Analytica Chimica Acta 706 (2011) 205–222

Contents lists available at SciVerse ScienceDirect

Analytica Chimica Acta

journal homepage: www.elsevier.com/locate/aca

Review

Recent applications in chiral high performance liquid chromatography: A review

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ARTICLE INFO

Article history:
Received 9 May 2011
Received in revised form 8 August 2011
Accepted 25 August 2011
Available online 22 September 2011

Keywords:
Chiral stationary phases
Chiral liquid chromatography
Polysaccharides
Macrocyclic antibiotics
Brush type chiral stationary phases
Cyclofructans
Oligoproline

ABSTRACT

The most important and broadly used chiral stationary phases (CSPs) for high performance liquid chromatography (HPLC) are reviewed. After a short description of the state of the art, for each kind of CSP the most important contributions published in the last couple of years are summarized. For the sake of classification, these works have been divided into studies on enantiorecognition mechanisms, new materials, and new applications. Emphasis is given to new, emerging CSPs that seem to possess all requisites to be considered potentially successful chiral separation media in the next future.

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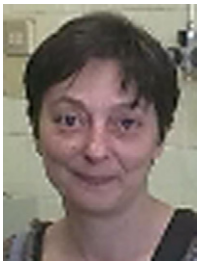

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doi:10.1016/j.aca.2011.08.038

Francesco Dondi, professor of analytical chemistry at the University of Ferrara, devoted his activity to the study of the fundamentals of separation science by means of stochastic theory and to the application in environmental and industrial contexts by employing gas chromatography (GC), high performance liquid chromatography (HPLC) and field flow fractionation (FFF) techniques. Recently, the exploitation of links between Ethics, Science and Environment with special emphasis to analytical chemistry concerns has become central in the research activity of Him.

1. Introduction

High performance liquid chromatography (HPLC) represents the most popular and highly applicable technology in the field of chiral analysis of a variety of racemic and scalemic mixtures. HPLC can be used to separate enantiomers either indirectly with chiral derivatization reagents or directly with chiral stationary phases (CSPs) or chiral mobile phase additives. Each of these techniques has advantages and drawbacks. Indirect separations are based on the formation of diastereoisomeric complexes between the enantiomers and suitable chiral derivatizing agents and their subsequent separation by an achiral liquid chromatographic method. This method is not very practical as derivatization represents an additional step which can involve undesirable side reactions, formation of decomposition products and racemization. Furthermore, the chiral derivatization reagent has to be of high enantiomeric purity and the presence of derivatizable groups in the analyte is a prerequisite. Other approaches to enantiomer purification, including destruction of the unwanted isomer in the racemic mixture by enzymatic reactions and crystallization from the racemic mixture, remain important but are often combined with chromatography. This review will not discuss indirect separations. On the opposite, we will only focus on direct separations based on the use of CSPs. This remains the most suitable and diffuse modality, thanks to its various advantages in comparison to other techniques. Its high speed, sensitivity and reproducibility make HPLC the method of choice in the analytical laboratories all over the world including those involved in drug development in pharmaceutical industries, pesticide development in agricultural industries, preparation of additives in the food industries, natural product research, agrochemicals and of pollutant analysis. There are countless materials that have been employed as CSPs. For the sake of simplification, CSPs can be divided into different classes depending on the chemical characteristics of the chiral selectors employed. According to this classification format, CSPs can be divided in (not exclusive list): cyclodextrin (CD) phases, CSPs based on polysaccharides, macrocyclic antibiotics, synthetic chiral macrocycles (crown ethers, other synthetic macrocycles), chiral synthetic polymers, chiral imprinted polymers, protein-based CSPs, ligand- and ion-exchange CSP.

Many excellent books [1–6] and reviews [7–9] have been published about CSPs and chiral separations by HPLC in general. In addition, there is a large number of reviews dedicated to specific categories of CSPs such as, just to cite a few, coated and immobilized polysaccharide-based CSPs [10–14], macrocyclic antibiotics [15–17], brush-type CSPs [18], etc.

Our review focuses on the most recent (last couple of years) contributions in the field of CSP developments and chiral liquid chromatography applications. For the sake of organization, the above classification of CSPs has been followed. For each CSP type, a short discussion about the most important developments that led to achievement of the chiral material together with the most recent applications of that kind of phase are presented. Scope of this review was not, on the other hand, to discuss in detail the fundamental principles of chiral recognition on CSPs for which we send to specific reviews published in the last years (see later on), first of all the excellent work from Lämmerhofer [19]. Finally, a few sections are dedicated to emerging CSPs that seem to possess important requisites to be successful enantioseparation media in the next future.

Before the discussion, a brief survey of general and specific reviews and books published in the field of chiral separation by HPLC since 2009 is given. First of all, in addition to the already cited paper from Lämmerhofer [19], general reviews about chiral recognition mechanisms and CSPs that have to be mentioned are those from Ward and Ward [20] and Grinberg [21]. As for it concerns reviews dedicated to specific subjects of chiral separation, on the other hand, many contributions in different fields have been published. Huhnerfuss and Shah [22] discuss the use of enantioselective chromatography as a tool to discriminate biotic and abiotic transformation processes of chiral environmental pollutants. A systematic evaluation of new CSPs for supercritical fluid chromatography using a standard racemate library has been proposed by Pirzada et al. [23]. Chromatographic separation of enantiomers through nanoscale design and microfluidic technology for chirality exploration have been described respectively by Sancho and Minguillon [24] and, very recently, by Nagl et al. [25]. Minoda [26] reports about chiral separations by means of simulated moving bed (SMB) technology. Samuelsson et al. [27] revised the fundamental concepts of chiral nonlinear chromatography by focusing on the potential of isotherm determination for closer elucidation of binding mechanisms in chiral liquid chromatographic phase systems. Ali et al. [28] reassessed the use of polysaccharide CSPs in HPLC. A significant attention has been also given to chiral monoliths and their applications as CSPs [29–32]. The use of chiral polymers for the resolution of enantiomers, on the other hand, has been reviewed by Okamoto [33]. Reviews dedicated to retention mechanism elucidation on macrocyclic glycopeptide-based CSPs and structure control of polysaccharide derivatives for efficient separation of enantiomers by chromatography have been published by Ilisz et al. [34] and by Ikai and Okamoto [35], respectively.

A book on chiral recognition in separation methods has been edited by Berthod in 2010 [36].

Several general reviews about pharmaceutical applications of chiral chromatography [37–40] have been published since 2010. They include, inter alia, a work about method development for pharmaceutical chiral chromatography [39] and an overview of HPLC methods for the enantiomer separation of active pharmaceutical ingredients in bulk and drug formulations [40]. Ahuja edited a book about chiral separation for pharmaceutical and biotechnological products [41].

2. Polysaccharide-based CSPs

2.1. State of the art

Polysaccharides such as cellulose and amylose are among the most abundant optically active biopolymers with perfectly defined structures. Cellulose is a highly crystalline polymer which occurs with various crystal structures, depending sometimes on the source, but mostly on the treatment during and after its isolation and purification. The two major crystallographic forms are native cellulose and the regenerated or mercerized product. Resolution of amino acid racemates on native cellulose was first reported sixth decades ago [42–44]. In the 1970s, Hesse and Hagel discovered that microcrystalline cellulose triacetate (MCTA) produces secondary structures upon swelling and forms chiral cavities which are able to include stereoselectively compounds with aromatic residues [45]. Beads of polysaccharide derivatives without support were also used

as CSPs and operated at pressures as high as 100 bar [46,47]. Many different classes of enantiomeric compounds have been resolved on MCTA [47–50]. In 1984, Okamoto and coworkers coated macroporous aminopropyl-silanized silica gel with cellulose triacetate [51–53]. They discovered that the enantioselectivity of this phase was quite different from that exhibited by pure MCTA. Okamoto et al. showed that selectivity could be enhanced by introducing various kinds of substituents on the hydroxyl group of the polysaccharide. Polysaccharide benzoate and phenylcarbamate derivatives are among the most used CSPs in organic, bioorganic and pharmaceutical chemistry [54–56].

Supporting the chiral polymer on silica gel enhanced the performances of CSPs in terms of mass transfer efficiency, resistance to pressure and swelling and mechanical stability. Since then, most chiral polymer-based CSPs have been prepared by coating the polymers to silica gel. Coated polysaccharide-based CSPs are restricted to the use with alkane–alcohol based normal phase conditions, polar organic conditions and hydro-organic reversed-phase. On the other hand, solvents such as dichloromethane, chloroform, ethyl acetate, tetrahydrofuran, dioxane, toluene and acetone are incompatible with polysaccharide coated CSPs since they induce swelling and/or dissolution of physical adsorbed chiral selectors. This limitation is particularly important in preparative applications as sample solubility in mobile phase is pivotal to increase the amount of racemate fed in a single run [10,57–59]. In 1987, Okamoto et al. described the first preparation of polysaccharide-based CSP in which the polymer was chemically bonded to aminopropylsilica gel [60]. Immobilization methods of polysaccharide derivatives onto silica gel have been reviewed by Minguillón et al. [13] and more recently by Okamoto [14]. Chiral recognition mechanisms on immobilized polysaccharide-based CSPs have been recently reviewed by Ikai and Okamoto [35].

The exceptional chiral recognition properties of polysaccharide CSPs stems from a combination of factors: molecular chirality due to the presence of several stereogenic centers of the glucopyranose units; conformational chirality due to the helical twist of the polymer backbone; and supramolecular chirality resulting from the alignment of adjacent polymer chains forming ordered regions [48]. Differently than for porous gel MCTA, where inclusion mechanisms are considered to be the most important for enantiorecognition, with coated/covalently bonded polysaccharide-based CSPs the main interactions between CSP and analytes are assumed to be hydrogen bonding and dipole–dipole interactions [11,61]. Such interactions are expected to take place between analyte molecules and CSP, mainly in the absence of strongly competing species such as water. Thus, chiral separations on polysaccharide-based CSPs are primarily explored in the normal phase separation mode using mixtures of alkanes (e.g., hexane) and low molecular weight alcohols (2-propanol) or ethers (tert-butylmethyl ether) as mobile phase. Additional separation modes use sub- or super-critical fluids or polar organic solvents (acetonitrile or alcohols) as mobile phase. Chiral recognition is, however, possible even under conditions unfavorable for hydrogen bonding as proved by the first reversed-phase method on polysaccharide-based CSPs described by Ikeda et al. [62]. Applications of reversed-phase liquid chromatographic separation of enantiomers on polysaccharide type chiral stationary phases were revised by Tachibana and Ohnishi [12]. Zhang et al. [63] developed simple and straightforward screening strategies for efficient method development with immobilized polysaccharide CSPs in reversed-phase mode.

2.2. Recent studies on enantiorecognition mechanisms

Very recently, Uccello-Barretta et al. reviewed the application of nuclear magnetic resonance (NMR) techniques to the investigation of the chromatographic enantiorecognition process on polysaccharide-based CSPs [64]. Among the available tools and methods to investigate retention and chiral recognition mechanisms, spectroscopy techniques represent a powerful mean to obtain information about structure and dynamics at a molecular level on the transient diastereoisomeric complexes formed by enantiomeric substrates and chromatographic chiral selectors or modifiers. Besides polysaccharide CSPs, the cited review [64] focuses also on brush-type CSPs, cyclodextrin CSPs, chiral micelles and chiral molecularly imprinted polymers. Through the presentation of many relevant examples, it is shown that the molecular basis of enantiorecognition phenomena involved in chromatographic separation technologies can be investigated in a comprehensive and direct way by exploiting the versatility of NMR spectroscopy.

