3 Chiral liquid chromatography: past and present

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3.1 Historical perspectives

Around 1812, the French physicist Biot discovered the existence of optical activity in crystals of a-quartz (O’Loane, 1980). Credit for the first resolution of enantiomers from a racemate goes to Louis Pasteur who, in 1848, separated manually the non-identical crystals of the enantiomers of sodium ammonium tartrate (Pasteur, 1848). In 1874, Le Bel and Van’t Hoff independently proposed the ‘asymmetric carbon atom’ to account for the chirality of organic compounds. Le Bel (1874) favoured a square pyramidal arrangement of substituents around an apical carbon atom whereas Van’t Hoff (1874) correctly postulated a tetrahedral arrangement around a central carbon atom. Not surprisingly, early attempts to obtain resolution of racemates utilized readily-available, naturally-occurring chiral materials such as wool, silk, quartz and polysaccharides such as starch or cellulose. At the turn of the century, WilsHitter (1904) postulated that it should be possible to resolve racemic dyes in solution by enantioselective adsorption onto wool.

Partial resolution of an optically active aniline dye using wool was achieved by Ingersoll and Adams (1922) but a similar claim by Porter and Ihrig (1923) could not be confirmed by independent studies (Brode and Adams, 1926; Henderson and Rule, 1939). Recently, Konrad and Musso (1984) found no resolution of Porter and Ihrig’s dyes on wool although partial resolution was obtained on powdered silk or potato starch used as chromatographic adsorbents. An investigation into the use of naturally-occurring chiral materials as chromatographic adsorbents led to the conclusion that potato starch (and cellulose triacetate, to be discussed later) was useful but that wool, silk and cellulose were unsuitable (Konrad and Musso, 1986). Column chromatography with lactose as the adsorbent was successfully employed by Henderson and Rule (1939) for the resolution of a racemic camphor derivative and by Prelog and Wieland (1944) for the resolution of Tröger’s base. Early uses of quartz in chiral resolution include the partial resolution of racemic cobalt complexes by Tsuchida and co-workers (1936) who allowed saturated solutions of the complexes to cool over d- or l-quartz. Shortly thereafter Karagunis and Coumoulos (1938) chromatographed a racemic cobalt complex on optically active quartz.

The classical method for the resolution of enantiomers involves reaction of the racemate with an optically active reagent to form a pair of diastereomers...
which have different physical properties. After separation of the diastereomers, for example by fractional crystallization or by chromatography (using achiral stationary and mobile phases), the individual enantiomers have to be retrieved from the diastereomers. Apart from being tedious, the method requires the availability of a suitable functional group in the racemate as well as sufficient quantities of optically pure reagent. In addition, there is always the problem of racemization during diastereomer formation or retrieval of the individual enantiomers. Direct chromatographic methods for chiral resolution (i.e. those which do not require prior formation of diastereomers) are based on the formation of transient diastereomeric adsorbates by making available in either the stationary phase or the mobile phase an optically active component (the chiral selector).

The first direct resolution of enantiomers by gas chromatography (GC) was achieved by Gil-Av et al. (1966) using an optically active stationary phase coated onto a 100-m capillary column. However, compared to HPLC, GC has the disadvantage that the higher operating temperatures required may lead to racemization of both the chiral stationary phase (with concomitant loss of chiral selectivity) and of the enantiomers to be separated. In the chromatographic methods, the covalent bond of a true diastereomer is replaced by the transient interaction between the chiral selector and the enantiomers of the racemate. If one enantiomer interacts more strongly with the chiral selector then it will be more strongly retained on the column and hence chromatographic selectivity ($\alpha > 1$) is achieved.

Whereas the direct resolution of enantiomers was relatively rare even two decades ago, there now exists an abundance of different LC solutions to this problem. This situation is a result of two factors, namely the breakthrough in HPLC technology in the late 1960s along with the insights gained into the chiral selection mechanism by Pirkle and others. The advent of modern HPLC in the late 1960s was made possible by the development of appropriate hardware (such as pumps, low dead-volume injectors and detectors) for fast, efficient LC. Of particular relevance to the chiral stationary phases (CSPs) currently being exploited were the advances made in the HPLC packing materials. Polymeric materials such as cellulose or polystyrene resins, being compressible, were not suitable for the higher operating pressures of HPLC and furthermore, their mass transfer characteristics were poor. These problems were overcome with the advent of the mechanically-stable, superficially porous supports in which a thin layer of silica was grafted on to the surface of glass beads, thereby reducing diffusion distances. These materials were further improved with the advent of commercially-available small diameter, porous silica particles (3–5 $\mu$m). The increasing popularity of HPLC in the 1970s has been well documented (Snyder and Kirkland, 1974; Pryde and Gilbert, 1979). The advantages of the HPLC packing materials have been incorporated into CSPs where modern phases are available with silica-bonded cellulose, proteins or synthetic chiral selectors.