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Insights into the impact of shape and electronic properties on the enantioseparation of polyhalogenated 4,4′-bipyridines on polysaccharide-type selectors. Evidence of stereoselective halogen bonding interactions

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ABSTRACT

Starting from the high-performance liquid chromatography (HPLC) enantioseparation data collected by using twelve polyhalogenated 2,2′-dichloro-3-substituted-5,5′-dihalo-4,4′-bipyridines as test probes on seven polysaccharide-based chiral stationary phases (CSPs) under multimodal elution, the impact of substitution pattern, shape and electronic properties of the molecules on the separation behaviour was investigated through the evaluation of the chromatographic parameters (k, α, R_s) and molecular properties determined by means of quantum chemistry calculations. The computational/chromatographic screening furnished relevant structure-chromatographic behaviour relationships and some molecular interactions involved in the chiral discrimination process could be identified. In particular, a halogen bonding interaction (I·O) could reasonably explain the high enantioseparation ($\alpha = 1.80$, $R_s = 8.2$) observed for the 2,2′-dichloro-3,5′-diiodo-5-bromo-4,4′-bipyridine on Lux Cellulose-1. To the best of our knowledge, this is the first report supporting the involvement of a stereoselective halogen bonding interaction in polysaccharide-based CSPs. Moreover, having at disposal a sufficient set of data, the unknown absolute configurations of the eluted enantiomers of 3-methyl-, 3-thiomethyl- and 3-diphenylphosphinoyl-2,2′-dichloro-5,5′-dibromo-4,4′-bipyridines could be deduced by chromatographic correlation with the enantiomer elution order (EEO) of the related compounds of known absolute configuration.

1. Introduction

In the last decades, cellulose and amylose derivatives (aromatic carbamate and benzoate) have been widely used for HPLC enantioseparations and several classes of chiral compounds have been successfully enantioseparated on polysaccharide-based chiral columns [1–3]. The high versatility of these families of macromolecular selectors is mainly due to their polymeric structure where molecular, conformational and supramolecular chirality cooperate to determine the separation outcome [4,5]. Conformational chirality depends on the peculiar helical twist generated by the D-glucose residues with β-1,4 linkage in cellulose or α-1,4 linkage in the amylose polymeric chain. The basic structural components of polysaccharide-based selectors are the backbone, namely cellulose or amylose, and the aromatic carbamate or benzoate side chains characterized by distinctive steric and electronic properties which can be tuned by changing type and position of the substituents onto the terminal aromatic ring. Previous studies [4–9] proved that polysaccharide-based selectors are schematically characterized by (a) a polar layer containing groups able to exert hydrogen bonding (HB) and dipole–dipole interactions, located inside the polymer chain, and (b) a hydrophobic layer containing substituted aromatic rings (Ar), located outside the polymer chain and able to exert π–π interactions (Fig. 1). Both backbone and side chains

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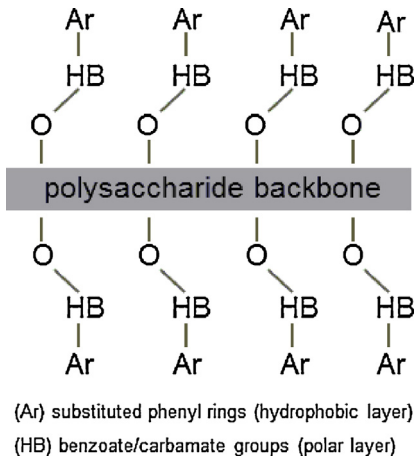

Fig. 1. Structural pattern of the polysaccharide-type selectors (HB hydrogen bonding moiety, Ar aromatic ring).

contribute to form chiral cavities into the groove which can match shape and size of the analyte, so favouring its stereoselective fit [6,7]. Thus, a multitude of interactions can potentially occur in the polysaccharide-type chiral stationary phases (CSPs) but, as matter of fact, only some of these interactions act to recognize the enantiomers of a given chiral analyte depending on its particular structure, size and shape. In this molecular context, the mobile phase (MP) can modulate strength and quality of the molecular recognition process [7,10,11].