Albert's group [65] characterized binding affinities between benzylmandelate enantiomers and polysaccharide based CSPs by coupling HPLC and NMR spectroscopy under high resolution/magic angle spinning conditions. Kasat et al. [66] coupled chromatographic and attenuated total reflection infrared spectroscopy to elucidate chiral recognition mechanisms between fourteen structurally similar chiral solutes with one or two stereocenters and amylose tris(3,5-dimethylphenylcarbamate). They claim that these results are consistent with the three-point attachment hypothesis of chiral recognition mechanism [67], even if recent investigations have challenged this model by showing that this is only a geometrical model and not a necessary condition to have chiral discrimination [61,68–70]. Grinberg et al. [71] studied the chiral separation on amylose tris(3,5-dimethylphenylcarbamate) and cellulose tris(3,5-dimethylphenylcarbamate) using liquid chromatography along with vibrational circular dichroism. They pointed out that the two CSPs undergo conformational changes as the polarity of the mobile phase changes and this result was correlated to the change in the elution order experimentally observed with N-substituted α-methyl phenylalanine esters.

Other applications of spectroscopic techniques combined with enantioselective HPLC include the determination of the absolute configuration of enantiomers as done by Cirilli et al. [72] for potential β-secretase inhibitors.

Docking studies were carried out to investigate the mechanism of chiral separation of metalaxyl and benalaxyl on amylose tris(3,5dimethylphenylcarbamate) by Li et al. [73].

Ciogli et al. [74] determined the enantiomerization barriers of hypericin and pseudohypericin by dynamic HPLC on derivatized cellulose and amylose in polar organic elution mode. Dynamic HPLC and stopped-flow techniques were also employed to assess the amount of acid and basic catalytic sites bonded on amylose tris (3,5-dimethylphenylcarbamate) by Cirilli et al. [75]. As probe compound, the authors used an α-substituted ketone whose optical isomers may interconvert one to each other through a base- or acid-catalyzed bimolecular generation of an achiral tautomeric intermediate. By changing the amount of the catalyzer (diethylamine) in the mobile phase and from the rate constants obtained by dynamic HPLC, it was possible to split off the contribution to speed the dynamic event coming from the stationary phase from those ones coming from diethylamine.

Solvent- and temperature-induced reversal of elution order in the chromatographic enantioseparation of bi-naphthol on cellulose tris(3,5-dimethylphenylcarbamate) was observed by Wheng's group [76,77]. Temperature-induced of the inversion of the elution sequence in the separation of 1-(phenylethylamino)- or 1-(naphthylethylamino)methyl-2-naphthol analogs was reported by Aranyi et al. [78]. Unusually high enantioselectivity with an enantioseparation factor as large as 138.5 was reported on cellulose tris(4-methylbenzoate) chiral stationary phase for the separation of the enantiomers of N-thiocarbamoyl-3-(4′-phenyloxy)-phenyl-5-phenyl-4,5-dihydro-(1H) pyrazole [79]. The stronger interaction energy of the (S) enantiomer compared to that of the (R) enantiomer

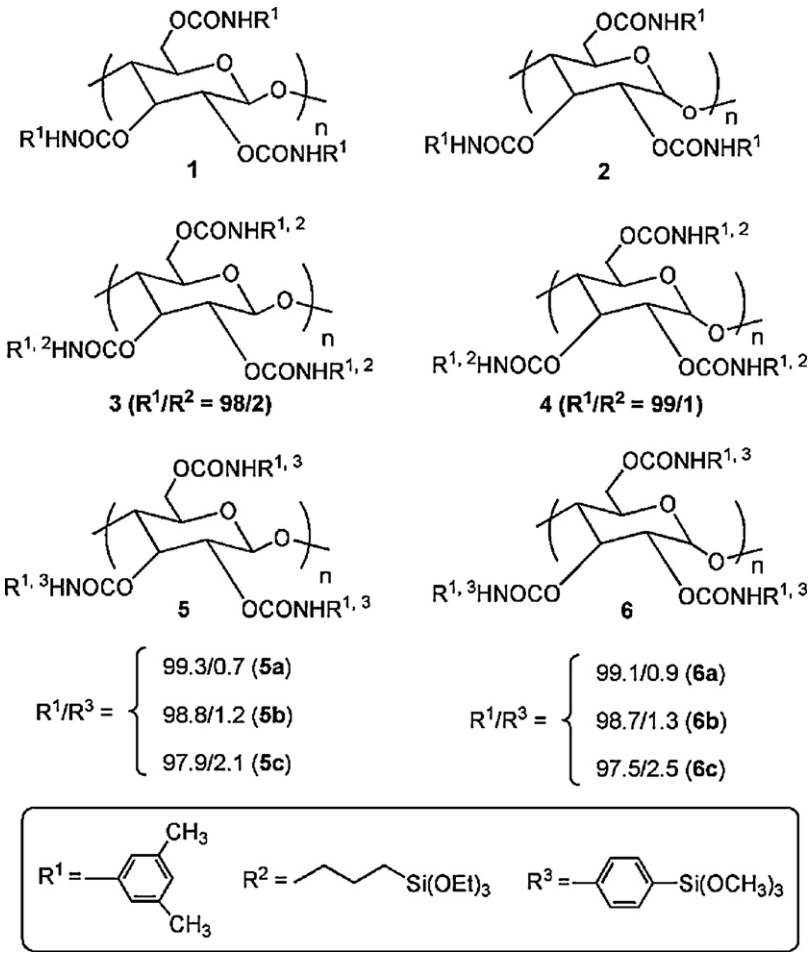


Fig. 1. Structures of cellulose (1, 3 and 5) and amylose (2, 4 and 6) derivatives prepared by Okamoto and coworkers [91].

was mainly attributed to the formation of a hydrogen bonding between the amino group of the thiocarbamoyl moiety and the carbonyl oxygen of the CSP. Putnam and Guiochon [80,81] studied the so-called memory effect on a tris(3,5-dimethylphenyl) carbamate CSP, that is when selectivity of pairs of enantiomers changes after the column had been exposed to acid/base mobile phase modifiers. Gebreyohannes and McGuffin [82] focused on the thermodynamics and kinetics of the separation of coumarin-based anticoagulants on amylose derivatized with tris-(3,5-dimethylphenyl carbamate) by changing the organic modifier and the temperature. Nonlinear Van't Hoff plots were observed with bulky modifiers and associated to conformational changes in the stationary phase. Their kinetic study demonstrates that sorption rate is always faster than desorption rate for all coumarins and for all mobile phase compositions. An increase in the concentration of alcohol modifiers in mobile phase causes, on the other hand, an increase in the desorption rate.

Very recently, West et al. [83,84] investigated chiral recognition mechanisms in supercritical fluid chromatography (SFC) with tris-(3,5-dimethylphenylcarbamate) amylose and cellulose CSPs by quantitative structure-retention relationships (QSRRs) by defining two additional descriptors (namely, flexibility and globularity of the solutes) with respect to those commonly employed in QSSR. SFC is a rapidly growing technique and has been most widely used for chiral separations. This is demonstrated by the large number of publications describing the separations of many enantiomers especially of pharmaceutical interest – such as paroxol [85], phosphine-containing α-amino acid [86], flurbiprofen [87], paroxetine intermediates [88], γ-lactone flavors [89], etc. – on polysaccharide-based CSPs under supercritical fluid conditions. A comprehensive review about fundamental challenges and opportunities for preparative supercritical fluid chromatography covering also enantiomeric separations has been recently published by Guiochon and Tarafder [90].

2.3. New polysaccharide-based CSPs

Significant efforts have been done to prepare new polysaccharide-based CSPs. Okamoto and his group [91,92] described the immobilization of 3,5-dimethylphenylcarbamate cellulose and amylose onto plain silica gels by means of intermolecular polycondensation of triethoxysilyl groups introduced with 3-glycidoxypropyl-triethoxylane (see Fig. 1). The solvent compatibilities of immobilized-type CSPs were investigated and it was demonstrated that the presence of chloroform and tetrahydrofuran in the eluents improved the chiral resolving abilities of the CSPs. The same group also prepared immobilized CSPs using amylose ester derivatives [93], 4-tert-butylphenylcarbamates of cellulose and amylose [94] and amylose derivatives containing benzoate and phenylcarbamate groups regioselectively introduced into the polysaccharide backbone [95].

The use of halomethylphenylcarbamate of cellulose and amylose as CSPs has attracted much interest. Peng et al. [96] studied in detail the performances of tris(halomethylphenylcarbamate) derivatives of cellulose and amylose showing how these CSPs possess wide chiral recognition ability, similar to the most widely

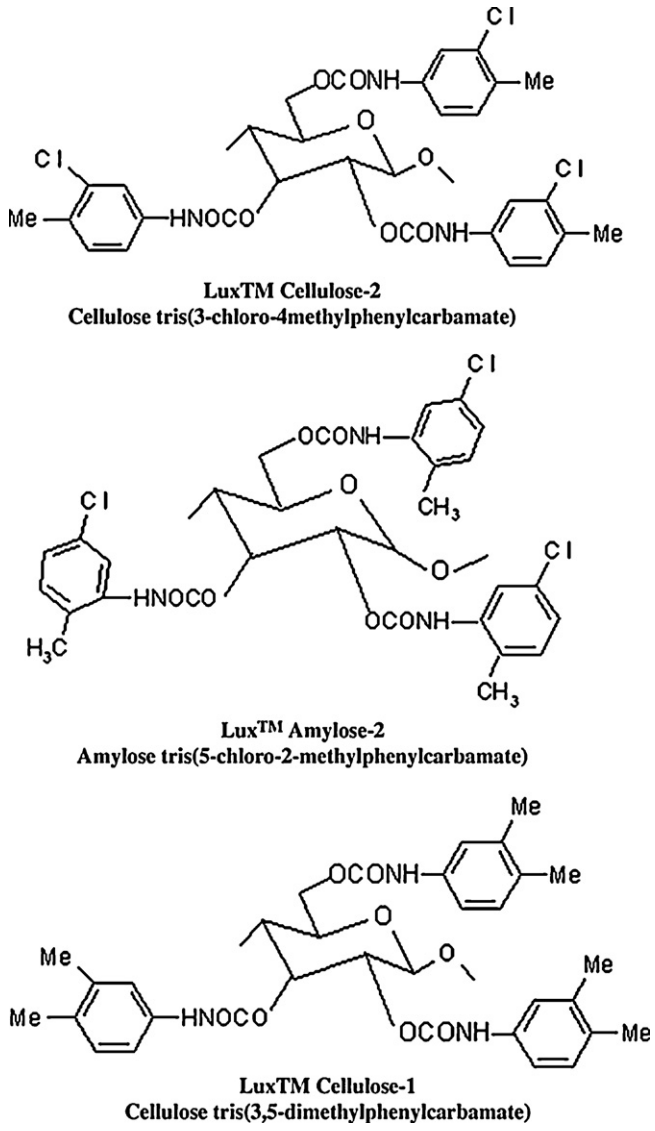


Fig. 2. Chemical structures of the three CSPs evaluated by Peng et al. [96].

