



# Dedicated comparisons of diverse polysaccharide- and zwitterionic *Cinchona* alkaloid-based chiral stationary phases probed with basic and ampholytic indole analogs in liquid and subcritical fluid chromatography mode<sup>☆</sup>

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## ABSTRACT

Normal phase (NP) high-performance liquid and sub- and supercritical fluid chromatographic (both acronymed as SFC) methods have been developed for the enantiomer separation of three basic and three ampholytic structurally related C-3-substituted indole analogs on seven non-ionic (neutral) polysaccharide-based and two chemically entirely different zwitterionic *Cinchona* alkaloid- and sulfonic acid-based chiral stationary phases (CSPs). In a systematic fashion the effect of the composition of the mobile phase, the nature of the alcohol and amine additives on the retention characteristics and enantioselectivity of the ionizable analytes were investigated. On all studied polysaccharide-based CSPs the three ampholytes remained unretained in NP-LC mode, while they were nicely retained and resolved in SFC mode. These unexpected results underline a specific property of liquid CO<sub>2</sub> as bulk solvent in combination with alcohols as co-solvents and amine additives thus creating an environment around the chiral selector sites which support the retention of ampholytes. The zwitterionic CSPs worked equally well for the resolution of the basic and ampholytic analytes using a polar ionic mobile phase in both LC and SFC modes.

Results acquired by studying the effect of temperature were used to calculate the changes in standard enthalpy  $\Delta(\Delta H^\circ)$ , entropy  $\Delta(\Delta S^\circ)$ , and free energy  $\Delta(\Delta G^\circ)$  applying van't Hoff plots. The values of the thermodynamic parameters depended on the nature of selectors, the structure of analytes and the properties of the mobile phases. On polysaccharide-based CSPs and columns operated in NP-LC mode enthalpically-, whereas in SFC mode both enthalpically- and entropically-driven enantiomer separations were observed.

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## 1. Introduction

Indole derivatives and particularly the ones with the  $\beta$ -carboline skeleton are widely distributed in nature and many of them dis-

play important biological activities. Moreover, a vast number of natural and synthetic indoles have found applications as pharmaceuticals [1,2] due to their diverse biological and pharmacological activities [3–8]. Because of this, the synthesis and functionalization of indoles have become hot topics of organic synthesis in recent decades [9–11]. Most of these new indole derivatives have chiral elements within their structure which requires the resolution of the enantiomers to fully characterize them.

For analytical and preparative separation of enantiomers, LC-based direct methods utilizing chiral stationary phases (CSPs) are applied most frequently and became a routine methodology in

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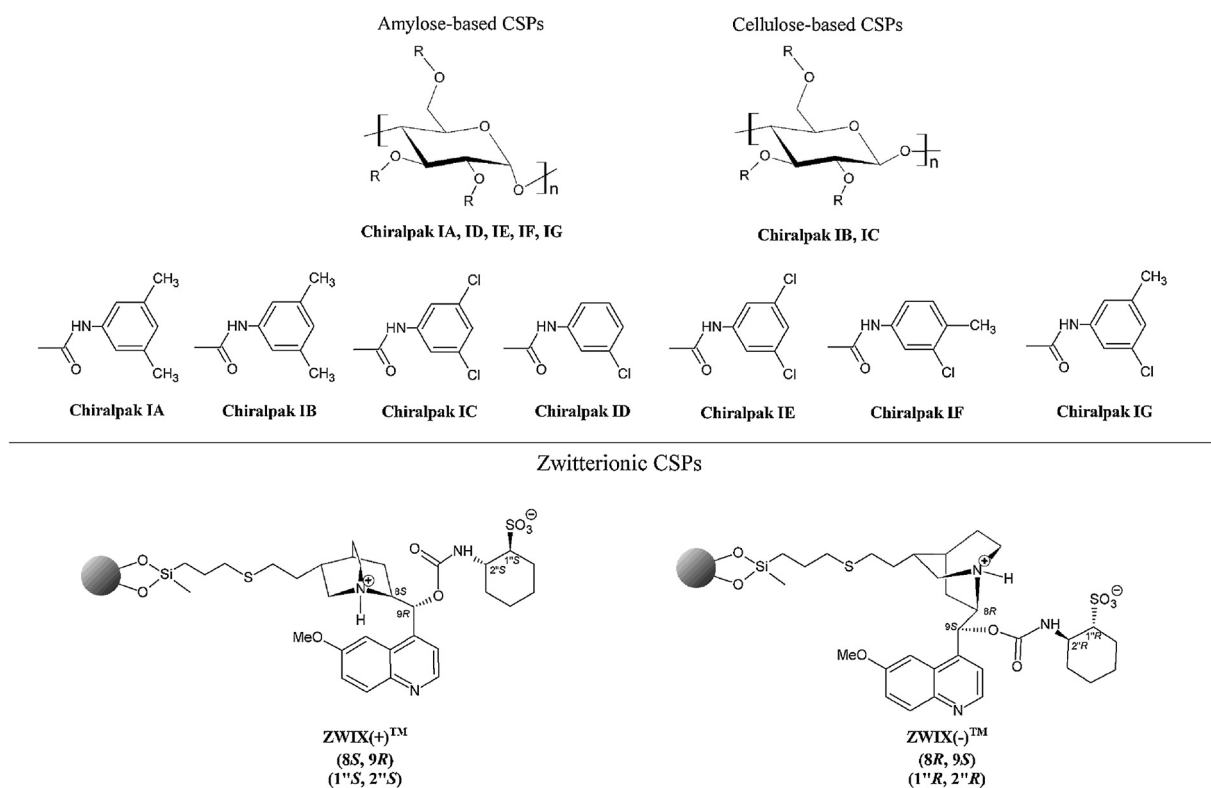


