phenyl-oct-2-enenitrile		20:1 hexane / 2-propanol	[385]

6.4.6.2. Antibiotic Phases

The glycopeptide macrocycle antibiotics are classes of compounds with highly enantioselective properties. They include vancomycin, teicoplanin and ristocetin A [386]. Such high enantioselective properties are due to their amphoteric character, their molecular structure (which in solution accentuates enantioselective interactions) and their hydrophilic and hydrophobic functional groups (which makes them soluble in aqueous and organic solvents) [387]. Such properties make them amenable for use as chiral selectors in either capillary electrophoresis or HPLC (Tables 6.20-6.22). There have been over a hundred different glycopeptide antibiotics identified in the fermentation broth of various bacteria. All have a heptapeptide core of seven amino acid residues with a covalently joined side chain and sugar substituents at various positions. In this classification scheme, vancomycin and eremomycin are assigned to group I. Groups II and III include compounds such as avoparcin, ristocetin and teicoplanin, which have aromatic residues at different positions in the molecule [388]. They possess multiple stereogenic centres and can interact with a solute through hydrogen bonding, dipole-dipole interactions, π - π interactions, hydrophobic interactions, electrostatic interactions and sterically-based interactions. Due to the multiple interactions that they can exhibit, these macrocyclic antibiotics have been immobilised on a silica matrix and used as chiral stationary phases. These columns show very good selectivity toward a large class of compounds [389]. They operate in different modes: normal phase, polar organic and sub/supercritical modes [125,389]. In reversed phase mode, the mobile phase should be buffered in the range of pH between 4 and 7. Electrostatic and hydrophobic interactions are the main types of interactions responsible for the enantiomeric separation on these phases.

Table 6.20. Mobile phase compositions for enantiomeric separation of selected compounds on Vancomycin bonded to silica (Chirobiotic V®) stationary phase

Name	Structure	Mobile Phase	Ref.
N-CBZ-Phenylalanine		90:10 1% triethylammonium acetate, pH 4.1 / acetonitrile	[184]
Nisoldipine		50:50 triethylammonium acetate buffer / methanol	[390]

Name	Structure	Mobile Phase	Ref.
Norephedrine		30-90% methanol or acetonitrile / aqueous 0.1% triethylammounim acetate (pH 4.0)	[391]
6-Hydroxybuspirone		98.8:0.8:0.4 methanol / acetic acid / triethylamine	[392]
5-Amino-6,7,8,9-tetrahydro-5H-benzocycloheptene-6-carboxylic acid		10:90 0.1% triethylammonium acetate pH 6.5 / methanol	[393]
1-[2-(3,3-Dimethyl-but-1-ynyl)-pyrimidin-5-yl]-2-methyl-propan-1-ol		Gradient 4% to 40% / methanol (SFC*)	[143]
Pregabalin (and its <i>R</i> -enantiomer)		80:20 ethanol / H2O	[394]
4-Biphenyl-4-yl-2,7,7-trimethyl-5-oxo-1,4,5,6,7,8-hexahydro-quinoline-3-carboxylic acid ethyl ester		80:20 hexane / 2-propanol	[395]

* SFC – supercritical fluid chromatography

Table 6.21. Mobile phase compositions for enantiomeric separation of selected compounds on Amphoteric teicoplanin covalently bonded to silica (Chirobiotic T[®]) stationary phase

Name	Structure	Mobile Phase	Ref.
N-CBZ-Phenylalanine		80:20 Triethylammonium acetate pH 4.1 / methanol	[184]
5,9-Dimethyl-2-(2-methyl-propenyl)-2,3-dihydro-furo[3,2-g]chromen-7-one		95:5 CO ₂ / methanol (SFC*)	[396]
2-Amino-3-(4-trifluoromethyl-phenyl)-propionic acid		70:30 methanol / H ₂ O	[397]
2-Aminomethyl-3-(3,4-dihydroxy-phenyl)-propionic acid		70:30 methanol / H ₂ O	[398]
Tyrosine		20:80 H ₂ O (0.2% triethylammonium acetate, pH 3.8) / methanol	[399]
2-[4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-3-oxo-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-propionic acid		100:0.1:0.1 methanol / acetic acid / triethylamine	[400]
3-Amino-4-methyl-pentanoic acid		70:30 methanol / 0.1% triethylammonium acetate (pH 4.1)	[401]

Name	Structure	Mobile Phase	Ref.
2-Aminomethylpentanoic acid		30:70 0.1% triethylammonium acetate (pH 4.1) / methanol	[402]
Warfarin		80:20 heptane / ethanol	[403]

