Journal of Chromatography A, xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Journal of Chromatography A

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

Separation of enantiomers of selected chiral sulfoxides with cellulose tris(4-chloro-3-methylphenylcarbamate)-based chiral columns in high-performance liquid chromatography with very high separation factor

Tamar Khatiashvili [a], Rusudan Kakava [a], Iza Matarashvili [a], Hadi Tabani [b], Chiara Fanali [c], Alessandro Volonterio [d,e], Tivadar Farkas [f], Bezhan Chankvetadze [a,*]

[a] Institute of Physical and Analytical Chemistry, School of Exact and Natural Sciences, Tbilisi State University, Chavchavadze Ave 3, 0179 Tbilisi, Georgia
[b] Department of Environmental Geology, Research Institute of Applied Sciences (ACECR), Shahid Beheshti University, P.O. Box 19396-4716, Evin, Tehran, Iran
[c] Department of Medicine, University Campus Bio-Medico of Rome, Via Alvaro, del Portillo 21, 00128 Rome, Italy
[d] Department of Chemistry, Materials and Chemical Engineering "G. Natta", Politecnico di Milano, Via Mancinelli 7-20131, Milano, Italy
[e] C.N.R. Istituto di Chimica del Riconoscimento Molecolare (ICRM), Via Mancinelli 7, 20131 Milano, Italy
[f] Phenomenex Inc., 411 Madrid Ave., Torrance, 90501 CA, USA

ARTICLE INFO

Article history:
Received 6 January 2018
Received in revised form 17 February 2018
Accepted 25 February 2018
Available online xxx

Keywords:
Separation of enantiomers
Polysaccharide-based chiral stationary phases
Enantioselective extraction
Thermodynamic quantities of adsorption

ABSTRACT

The present study reports successful separations of enantiomers of selected chiral sulfoxides with very high separation factor in high-performance liquid chromatography by using chiral columns prepared with the chiral selector cellulose tris(4-chloro-3-methylphenylcarbamate). High separation factors were observed in polar organic, as well as in hydrocarbon-alcohol-type mobile phases. The key structural components of the solute for obtaining high chiral recognition are discussed as well as thermodynamic quantities of analyte adsorption on the chiral stationary phase were determined. Experiment aimed at the enantioselective extraction of racemates from solution are also described.

1. Introduction

Polysaccharide phenylcarbamates are recognized as one of the most powerful group of chiral selectors for the liquid-phase separation of enantiomers on analytical, preparative and even on production-scale [1–3]. The application of polysaccharide-based chiral selectors together with classical high-performance liquid chromatography [1,2], is also described for the separation of enantiomers in batch low-pressure liquid chromatography [4], recycling mode [5], in different variations of simulated moving bed chromatography [6,7], supercritical fluid chromatography [8–10], nano-liquid chromatography [11–14] and capillary electrochromatography [11–13,15,16]. Despite the widespread application of polysaccharide-based chiral selectors their chiral recognition mechanism is currently not well understood. A lot of effort went over the years into getting more understanding of the underlying mechanisms of enantiomer discrimination with polysaccharide phenylcarbamates by using various experimental, statistical, screening and modelling approaches [17–20], but some major questions still remain unanswered. One of the very early assumptions made by Okamoto and co-workers regarding the key role played by carbamate moieties in chiral recognition with polysaccharide phenylcarbamates has been proven correct and remains undoubtedly valid after more than 3 decades [21]. By considering the carbamate moiety as a key interaction site for chiral analytes and also the effect of electron-donating and electron-withdrawing substituents on the phenyl moiety on the electron density on the carbamate moieties, one of the authors of the current study proposed an effective set of polysaccharide-based chiral selectors about two decades ago which were later commercialized by several companies and are in widespread use today [1,22–24]. In order to gain deeper insight in enantioselective recognition mechanisms involving polysaccharide phenylcarbamates more cases of exceptional behavior of these materials, such

* Corresponding author.
E-mail address: jpba_bezhan@yahoo.com (B. Chankvetadze).

https://doi.org/10.1016/j.chroma.2018.02.054
0021-9673/

as unusually high enantioselectivity, effect of mobile phase modifiers and temperature on elution order of enantiomers, etc. need be carefully studied in hope that these extraordinary effects may provide clues regarding the most critical structural characteristics of analytes and selectors, as well as about the forces involved in enantioselective selector-selectand binding.