Fig. 1. Structure of the applied chiral selectors and CSPs.

industry and academia [12]. However, for chiral separations, nowadays SFC is also becoming a more and more popular technique [13–20]. It is important to highlight the fact that despite of the dynamically growing scientific results and published literature on SFC, fundamental studies are still lacking, however, an excellent study describing several aspects of SFC has been published recently [21].

Concerning the operational conditions of SFC and their consequences on chromatographic parameters in comparison to LC conditions it is of essence to take the effects of the back pressure, the co-solvents and the temperature on the property of the pressurized liquid CO<sub>2</sub> containing mobile phase into consideration [22]. Using amines as additives their effects, particularly in context with the property and the thickness of the adsorbed layer formed on the surface of the stationary phase (which may be significantly more polar as the bulk mobile phase) should also be considered [23]. Recently Fornstedt *et al.* demonstrated very clearly the combined mobile phase property effect to be encountered of SFC-type operational conditions in context with the enantiomer separation of basic drugs using a polysaccharide-type CSP. It became evident that the normal phase (NP) retention and selectivity rules may not apply to the SFC conditions due to the fundamentally different operational properties of the mobile phases [24].

The aim of the present study was twofold. Firstly, to screen two chemically entirely different sets of CSPs, (i) neutral and non-ionizable but moderately polar polysaccharide-based CSPs, and (ii) polar and ionizable brush-type zwitterionic CSPs (Fig. 1) for their capability to resolve the three basic and three ampholytic chiral indole-type analytes (depicted in Fig. 2) in LC-mode. Secondly, to investigate the same CSPs and analytes when operated with SFC conditions.

Among numerous commercially available CSPs and “chiral columns” the polysaccharide-type phases are nowadays the most popular ones whereby recent innovations have led to the avail-

ability of immobilized polysaccharide-based CSPs with extended solvent compatibility and ruggedness. Compared to the neutral polysaccharide-based CSPs, the *Cinchona* alkaloid-based zwitterionic chiral selectors and CSPs, respectively, provide intrinsically ion-pairing and thus ion-exchange capabilities for cationic, anionic and ampholytic selectands. Although the neutral polysaccharide-type CSPs lack this property their excellent and wide application spectrum for the resolution of neutral, basic and acidic analytes has already been proven. The zwitterionic chiral selectors and CSPs do also allow enantiomer separation of a remarkably broad spectrum of ionizable chiral analytes ranging from acidic to basic and zwitterionic compounds, however, on a molecular basis the mechanisms causing retention and enantioselectivity will differ significantly from those of polysaccharide-type CSPs [25–28].

In this work, we present results obtained on enantioseparation of six structurally related C-3-substituted chiral indole analogs of basic or ampholytic character (see Fig. 2) on two structurally different sets of CSPs operated in LC and SFC conditions. The influence of mobile phase composition, different additives, the structure of chiral selectors and selectands (analytes), and the effect of temperature on the retention and separations of stereoisomers are described. On the basis of the obtained results, similarities and differences between LC and SFC mobile phase conditions are discussed also in the light of the above raised arguments for the use of liquid CO<sub>2</sub> in combination with alcohol as mobile phase co-solvent leading to subcritical fluid chromatography conditions. Focus was given towards mechanistic details of chiral recognition phenomena in context to the two different operational modes (LC vs SFC) and effects of mobile phase composition on the chromatographic behavior. It is important to realize that radial and axial temperature gradients in the column affect thermodynamics of adsorption and result in volumetric flow rate gradient through the column [29–31]. The problem of calculating the real operational conditions in SFC (in opposite to LC where the set values

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