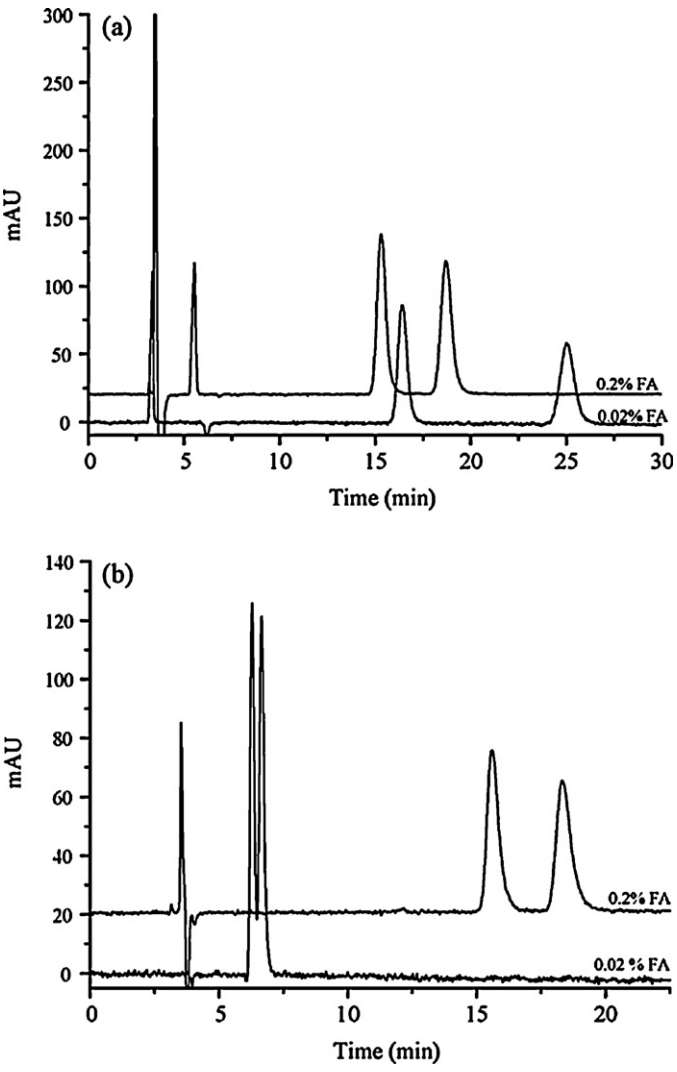


Fig. 3. Chromatograms of econazole (A) and mepivacaine (B) enantiomers illustrating the effect of formic acid proportion on enantioresolution. Mobile phase: acetonitrile/0.1% diethylamine/(0.02–0.2%) formic acid, temperature: 15°C [98].

used polysaccharide-based CSPs (dimethylphenylcarbamate-based derivatives), as well as significant complementarity in all commonly used separation modes. The structures of these CSPs, together with their commercial names, are reported in Fig. 2. Servais and coworkers [97,98] evaluated the resolving power of cellulose tris(4-chloro-3-methylphenylcarbamate) as chiral selector toward the enantioseparation of many basic drugs with different structures and hydrophobic properties, using acetonitrile as the main mobile phase component. Fig. 3 shows an example of the enantioseparation of enantiomers of econazole and mepivacaine under reversed-phase conditions. Toribio et al. [99] evaluated four different polysaccharide CSPs (tris-3,5-dimethylphenylcarbamate of amylose, tris-3,5-dimethylphenylcarbamate of cellulose, tris-5-chloro-2-methylphenylcarbamate of amylose and tris-3-chloro-4-methylphenylcarbamate of cellulose) using supercritical fluid chromatography. In these works, it was further demonstrated how the introduction of a chloro group on the phenyl moieties can produce a positive effect on the chiral recognition, as it was also pointed out previously by Okamoto and coworkers [35,100–102]. Fanali et al. [103] coated amylose tris(5-chloro-2-methylphenylcarbamate) onto native and aminopropylsilanized silica and used these CSPs in nano-LC.

2.4. Recent applications

Several classes of racemic compounds have been separated on polysaccharide-based CSPs: aminonaphthol analogs [104,105], stereoisomers of β-lactams [106], N-protected α-amino acids and their ester derivatives [107], venlafaxine and venlafaxine analogs [108], mexiletine derivatives [109], β-secretase inhibitors [72], glycidyl nitrobenzoate and 2-methyl glycidyl nitrobenzoate enantiomers [110], PPAR agonists [111], terazosin enantiomers [112], benzazoles and benzanilides [113], S-ropivacaine [114], (R)- enantiomer in eslicarbazepine acetate [115], amino acid esters as 9-anthraldimine Schiff bases [116], chiral oxadiazoline derivatives [117], chiral pesticides [118], quinazoline derivatives bearing α-aminophosphonate moiety [119], acidic drugs [120–122], neutral pharmaceuticals [123], aminonaphthol analogues [124], benzoxazolinone aminoalcohols and their aminoketone precursors [125], Tic-hydantoin sigma-1 agonists [126], N-protected β- and γ-amino acids, amides and nitriles [127], phthalans [128]. Preparative separations of flurbiprofen enantiomers [129], organophosphonate esters [130] and racemic chiral drugs [131] and have been reported as well. Armstrong et al. [132] compared the performances of different types of CSPs (cellulose- and amylose-based CSPs, cyclodextrins, synthetic polymer-based CSPs) for a total of

eight CSPs (including tris(3,5-dimethylphenylcarbamate) cellulose towards the separation of substituted binaphthyls.

3. Macrocyclic antibiotic CSPs

3.1. State of the art

Macrocyclic antibiotics have been introduced as chiral selectors for HPLC in 1994 by the pioneeristic work of Armstrong [133]. They were shown to possess unique characteristics, among the chiral selectors used as CSPs, in terms of degree of selectivity toward numerous compounds and chromatographic efficiency. Glycopeptides vancomycin [133], teicoplanin [134], teicoplanin aglycone [135], ristocetin A [136], A-40,926 [137,138] and avoparcin [139] as well as the polypeptide thiostrepton [133], the ansamycin rifamycin B [133] have been used for the preparation of chiral HPLC phases. Fig. 4 shows the structures of teicoplanin and its related analogs, while in Fig. 5 the chemical structure of vancomycin is reported.

Structurally, all glycopeptide antibiotics are characterized by a cyclic heptapeptide scaffold that is rich in aromatic fragments, surrounded by polar and ionizable groups and carrying carbohydrate moieties at the macrocycle periphery. The sugar units are attached to phenolic or secondary hydroxyl groups of the aglycone through glycosidic bonds [16]. The cyclic peptide backbone has a conformationally rigid cup-shaped architecture, with the aromatic fragments rigidly interlocked in a well-defined stereochemical disposition.

Macrocyclic antibiotics are characterized by the presence of many stereogenic centers and functional groups that allow multiple interactions with analytes, such as Van der Waals interactions, ionic forces, hydrogen bonding, dipole stacking, π–π aromatic stacking, enthalpic–entropic compensation effect, chelate effect, hydrophobic and steric effects [135,140–147]. Under specific experimental conditions, Donnan-like exclusion phenomena have been demonstrated to play an important role in the separation of enantiomers on macrocyclic-based CSPs [148]. These interactions were assumed to be attractive. From a stereochemical point of view, nowadays, repulsion is considered to play the same role as an attractive interaction as long as there is a net association leading to the formation of diastereoisomeric transient complexes. Bonded macrocyclic antibiotic CSPs for HPLC can be operated in normal, reversed, polar organic, polar ionic and supercritical fluid mode.

The enantioseparation mechanisms on macrocyclic glycopeptide-based chiral stationary phases have been recently reviewed by Ilisz et al. [34]. Issaq et al. [149] described the use of macrocyclic antibiotic CSPs for the separation of peptides. Berthod [150] reexamined the chiral recognition mechanisms on macrocyclic glycopeptide selectors ristocetin, teicoplanin, vancomycin and teicoplanin aglycone by evaluating the effect of the stationary phase polarity, the type of solvent, and the structure of macrocyclic glycopeptide on the enantiorecognition ability.

3.2. Recent studies on enantiorecognition mechanisms

Van't Hoff analysis has been applied by Pataj et al. [151] to study the chromatographic behavior of underivatized γ-amino acids and monoterpene-based 2-amino carboxylic acids on macrocyclic glycopeptide CSPs [152]. They estimated thermodynamic parameters such as changes in enthalpy, entropy and Gibbs free energy on different macrolides but no general predictive rules were obtained useful to predict the elution behaviour of these compounds. Van't Hoff analysis was also applied by Mericko et al. [153,154] to characterize the thermodynamics of adsorption of aryl–methyl sulfoxides on teicoplanin aglycone based CSP and by Flieger [155] to explain how the use of inorganic salts with chaotropic anions (perchlorate, hexafluorophosphate) as mobile phase additives leads to the improvement of chiral discrimination of acidic enantiomers on teicoplanin CSP in reversed phase mode. Some of the authors of this review [156] studied the binding of dipeptides and amino acids to teicoplanin CSP by showing that to properly describe their adsorption behavior an heterogeneous adsorption model is needed. In the same study, teicoplanin was demonstrated to exhibit a filter-like behavior towards the enantiomers of alanine–alanine dipeptide.

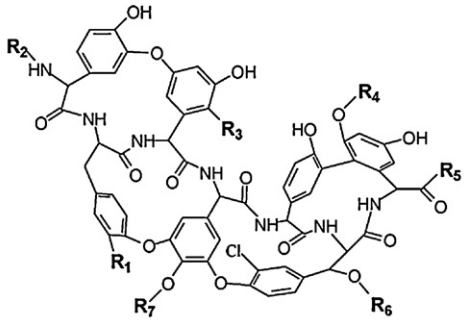
3.3. New macrocyclic antibiotic CSPs

Recently, Pittler and Schmid [157] prepared a CSP by dynamically coating a monolithic reversed-phase column with a vancomycin derivative by means of a hydrophobic alkyl-chain attached to the macrocyclic antibiotics. Gong's group describes the preparation and the HPLC characterization of two macrocyclic antibiotic capped β-cyclodextrins: a vancomycin-capped β-cyclodextrin [158] and a rifamycin-capped β-cyclodextrin-bonded CSP [159]. They report that, due to the cooperative functioning of macrocyclic antibiotics and β-cyclodextrin, these new type of chiral selectors outperform the single selector alone in the separation of aromatic positional isomers and enantiomers of a wide range of chiral compounds. Zhang et al. synthesized a new CSP based on dalbavancin, an antibiotic structurally related to teicoplanin [160]. By evaluating the enantioresolution of more than 250 racemates (including heterocyclic compounds, chiral acids, chiral amines, chiral alcohols., chiral sulfoxides and sulfilimines, amino acids and amino acid derivatives) under different mobile phase compositions, the authors conclude that dalbavancin-based CSP are complementary to teicoplanin CSPs. Hsiao and Chen [161] modified the macrocyclic antibiotic thiostrepton by the introduction of moieties containing aromatic groups and isocyanate and isothiocyanate-terminated groups. Even though no description of the modified molecule is given, so that no supposition can be made regarding the recognition process at molecular level, it was shown that the structural modifications were beneficial for the separation of enantiomers of aromatic compounds in polar organic mode.

3.4. Recent applications

In the last couple of years, several methods have been developed and validated for the determination of chiral drugs on macrocyclic antibiotics. Al-Majed [162] developed and validated a direct method for the resolution and quantification of the enantiomers of vigabatrin, an antiepileptic drug, in pharmaceutical products by using a CSP based on teicoplanin aglycone; Mostafa et al. [163] validated a method for the determination of clenbuterol on a vancomycin-based CSP; Saleh et al. [164] validated the separation and HPLC determination of promethazine enantiomers on a vancomycin-based CSPs.