Chiral sulfoxides have been identified in a variety of natural products and their synthetic derivatives. Synthetic chiral sulfoxides are widely used as valuable drug compounds (e.g. omeprazole, lansoprazole, pantoprazole, rabeprazole) [25,26], as pesticides (fipronil, propargit, methiocarb sulfoxide, fensulfothion, etc.) [26], chiral auxiliaries and chiral ligands to metals [27,28]. The synthesis of enantiomerically enriched or pure sulfoxides is currently of primary interest [29–31]. The enantioselective biological activity of chiral sulfoxides is well documented and became the reason for developing some of them as enantiomerically pure chiral drugs [25]. For instance, together with racemic omeprazole, its enantiomerically pure analogue, S-omeprazole is used in clinical practice and some other analogues are also under development [9,25]. Chromatographic methods have been used for the separation of enantiomers of chiral sulfoxides for more than 20 years [32–41] and together with analytical- [32–38,40,41], their preparative potential has been proven [38,39]. Polysaccharide-based chiral columns are well suited for the separation of enantiomers of chiral sulfoxides [32,33,36,37,39–41].

In our earlier study, high separation factors exceeding 100 were reported for one of the non-commercial chiral sulfoxidex with cellulose tris(3,5-dichlorophenylcarbamate) as a chiral selector and 2-propanol as a mobile phase [37]. More detailed studies on this group of analytes was impossible because they were not commercially available. In the frame of our on-going project the chiral sulfoxide reported in ref. 37 and many analogues of it were synthesized in order to investigate the effect of structural features of analyte on its enantioselective recognition by polysaccharide phenylcarbamates. This paper reports part of our results in this direction together with the effects of mobile phase composition and temperature on separation of enantiomers.

2. Experimental part

2.1. Materials

2-Mercaptobenzoic acid, benzyl bromide, amines (R-NH2), dioxane, triethylamine(Et3 N), trifluoroacetic acid (TFA), N,N-dimethylformamide (DMF), (benzotriazol-1-yloxy)tris(dimethylamino)phosphoniumhexafluorophosphate (BOP), 3-chloroperoxybenzoic acid (MCPBA), chloroform and anisole required for synthesis of chiral sulfoxides used in this study (Fig. 1) were acquired from Sigma-Aldrich (Milan, Italy). Chiral sulfoxides were synthesized based on general scheme shown in Fig. 2 and previously described in ref. [31]. The reaction of commercially available 2-mercaptobenzoic acid (1) with benzyl bromide was promoted by triethylamine in dioxane to form the corresponding sulfide derivative (2). Next, the carboxylic acid functionally was transformed in the corresponding amide (3) by coupling with methylamine, dimethylamine and 4-methoxybenzylamine. Finally, oxidation of the sulfide group with MCPBA in chloroform at 0 °C led to the formation of the sulfoxides (4), 2-(benzylsulfinyl)-N-methylbenzamide and 2-(benzylsulfinyl)-N,N-dimethylbenzamide, which were purified by flash chromatography on silica gel (silica gel 60, 60–200 μm, Merck, Darmstadt, Germany). The primary benzamide derivative (7), was obtained by deprotection of the corresponding 4-methoxybenzylamide (5) followed by oxidation with MCPBA (Fig. 2).