* SFC – supercritical fluid chromatography

Table 6.22. Mobile phase compositions for enantiomeric separation of selected compounds on Ristocetin A covalently bonded to silica gel (Chirobiotic R®) stationary phase

Name	Structure	Mobile Phase	Ref.
1,2,3,6-Tetrahydro-pyridine-2-carboxylic acid (baikaine)		50:50 H ₂ O / methanol	[404]
γ-phenyl-γ-butyrolactone		95:5 hexane / ethanol	[405]
α-benzyl-proline		Various percentages of methanol / H ₂ O or triethylammonium acetate 0.1% / methanol pH 4.1	[152]
4-Benzyloxymethyl-3-phenyl-tetrahydro-pyran-2-one		Gradient of 96:4 CO ₂ / methanol to 60:40 CO ₂ / methanol	[324]
6a,11a-Dihydro-6H-benzo[4,5]furo[3,2-c]chromene		60:40 H ₂ O / methanol	[73]

Name	Structure	Mobile Phase	Ref.
3,4-Dihydroxyphenylalanine		1:1 methanol / H ₂ O	[406]
[(<i>SS,RR</i>)-4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-5-methyl-3-oxo-1,3,4,5-tetrahydro-benzo[<i>c</i>]azepin-2-yl]-acetic acid		100:0.01:0.01 methanol / CH ₃ CO ₂ H / triethylamine	[400]
Camptothecin		100:0.1:0.1 methanol / CH ₃ CO ₂ H / triethylamine	[286]
(1 <i>RS</i> ,2 <i>SR</i> ,4 <i>SR</i> ,5 <i>RS</i>)-2-Amino-4,5-dihydroxy-cyclohexane-carboxylic acid		20:80 0.1% Aqueous triethylammonium acetate pH 4.1 / ethanol	[407]
(1 <i>SR</i> ,2 <i>RS</i> ,3 <i>SR</i>)-2-Amino-3-hydroxy-cyclopentane-carboxylic acid		20:80 0.1% Aqueous triethylammonium acetate pH 4.1 / ethanol	[407]

6.4.6.3. Protein Phases

Proteins are biopolymers consisting of amino acids linked together through peptide bonds arranged in a certain sequence. Molecular recognition in protein-ligand complexes is responsible for the selective binding of a low molecular weight ligand to a specific protein which can be characterised by a binding constant. All these interactions are usually non-covalent in nature. The experimentally determined binding constants, K_i , are typically in the range of 10^{-2} to 10^{-12} M⁻¹, which corresponds to a negative free energy of binding of 10 to 80 kJmol⁻¹ [408]. The interactions between ligands and proteins include a wide range of interactions including electrostatic, van der Waals, steric, hydrophobic and hydration forces [409] related to the active sites of the protein. The binding of a small molecule ligand to a protein requires shape and property complementarity. In the course of binding, the ligand and protein have to adapt to each other to achieve a successful recognition process. The small molecule ligand is usually the

more flexible partner, and thus can adopt a large variety of different low energy conformations upon interaction with a protein [408]. The enantioselective recognition of molecules with one chiral centre requires a protein to interact with a minimum of three substrate locations, while stereoselectivity towards a substrate with two or three stereocentres requires interactions with a minimum of four or five substrate locations, respectively [410]. The inherent chirality of proteins makes them very good candidates for the separation of enantiomers. Proteins which can tolerate organic solvents, as well as high temperatures, and which can function over a wide pH range are useful as chiral stationary phases. Several proteins such as α_1 -acid glycoprotein (AGP) (Table 6.23), bovine serum albumin (BSA) (Table 6.24), human serum albumin (HSA), ovomucoid from chicken egg whites (OVM) (Table 6.25), avidin, cellobiohydrolase I (CBH I) (Table 6.26), pepsin, ovotransferrin and β -lactoglobulin have been immobilised on silica gel and successfully used as CSPs for enantiomeric separation [389]. Mobile phase optimisation with these CSPs is done through variations in pH, ionic strength, temperature and organic modifiers. Enantioselectivity can be changed as a function of pH. Increasing ionic strength increases hydrophobic interactions between the enantiomers and the CSP. The nature of the organic modifier also influences the enantioselectivity, as reversal of the elution order has been observed to be dependent upon the organic modifier used. Temperature also influences enantioselectivity; a decrease in temperature generally enhances enantioselectivity. Reversal of elution order has also been observed with a change in temperature. The protein CSPs have a broad range of applications and have been used for the separation of neutral, acidic and basic enantiomeric drugs [125].