The performances of the four macrocyclic antibiotics vancomycin, teicoplanin, teicoplanin aglycone and methylated teicoplanin aglycone toward the separation of β-blocker drugs was evaluated by Hroboňová et al. [165]. Tesarova et al. [166] compared the chromatographic behavior of two teicoplanin-based CSPs with different teicoplanin coverage and distinct linkage chemistry for the separation of amino-alcohols (see Fig. 6), chlorophenoxypropionic acids and branched-chain amino acids. Berkecz et al. [167,168] described the enantioseparation of 2-aminomono-, dihydroxycyclopentanecarboxylic, 2-aminodihydroxycyclohexanecarboxylic and β^2-homoamino acids.



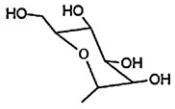
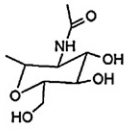
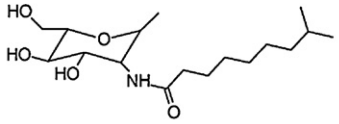
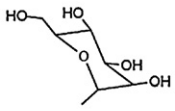
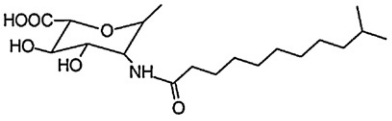
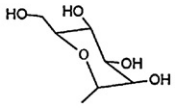
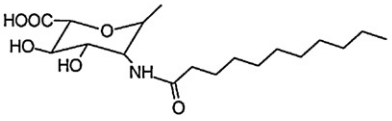
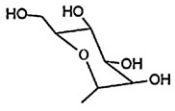
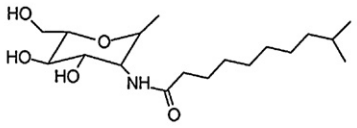
Compound	R_1	R_2	R_3	R_4	R_5	R_6	R_7
Teicoplanin A_{2-2}	−Cl	H	H		−OH		
Teicoplanin A-40,926 B_0	H	$-CH_3$	−Cl		−OH	H	
Teicoplanin A-40,926 B_1	H	$-CH_3$	−Cl		−OH	H	
Teicoplanin MDL 63,246 (Hepta-Tyr)	H	$-CH_3$	−Cl		$(CH_3)_2N-(CH_2)_3-NH-$	H	
Teicoplanin Aglycone	−Cl	H	H	H	−OH	H	H

Fig. 4. Structures of teicoplanin and its structurally related analogs [34].

4. Brush- or Pirkle-type or donor-acceptor CSPs

4.1. State of the art

Low molecular mass selectors linked to a solid support form a class of stationary phases – the so-called brush-type or Pirkle-type (in recognition of the pioneering role played by W.H. Pirkle in this field [169,170]) or even donor-acceptor CSPs – in which the individual chiral molecules are more or less regularly distributed onto the surface of an inert matrix and are easily accessible to analyte molecules. Rigid structural elements are often incorporated during the preparation of these chiral supports in order to create effective steric barriers triggering or amplifying their enantiorecognition ability [171]. The most relevant characteristics of brush-type CSPs include: good kinetic performance, broad applicability, chemical and thermal inertness, compatibility with any mobile phase, elevated sample loading capacities and the availability of such CSPs in both enantiomeric forms with opposite configurations displaying reversed elution orders [172,173]. There are several excellent reviews on CSPs based on low-molecular-mass selectors, such as those by Welch [174], Gasparrini et al. [18], Svec et al. [175] and Lämmerhofer [19]. Brush-type CSPs are most often operated is normal phase.

4.2. New brush-type CSPs

The number and type of brush CSPs is continuously growing. Pirkle and Lee [176] recently prepared a brush CSP derived from α-amino β-lactam for the separation of β-blockers. They demonstrated that an enhanced rigid conformation of the CSP gives to it enhanced enantioselectivity and greater scope with respect to its precursor derived from the α-amino phosphate. Gasparrini's group [177] synthesized the first sub 2-μm brush-type CSP (based on the known DACH-DNB selector, see Fig. 7) through a high reproducible synthetic methodology that allowed to assemble and surface-graft the whole chiral selector in only two steps. They compared the properties of columns packed with 1.9 μm particles with those of columns prepared with silica particles of 4.3 and 2.6 micron. Their conclusions show that the chiral stationary phases with reduced particle size and packed in short columns provide similar resolutions as those packed in standard column formats, but in considerably shorter times. Slater et al. [178] describe the in-column preparation of a brush-type CSP (based on a proline-derived chiral selector) using click-chemistry (copper-catalyzed azide-alkyne cycloaddition) to functionalize the surface of monolithic silica or packed beads of 10 μm particles. The performances of the CSP were demonstrated by considering the enantioseparation of a

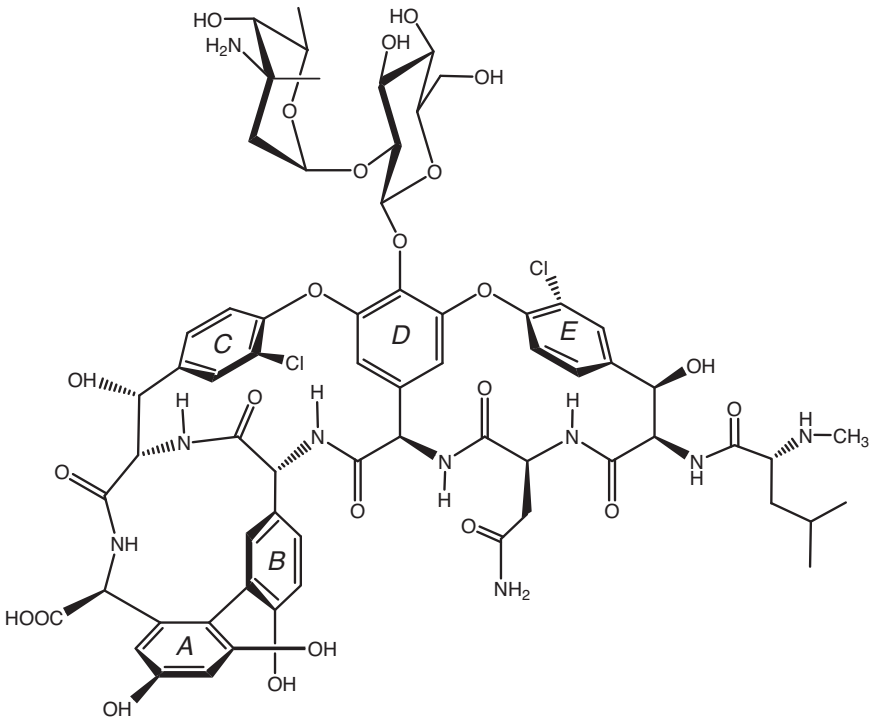


Fig. 5. Structure of vancomycin [16].

series of π-acidic amino acid amide derivatives. Wei et al. prepared two brush-CSPs by using derivatives of benzoylated tartaric acid and 1,2-diphenylethylenediamine as chiral selectors [179]. They also prepared a mixed CSP by simultaneously immobilizing the two selectors on aminated silica gel but the mixed selector CSP showed lower enantioseparation ability than the single selector phase.

Choi et al. [180] prepared a CSP based on the antibiotics cefaclor (belonging to the family of cephalosporins). The new CSP was demonstrated to be useful in the resolution of acidic analytes (N-dinitrobenzoyl-amino acid derivatives) through a molecular recognition mechanism based on enantioselective donor–acceptor interactions. Ohyama et al. [181] report about the preparation and the use as CSPs of peptide chiral selectors prepared by solid-phase synthesis.

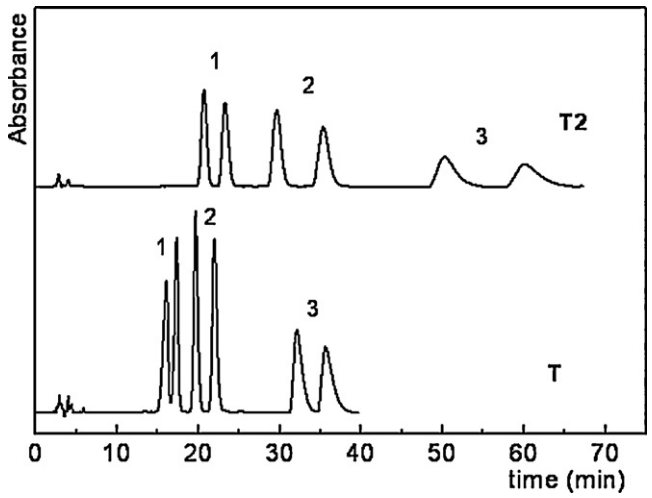


Fig. 6. Comparison of the chromatograms of oxprenolol (1), propranolol (2), and atenolol (3) enantiomers obtained on the Chirobiotic T2 and the Chirobiotic T commercial columns. Mobile phase: methanol/acetic acid/triethylamine 100:0.05:0.05 (v/v/v), flow rate 1.0 mL min^{-1}. [166].

4.3. Recent studies on enantiorecognition mechanisms

Works regarding the investigation of the mechanisms leading to chiral recognition in brush-type CSPs are those from Nita et al. [182] about the study of self-selectivity phenomena in two model dinitrobenzoyl-derivatized CSPs and from Guiochon's group [183–186] on the enantioselectivity of the mass transfer kinetics and the adsorption equilibrium of naproxen on a (R,R)-Welch-01 CSP. This is one of the most employed brush-type CSP. The study demonstrates that in the chromatographic resolution of naproxen enantiomers two groups of enantioselective sites are involved: sparse sites of strong affinity towards (R)-naproxen and a more numerous type of low energy sites exhibiting a somewhat different affinity toward the two enantiomers. In the same study, the investigation of the excess isotherm of water:methanol binary mixture showed that methanol preferentially adsorbs on the CSPs throughout the whole range of mobile phase compositions. Finally, the enantioselective character of the intraparticle transport processes was demonstrated by analyzing the dependence of the HETP on the flow velocity.

The impact of a nearby chiral surface on solvent was explored by Cann's group [187] through molecular dynamics studies. They evaluated the extent and characteristics of chirality transferred from the surface to the solvent by considering as interface the Whelk-01 CSP (in addition to a phenylglycine- and a leucine-derived CSP). Different alcohol–alkane mixtures were considered as solvents. The chirality induced in the solvent was assessed based on a broad series of related chirality indexes, and combinations of indexes were also employed to isolate specific contributions, such as individual torsions. Their conclusions are that chirality transfer is more significant and persists to larger distances away from the selector in alcohol/alkane mixtures relative to pure alcohol solvent. The same group used molecular dynamics simulations to evaluate three Whelk-01-modified CSPs towards the enantioseparation

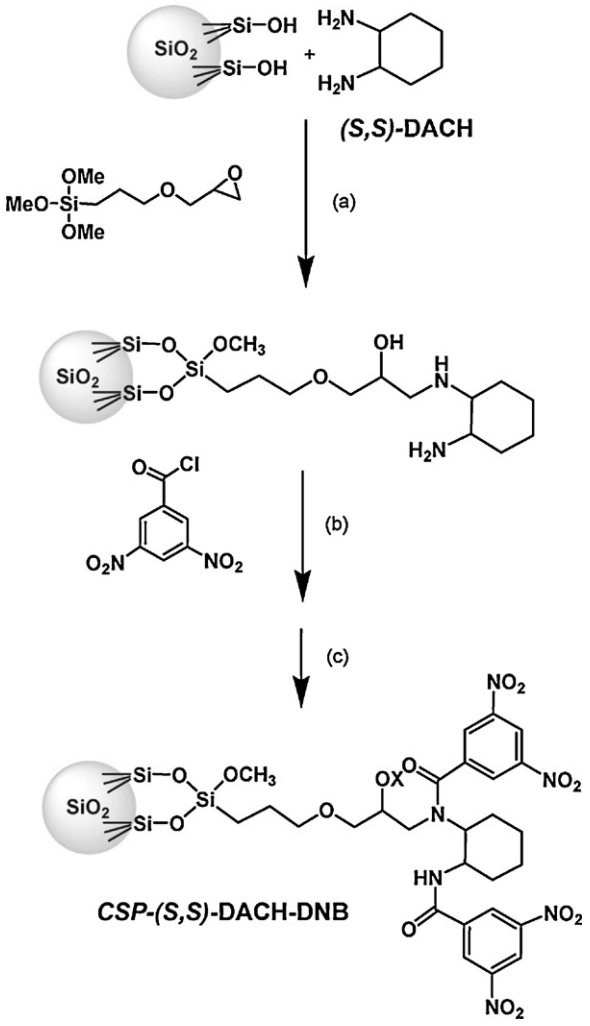


Fig. 7. Synthetic pathway to DACH-DNB CSPs [177].

of naproxen enantiomers [188], showing in silico that design and testing of novel CSPs is possible as long as care is taken to correctly model the selector flexibility and the model interface.

