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Review article

Chiral recognition in separation science – an update

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ABSTRACT

Stereospecific recognition of chiral molecules is an important issue in various aspects of life sciences and chemistry including analytical separation sciences. The basis of analytical enantioseparations is the formation of transient diastereomeric complexes driven by hydrogen bonds or ionic, ion-dipole, dipole-dipole, van der Waals as well as π-π interactions. Recently, halogen bonding was also described to contribute to selector-selectand complexation. Besides structure-separation relationships, spectroscopic techniques, especially NMR spectroscopy, as well as X-ray crystallography have contributed to the understanding of the structure of the diastereomeric complexes. Molecular modeling has provided the tool for the visualization of the structures. The present review highlights recent contributions to the understanding of the binding mechanism between chiral selectors and selectands in analytical enantioseparations dating between 2012 and early 2016 including polysaccharide derivatives, cyclodextrins, cyclofructans, macrocyclic glycopeptides, proteins, brush-type selectors, ion-exchangers, polymers, crown ethers, ligand-exchangers, molecular micelles, ionic liquids, metal-organic frameworks and nucleotide-derived selectors. A systematic compilation of all published literature on the various chiral selectors has not been attempted.

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1. Introduction

Stereospecific recognition of chiral molecules is an important issue in various aspects of chemistry and life sciences. With regard to analytical separation sciences, chromatographic techniques including gas chromatography (GC), (ultra) high-performance liquid chromatography (U)HPLC as well as super- and subcritical fluid chromatography (SFC) or capillary electromigration techniques such as capillary electrophoresis (CE), electrokinetic chromatography (EKC), micellar electrokinetic chromatography (MEKC), microemulsion electrokinetic chromatography (MEEKC) and capillary electrochromatography (CEC) have been employed. Most often, the so-called direct approach has been realized, in which stereoisomers, in most cases enantiomers, are separated in a chiral environment containing a chiral selector either fixed to an immobile support or added to the mobile phase or background electrolyte in chromatographic or electromigration techniques, respectively. This approach is based on the formation of transient diastereomeric complexes between the selector and the analyte enantiomers in thermodynamic equilibria.

While countless publications have appeared in the literature on the application of analytical enantioseparations, for example, in pharmaceutical analysis, food chemistry, environmental chemistry, clinical chemistry or synthetic and analytical chemistry, just to name a few, the underlying mechanisms responsible for the observed chiral separations are not fully understood. Therefore, further techniques have been used in combination with analytical separation techniques in order to elucidate the interactions between a chiral selector and the solutes. Especially NMR spectroscopy has proved to be valuable because techniques such as nuclear Overhauser effect spectroscopy (NOESY) and rotating-frame Overhauser enhancement spectroscopy (ROESY) allow conclusions about the spatial proximity of functional groups of selector and selectand. However, this approach is essentially limited to soluble selectors. Further spectroscopic techniques that have been utilized include UV spectroscopy, fluorimetry, Fourier transform and attenuated total reflectance IR spectroscopy, circular dichroism, and vibrational circular dichroism. X-ray crystallography yields the structure of the complexes in the solid state but these may not necessarily be identical to the complexes in solution. Furthermore, molecular modeling approaches have been used to illustrate selector-selectand complexes. Systematic variations of the analyte structure were applied to deduce structure-separation relationships.

The present review summarizes the literature published on chiral recognition mechanisms in analytical separation sciences published between 2012 and April 2016. Considering the multitude of compounds that have been evaluated as chiral selectors, a review on the topic cannot be complete. Thus, only frequently used types of selectors where progress has been achieved in recent years have been addressed but some new developments and additional aspects were included. Compilations of previous studies on chiral recognition mechanisms can be found in [1–6]. Furthermore, reviews on chiral selectors in chromatography [7–9] and CE [10–12] have been published in the considered period of time. General summaries on enantioseparation techniques can be found in reference [13] and a monograph [14].

2. Aspects of complex formation

The formation of the transient diastereomeric complexes between a chiral selector and a selectand is accomplished via diverse intermolecular interactions including ionic interactions, ion-dipole or dipole–dipole interactions, π-π interactions, van der Waals interactions and hydrogen bonds. The various types of interactions for the formation of (chiral) supramolecular complexes have been summarized [15]. Strong, long-range interactions such as ionic interactions are often believed to be primarily involved in the initial, non-stereoselective binding of analyte enantiomers to the selector because they are formed in the case of both enantiomers. In contrast, short-range directional interactions such as hydrogen bonds and π-π interactions would be primarily responsible for stereoselective binding. Moreover, steric factors resulting from the spatial arrangement of the binding cavity or cleft of the selector may contribute to chiral recognition. A conformational change of the selector upon binding of the selectand may also be considered. In addition to the intermolecular interactions, the expulsion of so-called high-energy water from the cavities of concave or barrel- and cup-shaped molecules such as cyclodextrins, calixarenes or cucurbiturils may play a role in the formation of (chiral) complexes. The cavities of these host molecules are occupied by water molecules with the number depending on the size of the respective cavity. These water molecules are “unorganized” due to the fact that only a limited number of hydrogen bonds are possible so that they cannot form a stable hydrogen-bonded network. Consequently, there is a strong enthalpic driving force for complex formation with guest molecules because this will expel the water molecules into the bulk phase where they can form more hydrogen bonds. For a discussion of the hydrophobic effect in complex formation see [16].

In chromatography, besides stereoselective interactions between a selector and the analyte enantiomers, non-stereoselective adsorption of the solutes to the solid support may occur and also contribute to the retention behavior of analytes. In an ideal situation, only enantioselective interactions, i.e. interactions with the chiral selector, occur. This situation is also referred to as a “single-site chiral stationary phase”. However, real adsorbents are displaying enantioselective (chiral selector) as well as non-enantioselective sites (e.g., the achiral support). Chromatography of such “real” adsorbents has been described by two-site models composed of one stereoselective and one nonselective site and multi-site models with 2 to N adsorption sites, which may be either selective or non-stereoselective. Furthermore, so-called secondary equilibria exist which are not directly related to adsorption to the stationary phase but may include analyte dimerization or dissociation. Finally, the solvent may adsorb to the stationary phase or participate in solute complexation. Enantioselective and non-enantioselective adsorption in chiral chromatography has been discussed and summarized by Asnin [17]. For brush-type chiral stationary phases, a method for the quantitative assessment of stereoselective and non-stereoselective interactions has been described [18]. It is based on the evaluation of the adsorption equilibrium constants obtained for chiral solutes on a series of columns packed with stationary phases containing different loading amounts of the chiral selector. As a prerequisite, the adsorption characteristics of the solutes do not change with increasing selector concentrations. The protocol also allowed to detect variation in non-enantioselective interactions, which occurred upon changes of the elution mode [18].

3. Chiral selectors

Below, recent studies on the recognition mechanisms of chiral selectors towards analyte enantiomers will be addressed. As stated above, given the multitude and diversity of potential chiral selectors and their interaction with chiral solutes, the discussion will focus on the most important selectors applied in (analytical) enantioseparation techniques. Studies involving enantioseparations were primarily considered but some publications describing only theoretical approaches will be addressed as well. Furthermore, new developments of chiral selectors will be discussed. An