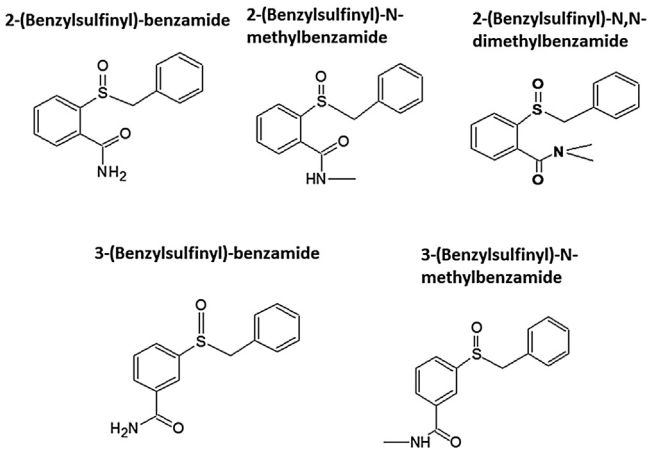

Fig. 1. Structure of studied chiral sulfoxides.

Chromatographic grade acetonitrile, *n*-hexane, methanol and 2-propanol used as mobile phase components were acquired from Carl Roth (Karlsruhe, Germany). Commercially available chiral columns (4.6 × 250 mm, 5 μm particle size) Lux Cellulose-1 (Cellulose tris(3,5-dimethylpnenylcarbamate coated onto silica), Lux Cellulose-3 (Cellulose tris(4-methybenzoate coated onto silica) and Lux Cellulose-4 (Cellulose tris(4-chloro-3-methylpnenylcarbamate coated onto silica) were provided by Phenomenex Inc. (Torrance, CA, USA). Other chiral columns used in this study were laboratory-made by coating appropriate amounts of chiral selector on aminopropylsilanized fully porous silica particles of 5 micrometer nominal particle size and 100 nm nominal pore size or alternatively on superficially porous silica particles with 3.6 micrometer nominal particle size and 20 nm nominal pore size. Silica particles were provided by Phenomenex Inc. Cellulose tris (4-chloro-3-methylpnenylcarbamate was synthesized as described in ref. [22].

2.2. Instruments

All HPLC experiments were performed with an Agilent 1200HPLC instrument (Agilent Technologies, Waldbronn, Germany) equipped with a G1367C HiP ALS-SL autosampler, G1316B TCC-SL temperature controller, G1311A quaternary pump and G1314DVWD variable wavelength detector. The Chemstation software (version B.03.02-SR2) was used for instrument control, data acquisition and data processing. HPLC separations were performed at 20 °C at 1 ml/min mobile phase flow rate if not indicated otherwise. UV-detection was performed at 240 nm. The optical rotation sign of resolved enantiomers of 2-(benzylsulfinyl)-benzamide was assigned based on ref. 37 in which a circular dichroism and polarimetric detectors were sequentially connected to a UV-detector.

2.3. Enantioselective adsorption

Enantioselective adsorption experiments were performed in a thermostated cell having a volume of 100 ml. The cell was immersed in a water bath and temperature was set at 20 °C. Mixing was provided by magnetic stir bar. Two mg of racemic 2-(benzylsulfinyl) benzamide and 1 mg of 1,3,5-tri-tertiary-butylbenzene were dissolved in 50 ml *n*-hexane/2-propanol mixture (70/70, v/v), 10 ml of this solution was diluted with 40 ml of *n*-hexane/2-propanol mixture (70/70, v/v) and placed in the thermostated adsorption cell. Before addition of adsorbent the sample was taken and analyzed for its enantiomeric composition. Afterwards a weighted amount of adsorbent was added under con-

Please cite this article in press as: T. Khatiashvili, et al., Separation of enantiomers of selected chiral sulfoxides with cellulose tris(4-chloro-3-methylphenylcarbamate)-based chiral columns in high-performance liquid chromatography with very high separation factor, J. Chromatogr. A (2018), https://doi.org/10.1016/j.chroma.2018.02.054