4.4. Recent applications

Applications of brush-type CSPs are rapidly expanding. Holzheuer et al. [189], in a comparative test between different kinds of CSPs (polysaccharide, macrolide and Pirkle) towards the enantioseparation of compounds of pharmaceutical interest, evaluated the performances of several Pirkle type CSPs under reversed phase mode. Badaloni et al. [190] extended the use of the so-called Inverted Chirality Columns Approach for enantiomeric excess determination in absence of reference samples to water-soluble camptothecin derivative, a potential anticancer agent, on Whelk-01 CSPs. Important class of molecules such as cyclophosphazenes [191], polynuclear aromatic hydrocarbon mixtures [192], phthalans [128], non-benzenoid and oligo-Troeger's bases [193] have been separated on brush-type CSPs. Wenzel et al. [194] compared the performances of a Pirkle-type CSP vs. polysaccharide- and macrolide-based CSPs for the separation of vesamicol and novel vesamicol analogs. Enantioseparation of methanobenzazocines was studied by Barker et al. [195] using Pirkle-type, polysaccharide, native and derivatized β-cyclodextrin CSPs.

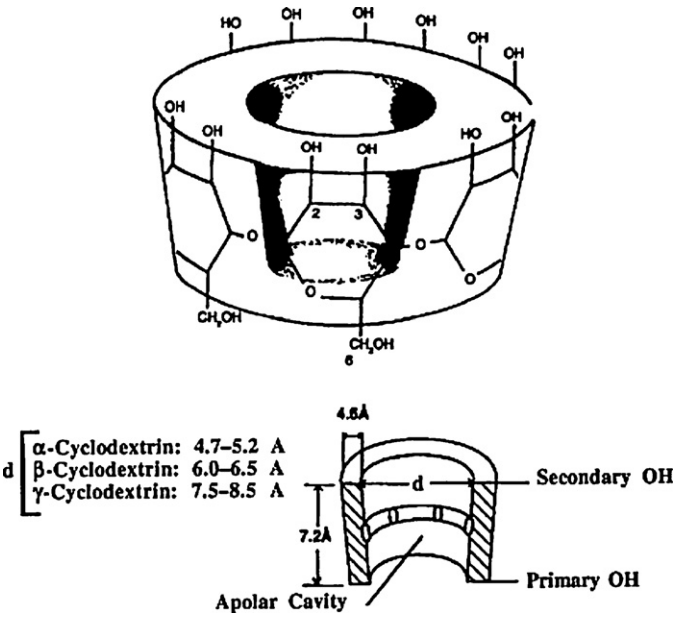


Fig. 8. Molecular model of cyclodextrins [5].

5. Cyclodextrin (CD) CSPs

5.1. State of the art

CD-based CSPs are some of the most popular materials used for contemporary chiral separations. One of the advantages of CD-based CSPs is their unrestricted and successful use with all type of solvents. They can be employed in normal-, reversed-phase, polar organic and polar ionic mode. Since CD have good sample capacity, they are often used for preparative purposes. Three of the most widely characterized are the α-, β- and γ-CDs (see Fig. 8). These cyclic oligosaccharides contain respectively 6, 7 and 8 D(+)-glucose residues bonded through α-(1-4)glycosidic linkages. Topologically, CDs can be represented as toroids with the larger and the smaller openings of the toroid exposing to the solvent secondary and primary hydroxyl groups, respectively. The size of the cavity increases with increasing the number of glucose units. Reported value ranges of upper ring diameters are 4.7–5.2, 6.0–6.5 and 7.5–8.5 Årespectively for the α-, the β- and the γ-structure [5]. X-ray data has indicated that the β and γ structures are quite rigid whereas the α appears to exhibit some flexibility. Thus solute molecules, if spatially suitable, can be included and interact by dispersive, polar or ionic forces with any neighboring groups to which they are appropriately close.

A number of different derivatives of CDs have been synthesized to provide specific types of interactions to increase enantioselectivity. To this end, secondary hydroxyl groups (positions 2 and 3 on the CD) can be derivatized selectively. The primary hydroxyl (position 6) serves to link the CD to the silica surface [5].

5.2. New CD-based CSPs

Wang et al. [196–198] synthesized several new CD-based CSPs via click chemistry. These phases exhibited good resolution for a series of dansyl amino acids and hydroxyl-substituted flavanones [198], racemic aryl alcohols, flavonoids, bendroflumethiazide, atropine, β-blockers, non-aromatic ionone derivatives [196], indoprofen, ketoprofen, Troeger's base, β-agonists [197]. They investigated the effect of the mobile phase composition on the performances of CSPs and studied the correlation between enantioselectivity and CD accessibility and peripheral functionality. Guo

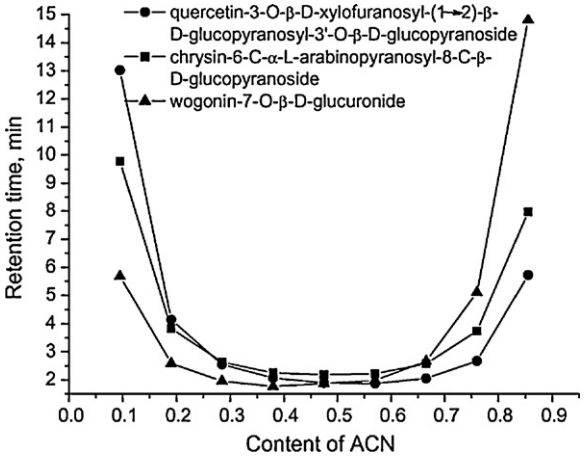


Fig. 9. Retention time dependency on acetonitrile content. Mobile phase: 10mM ammonium acetate in acetonitrile/water, pH 6.3, with content of acetonitrile as indicated; flow rate: 1.0 mL min^{-1}; UV detection: 270 nm [199].

et al. [199] prepared a native β-CD CSP by covalently bonding β-CD on silica particles via click chemistry. They evaluated the properties of this new CSP under hydrophilic interaction liquid chromatography (HILIC) mode in different mobile phase conditions towards a set of polar compounds, including nucleosides, organic acids, alkaloids and oligosaccharides. Retention vs. mobile phase composition U-shaped plots, typical of HILIC conditions, were observed (see Fig. 9). Zhao et al. [200] studied the retention properties of some CD-based CSPs designed to have complementary retention properties respect to traditional C18 stationary phases under reversed-phase mode. For this purpose, they linked 1,12-dodecyldiol and ethylene glycol to β-CD and prepared two CSPs via click chemistry. Similarities and differences in the behavior of C18 and functionalized β-CDs, in particular in terms of polar selectivity under reversed phase mode, were elucidated by means of comparative linear solvation energy relationships (LSERs). The impact of silica gel pore and particle sizes on HPLC column efficiency and resolution for CD-based CSPs was evaluated by Qin et al. [201]. β-CD functionalized silica- [202] and polymer-based [203–205] monolithic columns have been prepared and characterized as separative media for HPLC and electrochromatography.

Recently, the organic–inorganic hybrid monolithic columns have been attracting great attention since the organic functional moieties can be incorporated into the inorganic silica monolithic matrixes via the sol–gel process to achieve beneficial properties, such as good mechanical stability and solvent resistance. Zou's group [206] describes the so-called "one-pot" process for fabrication of organic-silica hybrid monolithic capillary columns using organic monomer and alkoxysilane. The same group has now improved the one-pot approach for the preparation of hybrid monolithic columns by getting round the problem of the incompatibility between hydrophobic organic monomer and aqueous prepolymerization mixture needed for the preparation of organic–inorganic hybrid monolithic materials [207].

β-CD based CSP were prepared by microwave irradiation for open tubular capillary electrochromatography [208]; sub-1-μm mesoporous silica particles were functionalized with CD derivative for ultra-high pressure liquid chromatography applications [209]; mixed binary chiral selectors preparated by grafting L-or D-valine tert-butylamide on permethylated CD with enhanced enantioseparation capabilities towards amino acid derivatives were prepared by Stephany et al. [210]; Si-Ahmed et al. studied the effect of the nature and length of the spacer used in the preparation of CSPs based on modified β-CDs [211]; phenylcarbamoylated β-CD based on π-acidic or π-basic chiral selectors were prepared as chiral selectors for HPLC [212]; cooperative effects of CDs and ionic-liquids in liquid chromatography have been exploited by Zhou et al. [213] who synthesized four ionic-liquid functionalized CDs by bonding to silica gel 6-tosyl-β-CD treated with 1,2-dimethylimidazole or 1-amino-1,2,3-triazole. They demonstrated as the presence of ionic groups enhances in some cases the enantioselectivity of the stationary phase. Cooperative separation processes employing ionic liquids and CDs have been recently reviewed [214]. Application and potentialities of CD-crown ether coupling system in supramolecular chemistry has been reviewed by Sun et al. [215]. The authors, in particular, focus on recent developments and applications of these coupling systems in fields such as molecule recognition, mimetic enzyme, isolation of isomers and energy transfer of light.

5.3. Recent studies on enantiorecognition mechanisms

Elucidation of molecular mechanisms leading to chiral discrimination on CD-based CSPs was realized by means of molecular modeling [216,217] and NMR techniques [218]. Armstrong and coworkers [218] studied the enantioselective host-guest complexation between racemic Ru(II) trisdiimine complexes and neutral and anionic derivatized CDs. NMR measurements allowed them to enlighten important features of the complexation phenomenon such as the complexation stoichiometry and the effect of different chemical moieties on the functionalized CD with respect to its enantioselective capacity. Molecular docking was employed to predict the enantiodifferentation of chiral styrene oxydes on a γ-CD by Aree's group [216].

5.4. Recent applications

Separation of flavanones and flavanone glycosides and hesperetin enantiomers by nano-liquid chromatography on β-CD CSPs have been described by Fanali and coworkers [219,220]. CD-based CSPs have been used for the separation of important classes of racemic compounds, including 4,5-disubstituted imidazole compounds [221], disubstituted benzenes and chiral drugs under both reversed and normal-phase HPLC mobile phase conditions [159,158,222]. Permethrin enantiomers [223], β-lactams [224], coumarin derivatives [225], stereoisomers of sertraline [226], DL-penicillamine and DL-cysteine [227], unusual β-amino acids (saturated or unsaturated alicyclic β-3-homo-amino acids and bicyclic β-amino acids) [228] have been resolved on CD-based CSPs.

