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Exploring the enantioseparation of amino-naphthol analogues by supercritical fluid chromatography☆

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ABSTRACT

The direct separation of the enantiomers of 1-(α-aminoarylmethyl)-2-naphthol, 1-(α-aminoalkyl)-2-naphthol, 2-(α-aminoarylmethyl)-1-naphthol analogues and 2-(1-amino-2-methylpropyl)-1-naphthol) was investigated in supercritical fluid chromatography. Five commercially available chiral stationary phases based on immobilized polysaccharide chiral selectors (Chiralpak IA, IB, IC, ID and IE) were evaluated. Chiralpak IB was by far the most efficient to achieve the separation of these racemates and was further selected for optimization of elution conditions. The effects of column temperature (varying between 5 and 45 °C) and co-solvent added to carbon dioxide (methanol, ethanol, isopropanol and dichloromethane) were investigated. A particular attention was paid to mobile-phase additives. Several of them, acids, bases or salts (namely water, formic acid, acetic acid, trifluoroacetic acid, diethylamine, diethanolamine, triethylamine, triethanolamine, dimethylethanolamine, ammonia and ammonium acetate), were tested in order to improve peak shapes while maintaining selectivity. With the help of other achiral naphthol derivatives, the additive effects were examined.

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1. Introduction

Chirality has a significant impact on the interaction between biologically active compounds and their receptor binding sites. Thus, direct preparative chiral chromatography remains the most important and cost-effective approach to resolve synthesized racemates into enantiopure test substances. However, when the most active enantiomer (eutomer) is identified, atom economy requires asymmetric synthesis methods to produce only this molecule. At this stage, chiral chromatography is still necessary to measure enantiomeric purity.

The synthesis and application of new chiral ligands in asymmetric transformations is currently a field of great interest in organic chemistry. With the modified Mannich reaction, Betti achieved a straightforward synthesis of 1,3-diphenylnaphthoxazine in methanol. Acidic hydrolysis of the ring compound produced led to 1-aminobenzyl-2-naphthol. The synthesized aminonaphthol is known in the literature as “Betti base”, and the protocol as the “Betti reaction” [1,2]. Naphthoxazinone derivatives have already received considerable attention because of the interesting pharmacological properties associated with their heterocyclic scaffold. Screening of a virtual database indicated that the N-containing analogues of aminonaphthols, such as 7-[anilino(phenyl)methyl]-2-methyl-8-quinolinol, are a promising new class of non-peptide inhibitors of the MDM2-p53 interaction [3]. The chemical and biological importance of Betti base enantiomers demands highly efficient methods for separation. The resolution of enantiomers may involve classical diastereomeric salt formation, use of chiral auxiliaries, enzymatic resolution, chromatographic methods, *etc.* Aromatic- and aliphatic-substituted 1- and 2-naphthol analogues were separated by normal-phase high-performance liquid chromatography (NPLC) on cellulose-based chiral stationary phases (CSP) by Sztojkov-Ivanov et al. [4,5] and Ilisz et al. [6], or on a β-cyclodextrin-based CSP by Berkecz et al. [8], whereas the separation by capillary electrophoresis was achieved with the application of cyclodextrins and chiral crown ethers [7].

Supercritical fluid chromatography (SFC), qualifying chromatography with mobile phases composed of pressurized carbon dioxide and co-solvents, is a powerful technique for the enantioseparation of a wide range of molecules. CO_2 is by far the most used

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SFC eluent for several reasons: the values of critical pressure and temperature are easily reached, it is available in sufficient quantity and purity, and it is non-flammable and non-toxic. Thus SFC with CO_2 as the major mobile-phase component is often considered as a "green" technology. Moreover, fast and highly efficient separations can be achieved at reasonable pressures due to the low viscosity of supercritical fluids ensuring high diffusivity even at high flow rates [9].

Since CO_2 has a polarity comparable to that of *n*-hexane, polar organic modifiers are required in the mobile phase to increase analyte solubility and reduce analysis time. These modifiers affect the chromatography results, mainly through an increase in the mobile phase polarity and density leading to increased solvent strength. Moreover, so-called "additives"—which are usually basic or acidic substances, or salts—are frequently added to the mobile phase [10]. Indeed, while neutral and acidic compounds are usually well eluted by SFC, basic analytes often set problems with poor peak shapes or strong retention on polar stationary phases. Therefore, mobile-phase additives are usually introduced in the mobile phase to avoid this problem [11–14].

Although more than 1500 chiral stationary phases have been reported in the scientific literature, none of them possesses a universal chiral selector. Based on literature survey, most enantioseparations in SFC were achieved with CSP based on chemically derivatized amylose or cellulose deposited on silica. While the original versions of these columns were made of a coated polysaccharide and are thus the most frequently reported, the immobilized polysaccharide CSP that were introduced more recently are now also often cited [15–18]. They are produced by Daicel Corporation and trademarked as Chiralpak IA, IB, IC, ID, IE and IF. The most important difference between immobilized and coated polysaccharide columns is their robustness and stability to mobile-phase composition. Coated polysaccharides are highly efficient chiral selectors, but the possible co-solvents to use with these columns are limited to weak solvents like short-chain alcohols. The use of stronger solvents like dichloromethane, tetrahydrofuran or ethylacetate would dissolve the polysaccharide thus permanently damaging the column. Immobilized stationary phases in contrast cannot be destroyed by the use of "exotic" solvents, which means new method development with a total freedom of choice of solvents.

Our work presents the enantioseparation of different Betti-base analogues by SFC. The chiral selectors are derivatized amylose or cellulose immobilized onto silica gel. The influence of the chiral selector, mobile-phase composition and temperature on chromatographic performance is described. In addition, a detailed study on the effect of additives (acids, bases or salts) was undertaken.