Table 6.23. Mobile phase compositions for enantiomeric separation of selected compounds on α_1 -acid glycoprotein silica (Chiral-AGP®) stationary phase

Name/Structure	Structure	Mobile Phase	Ref.
1-(2,2-Dimethyl-8,8a-dihydro-3aH-indeno[1,2-d]oxazol-3-yl)-3-phenylpropan-1-one		88:12 10 mM potassium phosphate buffer (pH 7) / 2-propanol	[411]
(2-Phenyl-2,3-dihydrobenzofuran-3-yl)-methanol		90:10 0.01M phosphate buffer / 2-propanol	[25]
Bupivacaine		97:3 H ₂ O / 2-propanol ammonium acetate 5 mM (pH 7.0)	[412]

Name/Structure	Structure	Mobile Phase	Ref.
Bromoketamine		94:6 10 mM ammonium acetate buffer (pH 7.6) / 2-propanol	[413]
5-Ethyl-1,2-dimethyl-4,4-diphenyl-3,4-dihydro-2H-pyrrolium		Gradient of methanol / 20 mM ammonium formate (pH 5.7)	[414]
Reboxetine, 2-[(2-Ethoxyphenoxy)-phenyl-methyl]-morpholine		12:88 acetonitrile / phosphate buffer (pH 6)	[415]
EDDP D3		82:18 ammonium acetate buffer 10 mM (pH 7.0) / CH ₃ CN	[416]
Ibuprofen		990:10:0.2 phosphate buffer (pH 6.9) / acetonitrile / dimethyloctylamine	[417]
tris(1,2-Dimethyl-3-indolyl)phosphine oxide		30:70 CH ₃ CN / phosphate buffer (pH 4.6)	[418]

Name/Structure	Structure	Mobile Phase	Ref.
Pindolol		90:10 phosphate buffer / acetonitrile	[419]
2-(2-Fluoro-phenyl)-4,5-di-phenyl-4,5-dihydro-1H-imidazole		80:20 0.1% acetic acid, H ₂ O with NH ₄ OH (pH 7) / acetonitrile	[231]
N-(2,4-Dinitrophenyl)tyrosinol		98:2 sodium phosphate buffer 10 mM (pH 4) / acetonitrile	[88]
<i>trans</i> -2-(4-Methoxyphenyl)-3-phenyl-1-tosylaziridine		1:99 2-propanol / aqueous 10 mM sodium phosphate buffer (pH 7)	[420]

Table 6.24. Mobile phase compositions for enantiomeric separation of selected compounds on Bovine serum albumin (BSA) immobilised on silica gel (Chiral BSA-RP®) stationary phase

Name/Structure	Structure	Mobile Phase	Ref.
2-Phenyl-pentanenitrile		88:10:2 phosphate buffer (0.1 M, pH 7.4) / acetonitrile/ 1-butanol	[421]

N-Benzoylisoleucine		50 mM phosphate buffer (pH 7)	[422]
Ibuprofen		50 mM phosphate buffer (pH 7.8) / 1-propanol 4.5% / octanoic acid 4 mM	[423]
Leucovorin		98:2 50 mM Na ₂ HPO ₄ buffer (pH 5.2) / 1-propanol	[424]
N-Formyltetrahydrofolate		10 mM sodium phosphate buffer (pH 7.0)	[425]

Table 6.25. Mobile phase compositions for enantiomeric separation of selected compounds on Ovomuroid protein immobilised to silica (OVM®) stationary phase

Name/Structure	Structure	Mobile Phase	Ref.
Ibuprofen		90:10 20 mM phosphate buffer (pH 5.1) / ethanol	[426]
Benzoin		90:10 20 mM phosphate buffer (pH 5.1) / ethanol	[426]
NK-104 3-epimer and enantiomer		100:5:10 20 mM KH ₂ PO ₄ in H ₂ O / acetonitrile / methanol	[427]

Table 6.26. Mobile phase compositions for enantiomeric separation of selected compounds on Cellobiohydrolase (CBH I) immobilised onto silica (Chiral-CBH®) stationary phase

Name/Structure	Structure	Mobile Phase	Ref.
4-(2-Methanesulphonyl-4-methoxy-phenyl)-piperidine		2-propanol	[428]
O-Desethyl-reboxetine		6:9:85 acetonitrile / 2-propanol / 50 μ M EDTA in 10 mM phosphate buffer (pH 6.1)	[429]
Synephrine		95:5 10 mM sodium phosphate buffer (pH 6.0) / 2-propanol	[430]

6.5. CONCLUSION

The separation of enantiomers is a technique which is driven by the development of enantiomerically pure drugs. A large number of chiral stationary phases are available on the market, providing the opportunity to choose the right column for the separation of enantiomeric drugs. Understanding the interactions between these CSPs and enantiomeric analytes can provide a rationale for the development of an enantiomeric separation method.

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