6. Derivatized-cyclofructan based CSPs

Among the various CSPs developed in the last few years, cyclofructan and derivatized-cyclofructan based selectors are those that probably present more interesting properties in terms of applicability, superior separations for specific groups of compounds (with respect to the CSPs nowadays available), elevated "loadibility" (very important for preparative applications), possibility of operating in different chromatographic modes included HILIC conditions. From a chemical point of view, cyclofructans (CFs) consist of six or more β-(2,1) linked D-fructofuranose units. Each fructofuranose unit of CFs contains four stereogenic centers and three hydroxyl groups. The central core of CFs has the same structure as the respective crown ethers. CFs belong to the class of macrocyclic oligosaccharides exactly as CDs even though cyclofructrans are quite different in both their structure and behavior.

Armstrong and coworkers introduced native and derivatized cyclofructans made of six D-fructofuranose units (CF6) as chiral selectors for HPLC in 2009 [229]. In Fig. 10 the molecular structure of

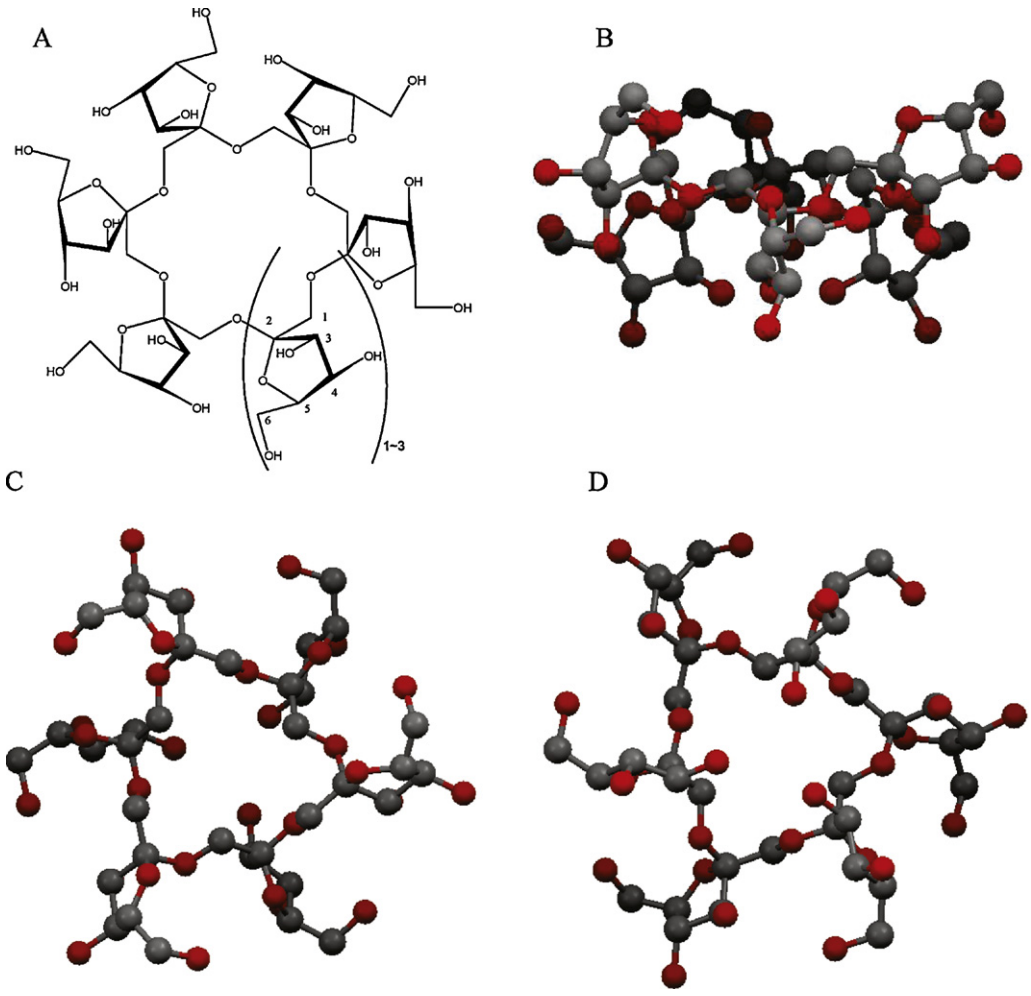


Fig. 10. Structure of cyclofructan: (A) molecular structure of CF6, CF7, and CF8; (B–D) crystal structure of CF6 (B) side view; (C) hydrophobic side up; (D) hydrophilic side up. Color scheme: oxygen atoms are red and carbons are black. Hydrogens are not shown. [229].

cyclofructans with 6, 7, and 8 D-fructofuranose units (respectively CF6, CF7 and CF8) are reported. They showed that derivatization of cyclofructans leads to structures that, depending on the type of functionalization, can be "tuned" to enantiodiscriminate different types of optically active molecules. Partial derivatization of the cyclofructan hydroxyl groups disrupts internal hydrogen bonding and relaxes the structure. If "lightly" derivatized with aliphatic functionalities, CF6 exhibits an extraordinary capability to separate enantiomers of primary amines in both organic solvents and supercritical CO_2. This is in contrast to all known chiral crown ether based CSPs that work exclusively with aqueous acidic solvents. When CF6 is extensively functionalized with aromatic moieties, it no longer separates primary amine racemates but it does separate a broad variety of other enantiomers.

Isopropyl-carbamate functionalized CF6 was prepared by the same group and it was demonstrated to be able to enantioselectively separate primary amine-containing compounds, including amino acid alcohols, amino acid esters, amino acid amides, amino acids and Betti base analogs [78,230].

The performances of CF6-based CSP were compared with those of a R-naphthylethyl-functionalized β-cyclodextrin CSP by considering 46 different solutes as probes. Linear free energy relationship (LFER) analysis allowed to point out the role that hydrogen bonding and polarity/polarizibility have in the enantiorecognition process [231]. A comparative study between aromatic-derivatized cyclofructans with 6 and 7 D-fructofuranose units (CF7) showed that the two CSPs exhibit an interesting complementary selectivity in the separation of chiral acids, amines, metal complexes, and neutral compounds [232].

Very recently, Qiu et al. [233] demonstrated that CF6-based CSP can be successfully used also in HILIC mode, thus enlarging the already broad spectrum of applications for this novel kind of CSPs. This is shown in Fig. 11, where the chromatographic behavior for the separation of nucleic acid bases and nucleosides of 3 differently prepared CF6-based CSPs is compared with those of three commercial columns under HILIC conditions.

7. Crown ether-based CSPs

7.1. State of the art

Crown ethers are macrocyclic polyethers with a cavity of specific size. They were first introduced by Pederson in 1967 [234]. The ether oxygens, placed regularly around the inside wall of the cavity, can act as electron donor ligands. In consequence of this, metal or ammonium cations can be incorporated into the cavity. In 1979, Sogah and Cram [235] immobilized bis-(1,19-binaphthyl)-22-crown-6 on polystyrene or silica gel by preparing the first crown ether-based CSP. In 1987, Shinbo and coworkers [236] coated on octadecyl silica gel structurally related chiral crown ethers based on disubstituted 1,19-binaphthyl- 20-crown-6 and used these materials as CSPs for HPLC application. A very important step in the production of chiral crown ether-based CSPs was the preparation of chemically bonded stationary phases, described almost

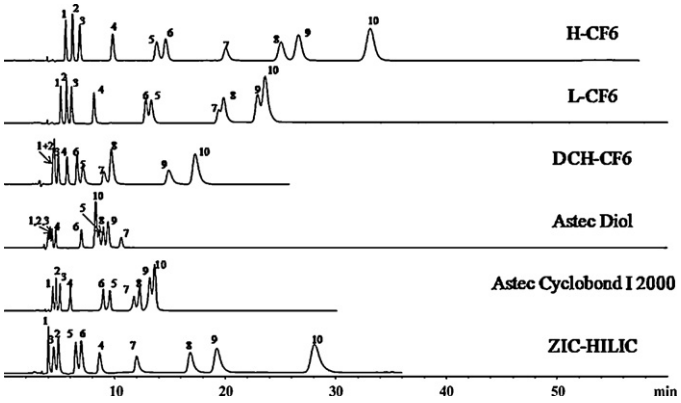


Fig. 11. Separation of nucleic acid bases and nucleosides on six columns (H-CF6: high coverage propyl carbamate cyclofrutan 6; L-CF6: low coverage propyl carbamate cyclofrutan 6; DCH-CF6: dicarbamoxyl-hexyl linked cyclofrutan 6; Astec Diol, Astec Cyclobond I 2000 and ZIC-HILIC are commercial columns). Mobile phase: acetonitrile/20 mM ammonium acetate, pH = 4.1, 90/10 (v/v); flow rate: 1.0 mL min^{-1}; UV detection: 254 nm. Compounds: (1) thymine; (2) uracil; (3) thymidine; (4) uridine; (5) adenine; (6) adenosine; (7) cytosine; (8) guanine; (9) cytidine and (10) uanosine [233].

simultaneously by Hyun et al. [237] and Machida et al. [238], in which the crown-ether was covalently linked to an inert support. Since there, chiral crown ethers have been developed by incorporating appropriate chiral units into crown ethers. For instance, bulky chiral aromatic rings such as binaphthyl or biphenanthryl units, helicene derivatives, and suitable optically active natural compounds such as tartaric acid or carbohydrates have been used to this end [239].

7.2. New crown ether based CSPs

Chiral crown ethers incorporating tartaric acid units have been most successfully used for the separation of racemic compounds containing primary amino functional groups. Among them, the (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid-based CPS and its derivatives have been the most studied since 2009. Hyun's group [240] prepared a new crown ether-based CSP containing the thioester linkage by bonding (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid to mercaptopropylsilica gel. This CSP is reported to outperform previous CSPs containing the amide linkage in the resolution of various α-amino acids, racemic amines and amino alcohols. The same group also studied the effect of the modification of the free carboxylic acid groups of a CSP based on (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid on the chiral recognition [241]. Ilisz et al. [242] designed and synthesized a long-tethered crown ether based CSP displaying the 11-methylene-unit of aminoundecylsilica gel as the spacer between the support and (+)-(18-crown-6)-2,3,11,12-tetracarboxylic acid chiral selector. They successfully used this CSP for the separation of unnatural β2-amino acids under reversed-phase conditions.

7.3. Recent studies on enantiorecognition mechanisms

Lee et al. [243] extended the application scope of (18-crown-6)-2,3,11,12-tetracarboxylic acid-based CSP to preparative conditions. They studied the adsorption equilibria of D- and L-tryptophan from diluted aqueous solutions. Measurement of adsorption isotherms and estimation of intrinsic parameters for the two enantiomeric amino acids were achieved by the use of the inverse and the elution by characteristic point (ECP) methods.

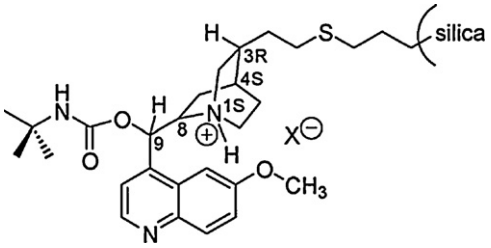


Fig. 12. Quinine and quinidine carbamate-based chiral stationary phases. Chiralpak QN-AX: (8S,9R), quinine derived; Chiralpak QD-AX: (8R,9S), quinidine derived. [253].

7.4. Recent applications

Recent applications of crown ether-based CSPs include the separation of thyroxine in pharmaceuticals [244], α-amino acid derivatives [245], flecainide and its analogs [246], tocainide and its analogs [247] and β2-homoamino acids [248].