2. Experimental

2.1. Chemicals

Solvents used in this study were HPLC-grade methanol (MeOH), ethanol (EtOH), iso-propanol (iPrOH) and dichloromethane (DCM) provided by VWR (Fontenay-sous-Bois, France). Additives were diethylamine (DEA), diethanolamine (DEOA), triethylamine (TEA), triethanolamine (TEOA), dimethylethanolamine (DMEOA), ammonia (NH_4OH), ammonium acetate ($AcONH_4$), formic acid (FA), acetic acid (AcOH), trifluoracetic acid (TFA) and were obtained from VWR (Fontenay-sous-Bois, France), Sigma-Aldrich (Saint-Quentin Fallavier, France) and Fisher Scientific (Illkirch, France). Carbon dioxide was provided by Messer (Puteaux, France).

All Chiralpak stationary phases are commercially available. The phases tested were: Chiralpak IA (amylose *tris*-(3,5-dimethylphenylcarbamate)), Chiralpak IB (cellulose *tris*-(3,5-dimethylphenylcarbamate)), Chiralpak IC (cellulose *tris*-(3,5-dichlorophenylcarbamate)), Chiralpak ID (amylose *tris*-(3-chlorophenylcarbamate)) and Chiralpak IE (amylose *tris*-(3,5-dichlorophenylcarbamate)). They were all 150 mm × 4.6 mm. Chiralpak IA and IB were 3 μm, while Chiralpak IC, ID and IE were 5 μm.

Betti-base analogues were prepared by the aminoalkylation of 2-naphthol with benzaldehyde or other aromatic aldehydes in the presence of NH_3 [19] (in some cases, methanolic NH_3 was replaced by ammonium carbamate or ammonium hydrogen carbonate as solid ammonia sources [20] to obtain 1,3-diaryl-2,3-dihydro-1*H*-naphth[1,2-e][1,3]oxazines: **1B-1K** (**1B**, 1-[amino-(4-methylphenyl)methyl]2-naphthol; **1C**, 1-[amino-(4-methoxyphenyl) methyl]-2-naphthol; **1D**, 1-[amino-(4-fluorophenyl)methyl]-2-naphthol; **1E**, 1-[amino-(4-chlorophenyl)methyl]-2-naphthol; **1F**, 1-[amino-(4-bromophenyl)methyl]-2-naphthol; **1G**, 1-[amino-(4-nitrophenyl)methyl]-2-naphthol; **1H**, 1-[amino-(3-bromophenyl)methyl]-2-naphthol; **1I**, 1-[amino-(3-nitrophenyl) methyl]-2-naphthol; **1J**, 1-[amino-(2-thienyl)methyl]-2-naphthol; and **1K**, 1-[amino-(3-thienyl)methyl]-2-naphthol) (Table 1). After that, acidic hydrolysis gave the desired aminonaphthols. 1-(a-Aminoalkyl)-2-naphthol analogues **1L-1O** (**1L**, 1-(1-aminoethyl)-2-naphthol; **1M**, 1-(1-aminopropyl)-2-naphthol; **1N**, 1-(1-aminobutyl)-2-naphthol; and **1O**, 1-(1-amino-2-methylpropyl)-2-naphthol were prepared *via* the reactions of aliphatic aldehydes with 2-naphthol or 1-naphthol in the presence of methanolic NH_3 solution at 60 °C or of ammonium carbamate, yielding dialkylnaphthoxazines. Acidic hydrolysis of these naphthoxazines led to the desired aminonaphthol hydrochlorides (Table 1) [21]. 2-(α-Aminoarylmethyl)-1-naphthols **2A-2F** and **2H, 2I** (**2A**, 2-(α-aminobenzyl)-1-naphthol; **2B**, 2-[amino-(4-methylphenyl)methyl]-1-naphthol; **2C**, 2-[amino-(4-methoxyphenyl)-methyl]-1-naphthol; **2D**, 2-[amino-(4-fluorophenyl)methyl]-1-naphthol; **2E**, 2-[amino-(4-chlorophenyl) methyl]-1-naphthol; **2F**, 2-[amino-(4-bromophenyl)methyl]-1-naphthol; **2H**, 2-[amino-(3-bromophenyl)methyl]-1-naphthol; **2I**, 2-[amino-(3-nitrophenyl)-methyl]-1-naphthol were prepared in a manner similar to that of their regioisomeric 1-(α aminoarylmethyl)-2-naphthol counterparts [22]. Analytes **3A-3S** (Table 1) were commercially available and obtained from Sigma-Aldrich (Saint-Quentin Fallavier, France). Solutions of all these compounds were prepared in methanol (MeOH). The stock solution was 1.0 mg/ml concentration while the 100 μg/ml diluted solutions were injected.

2.2. Instrumentation and chromatography

The Waters Acquity Ultra Performance Convergence Chromatography™ (UPC²) system was equipped with a binary solvent delivery pump compatible with mobile-phase flow rates up to 4 mL/min and pressures up to 400 bar, an autosampler which included partial loop volume injection system, a backpressure regulator, a column oven (compatible with 150 mm length columns) and a PDA detector. The Empower software was used for system control and data acquisition. The mobile phase used in this study is CO_2–co-solvent 80:20 (v/v) with co-solvent comprising 20.72 mM of various additives. Flow rate was 3 mL/min. Temperature was set at 25 °C (apart from temperature studies where it was varied from 5 to 45 °C) and the outlet pressure was maintained at 150 bar for all columns. Retention factors (k) were calculated based on the retention time t_R, determined using the peak maximum (even when tailing did occur) and on the hold-up time t_0

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