Recently, we have focused our interest on the preparation of atropisomeric 4,4′-bipyridines, a new generation of promising organic bridging ligands for building homochiral metal organic frameworks (MOFs), a class of organic-inorganic hybrid materials built from metal-connecting nodes and organic-bridging ligands [12]. The chemistry of atropisomeric 4,4′-bipyridines is in its infancy and, to date, only few examples are reported in the literature [13–15]. For this reason, no asymmetric synthesis to produce enantiopure 4,4′-bipyridines is available. Even nowadays pure enantiomers can be obtained only by separating racemate mixtures of synthesized compounds and, for this purpose, high-performance liquid chromatography (HPLC) methods can play a key role in the research plan development. In our previous work, the HPLC technique was used to enantioseparate atropisomeric 3,3′-dibromo-5,5′-disubstituted-4,4′-bipyridines at multimilligram scale [16,17] by using polysaccharide-based chiral columns which are known to efficiently enantioseparate molecular systems featuring a chiral axis as exclusive source of molecular dissymmetry [18,19]. Recently, the new family of chiral polyhalogenated 4,4′-bipyridines **1**–**12** was prepared by our group (Table 1) [15]. These compounds present interesting structural characteristics to design chiral ligands able to drive the topology as well as the stereochemistry of new MOF materials: (i) the substituents surrounding the chiral axis make the chiral 4,4′-bipyridines conformationally stable; (ii) the chlorine substituents at 2 and 2′-positions are able to sterically and electronically control the nitrogen sites; (iii) the presence of halogen atoms of different nature offers the possibility to selectively tune the reactivity of the 4,4′-bipyridine system; (iv) thus, the halogenated scaffold is suitable for selective transformations, opening the way to more complex and interesting structures [20].

On these bases, the selectivity of cellulose- and amylose-based CSPs towards the polyhalogenated 4,4′-bipyridines **1**–**12** was investigated under multimodal elution and twenty CSP/elution mode combinations were checked. The chromatographic performances of analytes and CSPs were expressed as rate of baseline ($R_s \geq 1.5$) separation (r.b.s.) (Table 1). Starting from the collected chromatographic results, the identification of the involved molecular interactions between the polysaccharide selector and the analyte enantiomers appeared essential for understanding some aspects of the enantiorecognition processes and approaching further enantioseparation tasks into the field.

Thus, analytes, CSPs and MPs were considered as experimental variables and examined individually, on the basis of the following preliminary remarks:

(i) compounds **1**–**12** were considered as test probes inside the columns and the influence of a specific functional group on retention and selectivity could be recognized through the parallel evaluation of retention factors (k), separation factors (α) and resolution (R_s). In fact, the substitution pattern of the series could be correlated by means of the systematic addition or deletion of specific functional groups leading to the identification of subgroups dependent on the characteristics of the 3-substituent. The structure of the analytes was pointed by some chemical functional descriptors (CFDs), which are descriptors given to a molecule in order to characterize or anticipate its chemical behaviour or to identify commonality among molecules with different structures: hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), hydrophobic and aromatic group (Ar);

(ii) the structure pattern of the considered CSPs could be correlated through the systematic modification of certain basic structural elements and, consequently, the effect of side chain substituents (Lux Cellulose-1 vs Chiralpak IC) and backbone (Lux Cellulose-1 vs Chiralpak IA) could be evaluated;

(iii) from the wealth of chromatographic results, focused analyses were carried out in order to evaluate the effect of the structure of the couple analyte/CSP on the enantioseparation. In all studied cases, homogeneous or identical elution conditions were considered in order to ensure a common environment in assisting the interactions under investigation [3,16];

(iv) to investigate in detail on the molecular shapes, which are the sum of geometry and electron distribution, the molecular geometries and the generated molecular electrostatic potential (EP) of the analytes (Supplementary data, Table S1), CSP side chains (Table S2) and solvents (Table S3) were computed at density functional theory (DFT) or Hartree Fock levels of theory. Calculations were performed in the vacuum, thus the solvent effect was not considered. In particular, the computation of properties at the vacuum is a quite realistic situation when non polar hydrocarbon-based eluents are used. Despite calculation in the vacuum can be a poor approximation for a molecule placed in a polar medium, this type of calculations can furnish useful information about the effect of the structure of the analyte by comparing enantioseparations performed under identical polar elution conditions.

On these bases, in this paper we report the main results of the chromatographic/computational study, from which interesting structure-chromatographic behaviour relationships emerged and some molecular interactions involved in the chiral discrimination process could be identified.

Then, considering that similar compounds show the same enantiomer elution order (EEO) when they are enantioseparated through the same recognition mechanism under identical elution conditions [3,16], the unknown absolute configurations of the eluted enantiomers of *rac*-**3**, *rac*-**4** and *rac*-**7** (named *X* and *Y*) were deduced by correlation with the EEO of the related compounds of known absolute configuration.