8. Restricted-access CSPs

Restricted-access materials (RAMs) are nowadays largely employed for the direct HPLC injection of untreated biological samples. They are characterized by having an external bio-compatible surface and a bonded phase inside the pores which are accessible only to molecules of suitable dimensions.

Dong's group reports about the preparation of new chiral RAMs [249]. They made use of atom transfer radical polymerization to graft poly(glycidyl methacrylate) (pGMA) on the surface of porous silica gel. The internal layer of pGMA was used for immobilizing β-CD as a chiral selector. Hydrolysis of the outer layer of pGMA created the bio-compatible hydrophilic polymeric network. This approach has been recently improved [250] thanks to the use of click chemistry for the immobilization of β-CDs in the synthesis of a "comb-like" RAM (CD-click-RAM). Click chemistry allowed to obtain well-defined structures and to avoid undesired side-reactions in the preparation of chemically bonded β-CD CSP.

9. Ion- and ligand-exchange CSPs

The class of chiral ion-exchangers includes generically CSPs with ion-exchange capabilities. To this class may belong macromolecular selectors such as proteins, intermediate-size selectors of the class of macrocyclic antibiotics or low-molecular weight selectors like derivatized amino acids. Under ion-exchange mechanism it is assumed that the long range electrostatic ion–ion interaction forces operate to guide the analyte towards the binding site of the chiral selector.

Lindner and coworkers have been particularly active in the two last years in the characterization and development of cinchona alkaloid and derivatized cinchona alkaloid based ionic exchanger CSPs [251–257]. These low molecular mass chiral selectors are characterized by having both anionic- and cationic-exchange moieties, thus giving to the CSP zwitterionic properties. As an example, in Fig. 12 the chemical structures of quinine (8S,9R) and quinidine (8R,9S) carbamate-based chiral stationary phases are reported. Consequently, these novel chiral separation materials exhibit enantioselectivity for a wide spectrum of chiral ionizable analytes ranging from chiral acids over chiral amines to chiral amino acids and peptides. Hoffmann et al. [256] made a systematic investigation of the working principles of the three ion-exchange modes – cation- anion- and zwitterion-exchange – offered by these CSPs under polar organic mode. They demonstrated that ion pairing and ion exchange are the primary processes responsible for analyte

retention in all three operational modes. The negative slopes for the curves representing the logarithm of the retention factor vs. the concentration of the counterion in the mobile phase for a series of analytes with specific basic, acidic or zwitterionic characteristics is consistent with a stoichiometric displacement model where buffer ions compete with solutes at the charged center of the ion-exchanger [256,258]. In a successive work, they studied in detail the effect of the mobile phase composition on the chromatographic performances of zwitterionic CSPs [257]. To achieve this goal, the chromatographic behavior of a series of acidic analytes and amino acids was evaluated by varying mobile phase characteristics such as acid-to-base ratio, type of acidic and basic additives and type of bulk solvent in nonaqueous polar organic and aqueous reversed-phase conditions. Major conclusions of this study were that weakly acidic methanolic mobile phases provided the most general and successful conditions in zwitterionic mode. In aqueous eluents reversed phase contributions to retention came into play but only at low organic modifier content because of the highly polar character of zwitterionic analytes. At higher acetonitrile content, HILIC-related retention phenomena were observed.

The role of additive on quinidine carbamate-based chiral stationary phase was further investigated by nonlinear chromatography techniques by Arnell et al. [255]. When weakly acidic hydroorganic, polar organic or normal-phase eluents are employed, the basic quinuclidine nitrogen is protonated and then acts as fixed ion-exchange site. For chiral acids, thus, an ion-exchange retention mechanism is established. In consequence of this, anions or organic acid additives are required as counter-ions and competitors, respectively, in the mobile phase to displace the solutes from this strong adsorption site. The adsorption behavior of 9H-fluoren-9-ylmethoxycarbonyl-allylglycine (Fmoc-allylglycine) enantiomers in presence of methanol/glacial acetic acid/ammonium acetate eluent was modeled by the equilibrium-dispersive model of chromatography and a competitive Langmuir adsorption isotherm including also the equilibrium constant for the adsorption of the additive.

It was recently demonstrated that replacement of the flexible thioether linker for the rigid 1,2,3-triazole spacer group had beneficial effect on the enantiodiscrimination power of cinchona alkaloid based CSPs [252]. Triazolo-linked cinchona alkaloid carbamate anion exchange-type CSPs have been recently prepared via click chemistry [251] and characterized in terms of chiral recognition ability towards a representative set of acidic analytes under polar organic and reversed phase conditions. Levkin et al. [254], finally, demonstrated that a critical point in the preparation of derivatized quinine and quinidine based CSPs is the enantiomeric purity of the highly enantioselective chiral selectors. Even traces of the opposite enantiomer of a selector or an impurity possessing strong interactions with the analyte can cause a strong decrease of the observed enantioseparation factor.

A critical evaluation of the performances of anion-exchange CSPs and polysaccharide-based CSPs towards the separation of chiral pirinixic acid derivatives was proposed by Lämmerhofer et al. [253]. The study aimed to assess the feasibility of indirect chromatographic absolute configuration prediction by chromatographic elution orders. The conclusion was that chromatographic absolute configuration assignments based on elution orders, which have been validated for a pair of enantiomers with known configuration, is always safely possible for this pair of enantiomers, while predictions for structural analogs assuming an identical chiral recognition mechanism bears a considerable risk for false assignments if the molecular recognition mechanism is unknown. In consequence of this, configuration predictions of structural analogs based on elution orders on polysaccharide CSPs should be strongly avoided because of the high susceptibility to alterations of the chiral recognition mechanisms even with minute structural changes. On the opposite, predictions are much safer on anion-exchange CSPs.

Ligand exchange chromatography is based on the formation of reversible ternary diastereomeric coordination complexes between a chelating chiral selector anchored to an inert support (silica gel or polystyrene), a metal ion immobilized through complexation by the chelating chiral selector and a chelating analyte species adsorbed in the coordination sphere of the metal ion. Differences in rates of formation and/or thermodynamic stability of selector/metal-ion/solute transient diastereomeric ternary complexes provoke the differential migration of the enantiomers inside the chromatographic column. Recent applications of chiral ligand-exchange chromatography include the separation of native amino acids on a porous graphitic carbon coated with a dinaphthyl derivative of neamine CSP [259]; the use of click chemistry for the preparation of L-proline derivative based CSPs [260]; the study of the effect of the copper(II) salt counter-ion in the chiral ligand-exchange separation of amino acids by a coated CSP based on S-trityl-(R)-cysteine [261] and, finally, the chromatographic resolution of proton pump inhibitors including omeprazole [262].

10. Molecular imprinted CSPs

Molecular imprinted technology entails the prearrangement of functional monomers with the molecule of interest (the template). After copolymerization of functional monomers and cross-linker, the template is removed from the polymer by extraction, resulting in a polymer with specific recognition sites, complementary to the template in the positioning of the functional groups and in the shape [263]. The interactions responsible for the recognition of the substrate by the polymer can be either non-covalent forces such as ionic and hydrogen bonding or the formation of reversible covalent bonds, such as ketals, boronic esters and Schiff's bases.

The most recent activity in the field of molecular imprinted CSPs has focused on the preparation and characterization of new imprinted monolithic polymers for the separation of racemic antiparasitic drugs [264]; Huang and coworkers report on synthesis of low-density (S)-naproxen imprinted polymers [265] for the separation of racemic naproxen; Silva et al. [266] describe the use of supercritical CO_2 technology for the 1-step preparation of molecularly imprinted polymers of poly(ethylene glycol dimethacrylate) and poly(N-isopropylacrylamide-coethylene glycol dimethacrylate and their use as CSPs for the separation of the enantiomers of tryptophan. As it has been already mentioned, very recently separation processes in presence of CD using molecular imprinting technology and ionic liquid cooperating approach have been reviewed [214].

11. Oligoproline-based CSPs

Oligoproline CSPs are considered to constitute a new class of peptide-based CSP even though, admittedly, they share many common features with brush-type CSPs. They are composed of several proline units linked together and covalently anchored to silica gel. Proline chains up to 10 units (decaproline) have been reported [267]. Proline displays a secondary amine functionality in a cyclic structure that results in an extraordinary rigid conformation and enhanced enantiorecognition properties. Oligoproline CSPs were reported to have high and broad-spectrum enantioselectivity [268,269].

Lao and Gan have been very active in the development of new oligoproline-based CSPs and in the evaluation of their chromatographic performances [270–273]. Due to the low reproducibility observed in the preparation of long chain of proline units and the need for economically attractive manufacture processes, these authors essentially focused on diproline- and triproline-based

CSPs and their derivatives. They prepared covalently (by a doubly tethered tertiary amide linker) and ionically bonded diproline CSPs demonstrating that the rigid structure of the double tethered linker was not only beneficial in terms of stationary phase stability but also, in some cases, it favored the enatiorecognition process [273]. On this CSP, the effect of temperature on the enantioseparation was evaluated [271]. A triproline and a tri-α-methylproline based CSP was prepared and their chromatographic behavior evaluated with a series of analytes classified as having none, one, two or three hydrogen-bond donors [272]. By comparing the performances of the two CSPs, the authors acknowledged the importance of the hydrogen atom on the proline stereocenter in enantioseparation. Unusual peak profiles of warfarin enantiomers were observed under normal phase conditions on both diproline and triproline-based CSPs by changing alcohol concentration in the mobile phase [270]. Similar effects were also reported for coumachlor enantiomers on a diproline-based CSP. An explanation of these phenomena was given by considering the competition for the adsorption to the stationary phase by the strong mobile phase modifiers.

12. Protein-based CSPs

Protein-based CSPs exhibit enantioselectivity for a wide range of compounds because of multiple binding sites on the surface of chiral selectors and/or multiple binding interactions between chiral selectors and ligands [274]. The most important protein-based CSPs are based on human serum albumin (HSA), α_1-acid glycoprotein (AGP), crude ovumocoid (OVM) and cellobiohydrolase I (CBH I) [19]. In the last couple of years, research on protein-based CSPs has manifested a significant decrease in interest, at least by judging from the reduced number of publications on the subject. Bhushan and Kumar [227] described the analytical and preparative enantioseparation of D,L-penicillamine and D,L-cysteine on AGP CSP; the same CSP was used for the separation of the enantiomers of the β_2 agonist formoterol [275].

Michisita et al. [276] described a screening approach for AGP-based CSPs whose enantioselective properties may be influenced by several chromatographic parameters such as the buffer nature and its pH, the organic modifier (kind and amount), etc. With respect to the established guidelines for method development on AGP –essentially based on the use of MS-incompatible phosphate buffers – they developed a simplified protocol for sample screening leading to MS-compatible HPLC methods with high success rate. The use of NMR technique for the screening of protein-free ligand interactions has been proposed as a tool to simplify the chiral chromatographic method development [277]. A molecular simulation study to get insight on chiral recognition mechanisms at molecular level for the separation of racemic phenylglycines on a thermolysin crystal-based CSP and water as the mobile phase was proposed by Hu et al. [278].

Finally, chip-based enantioselective open-tubular capillary electrochromatography using bovine serum albumin (BSA)-gold particle conjugates as stationary phase was described by Li et al. [279].

13. Synthetic polymer CSPs

In addition to brush-type CSPs based on low-molecular-mass selectors, CSPs based on synthetic polymers as chiral selectors have been proposed to mimic the enantiodiscrimination power of the semi-synthetic polysaccharides. In the classical method of radical polymerization for the preparation of polymeric CSPs – the so-called "grafting-to" approach – the chiral monomer and the radical initiator are both kept in solution and the solid support is usually activated with a polymerizable group, such as a vinyl or acryloyl fragment (see Fig. 13). By this method, the chiral polymer is mainly formed in solution, and subsequently, it becomes end-grafted to the support surface. In the newer "grafting-from" approach [280], the polymer chain grows starting from the surface of silica particles on which initiators were immobilized. This, in theory, permits the generation of polymer molecules directly grafted on the surface of mesoporous silica particles. In the ideal case, the "grafting-from" process is not only surface-initiated but is also surface-confined, so that polymer growth is not occurring in solution. This permits the achievement of materials with enhanced characteristics, especially in terms of mass transfer properties, which were successfully employed in linear and nonlinear chromatography [280,281]

Tian at al. [282] synthesized polymeric brush type CSPs starting by optically active acrylamide derivatives (N-(oxazolinylphenyl)acrylamides, (S)-N-[o-(4-methyl-4,5-dihydro-1,3-oxazol-2-yl)phenyl]acrylamide and (R)-N-[o-(4-phenyl-4,5-dihydro-1,3-oxazol-2-yl)phenyl]acrylamide). The performances of the new CSPs were compared by considering the enantioseparation of several racemic compounds, including 1,1′-bi-2-naphthol, benzoin, 2-amino-1-butanol, and loxoprofen sodium under normal-phase mode. The CSPs were prepared in two versions via the "grafting-to" and "grafting-from" approaches, respectively. They found that the "grafted-to" CSP outperforms its "grafted-from" counterpart. However, in the experimental procedure described to obtain the "grafted-from" CSP, it appears that both the monomer and the radical initiators are in solution. Under these conditions, some of the intrinsic advantages associated to a true "grafting-from" procedure (first of all the formation of an ordered polymeric layer architecture attached to the silica support which is very important to have efficient mass-transfer) are lost [280]. Ciogli et al. [283] report about the preparation of a new hybrid polyacrylamide CSP prepared by surface-initiated photopolymerization. Their system is based on the activation by UV irradiation of mesoporous silica microparticles by covalently bonded trichloroacetyl groups and dimanganese decacarbonyl as catalyst. Enhanced grafting density is reported with respect to that of the homolog CSP obtained by the "grafting-from" thermal-induced process.

Lourenco et al. [284] describes the enantioseparation of chiral sulfoxides including aryl alkyl sulfoxides, benzoimidazole sulfoxides and the drugs modafinil, albendazole sulfoxide, omeprazole, lansoprazole, pantoprazole and rabeprazole on new synthetic polymeric CSPs derived by the monomers of N-(2-acryloylamino-(1R,2R)-cyclohexyl)-acrylamine (P-CAP), N,N'[(1R,2R)-1,2-diphenyl-1,2-ethanediyl]bis-2-propenamide (P-CAP DP) and trans-9,10-dihydro-9,10-ethanoanthracene-(11S,12S)-11,12-dicarboxylic acid bis-4-vinylphenylamide (DEAVB). They explored different experimental conditions, included the non-standard (for these materials) reversed-phase mode.

14. Miscelaneous

Monosaccharide CSPs based on arabinose, fucose, ribodesose, lyxose, and ribose were used as chiral stationary phases in HPLC under normal phase conditions [285]; synthetic macrocyclic chiral selectors with multiple hydrogen-bonding sites in macrocyclic cavities were covalently bonded to silica gel to give CSP showing excellent abilities to resolve various chiral compounds including ketones, esters, carboxylic acids, sulfoxides, amines, amino acid derivatives and metal complexes [286]; Yin et al. [287] studied the effect of the spacer and functional group employed to connect the chiral selector to silica gel by using a (1S,2R)-(1)-2-amino-1,2-diphenylethanol derivative as chiral selector. Spacers differed for

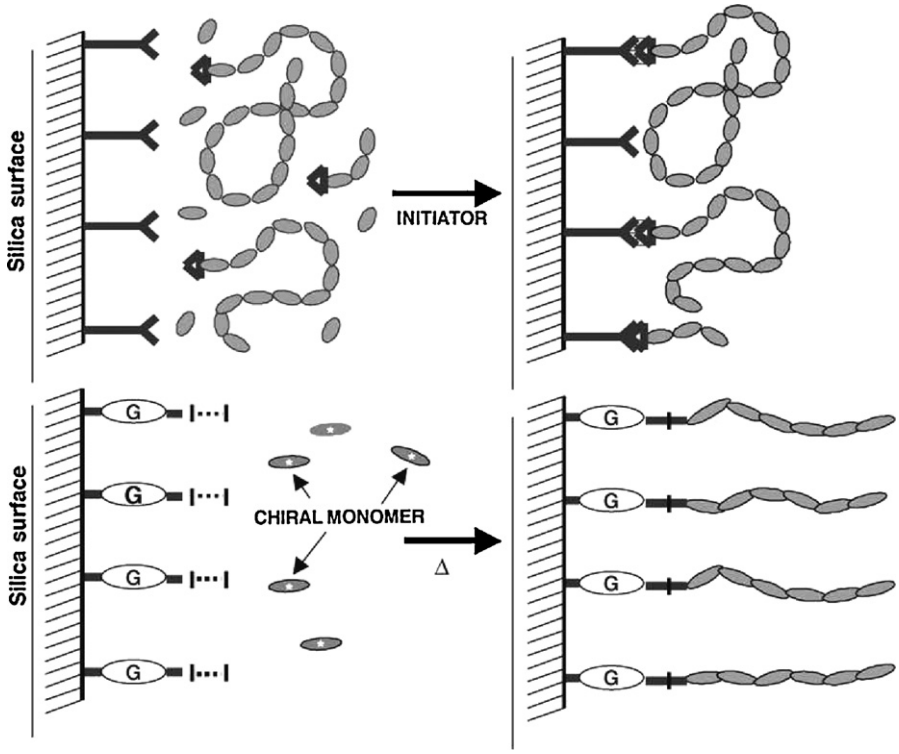


Fig. 13. Schematic representation of g-to (top) and g-from (bottom) polymerization approches. [280].

their chemical properties, in particular with respect to the π-acid or π-basic character. In spite of this, the authors did not find a straightforward correlation between linker properties and CSP performances; the enantiomers of mandelic acid and its analogs were separated on a CSP derived from 4-(3,5-dinitrobenzamido) tetrahydrophenanthrene [288]; unusual dendrimer-type CSPs based on the selector of (1S,2R)-(+)-2-amino-1,2-diphenylethanol derivate were prepared and characterized by HPLC [289]; Sun et al. [290] report about CSPs based on ruthenium tris(diimine) complexes and their use to separate binaphthyl compounds in normal phase mode and acidic species in polar organic mode; diastereomeric right- and left-handed helical poly(phenyl isocyanide)s bearing L-alanine pendants immobilized on silica gel were evaluated as CSP for the separation of cyclic ether, carbonyl compounds, cyclic dianilides and dibenzamides and racemic metal acetylacetonate complexes [291]. Interestingly, the left- and right-version of the CSP exhibited complementary enantioresolution abilities and, in some cases, the elution order of enantiomers was reversed in the two CSPs indicating that helicity of the L-alanine-bound-polyisocyanides played a critical role in the enantioselectivity.

15. New perspectives

The development of chiral separations by HPLC is continuing to attract interest. This not only regards the preparation of new chiral materials to be employed as CSPs but also the use of new technological advances in material and column preparation.

Among the different classes of chiral selectors one of the most promising is, in the opinion of the authors of this review, the class of asymmetric organocatalysts [292,293]. These are metal-free, low-molecular-weight organic molecules either of natural origin readily available from the "chiral pool" (amino acids, short peptides, and alkaloids, etc.), or synthetically prepared. They are usually robust, inexpensive and compatible with many kinds of solvents. Therefore, for the easy of manipulation and the high tunability of their chemico-physical properties, these molecules possess all requisites necessary to be successful targets for the preparation of new CSPs. Today, organocatalysts are deeply investigated and utilized in a different area of chemistry, that is organic synthesis (asymmetric catalysis), in virtue of their activity as promoters of a variety of stereoselective transformations. On the other hand, in many instances, organocatalysts can be regarded as "simplified" or "minimum" versions of metal-free enzymes and it has been demonstrated that the mechanisms of enzymatic catalysis apply to organocatalysts as well. It is now tempting to investigate whether the mechanisms of chiral induction due to organocatalysts (asymmetric synthesis) might be exploited for chiral discrimination (chiral chromatography) with their immobilized counterparts. Indeed, some organocatalysts (such as proline and quinine) have been already employed as CSPs for years [251–254,269,270,272]. However, there are many other molecules belonging to the class of organocatalysts to be evaluated as chiral selectors. "Privileged structures" are: thioureas, TADDOls, BINOls, and phosphoric acids, which are hydrogen-bond donors, eventually coupled with bases such as Cinchona alkaloids to generate highly active bifunctional species. In addition, even for some organocatalysts already employed to prepare CSPs for HPLC, some aspects can be further investigated on the basis of the above catalysis-discrimination parallelism. This is the case, for instance, of proline-based CSPs. All proline-based CSPs described in literature (see, for instance, references [268–270,272]) were obtained by covalently linking the chiral molecule to an inert support through the carboxylic functionality of proline. The activity of proline as asymmetric organocatalyst, however, has been recognized to be connected to the availability of both the amino and the carboxylic functionalities [294,295]. In light of these results, it seems important to prepare CSPs in which both moieties of the molecule will be preserved during the ligation process [295].

Important technological advances will affect the field of chiral separations by HPLC. In particular, we think about the relevant improvements in the technology of preparing and packing sub 2-μm and core–shell particles. The first examples of sub-2 μm CSPs

have already been published [177]. Following what happened for non-chiral phases, in the next future, it is expected an outstanding production of columns packed with already known- or new-CSPs with these geometrical characteristics. The gain in separation efficiency achievable with these materials [296–299] will definitely be beneficial also for chiral separations, as resolution increases by increasing efficiency.

Another, more fundamental aspect that in our opinion could be very relevant to the further development of liquid chiral chromatography is connected to a deeper understanding of the role of solvent. Even though it is well known that a solvent may completely change the performances of a chiral separation [300] – sometimes even inducing changes in the elution order of enantiomers – systematic studies on the role of solvents have not been yet performed [61]. On the other hand, these studies will eventually lead to new information for the understanding of chiral separations. In normal-phase chromatography, the most often employed mode for chiral separation, polar solvents (the so-called strong modifiers or additives) are added to the mobile phase to control analyte retention [301]. Solvent molecules are always present at a concentration far in excess of the analyte [61,281,301,300]. They may affect chromatographic separations through different mechanisms, such as competition for the adsorption on the stationary phase, by changing analyte solubility, or even through secondary equilibria formation (solute solvation, complex equilibria, etc.) [302–305]. In order to understand the role of solvents, their adsorption isotherm (excess isotherm) should be measured [300]. Through these measurements it is possible to gather extremely important information such as the adsorption binding constants of solvent molecules on the adsorption sites, the coverage degree, the structure of the layer of solvent adsorbed molecules. Eventually, the adsorption behavior of the strong solvent could be modeled and the strong solvent used in a similar way as in so-called elution-modified displacement chromatography of trace components [306–310], where the strong modifier and the analytes are injected together, in a column equilibrated with the pure weak solvent, to exploit the displacement effect played by the strong solvent able to induce considerable increase of the apparent column efficiency [300].

Acknowledgements

This work has been supported by the Italian University and Scientific Research Ministry (CHEM-PROFARMA-NET, RBPR05NWWC_008) and by the XVII Executive Program of Scientific and Technological Cooperation between Hungary and Italy.

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