Journal of Chromatography A, 1316 (2013) 119–126

Contents lists available at ScienceDirect

Journal of Chromatography A

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

Investigation of the synergistic effect with amino acid-derived chiral ionic liquids as additives for enantiomeric separation in capillary electrophoresis

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ARTICLE INFO

Article history:
Received 10 February 2013
Received in revised form
14 September 2013
Accepted 17 September 2013
Available online 25 September 2013

Keywords:
Chiral ionic liquids
Capillary electrophoresis
Amino acid-derived ionic liquids
Chiral separations

ABSTRACT

Recently, chiral ionic liquids (ILs) have drawn more and more attention in chiral separation by capillary electrophoresis (CE). In this paper, two chiral ILs based on amino acid derivatives, L-alanine and L-valine *tert* butyl ester bis (trifluoromethane) sulfonimide, were applied for the first time in CE to evaluate their potential synergistic effects with classical chiral selectors (β-cyclodextrin derivatives) for enantiomeric separation. As observed, improved separation of tested drug enantiomers was obtained with the presence of chiral ILs compared to the conventional β-cyclodextrin derivatives separation system. Parameters such as type and proportion of organic modifier, type and concentration of chiral ILs, concentration of chiral selector, buffer pH and applied voltage were systematically investigated with Me-β-CD/chiral ILs as model system to optimize the novel synergistic system, and the best results were obtained when 15 mM chiral ILs were introduced into the 30 mM sodium citrate/citric acid (20% organic modifier included) buffer solution containing 20 mM Me-β-CD at pH 5.0 with a 20 kV applied voltage for naproxen, pranoprofen and warfarin.

1. Introduction

Enantiomeric separations represent a critical subject in pharmaceutical analysis, because enantiomers of a racemic drug usually display markedly different pharmacological activities. For this reason, establishment of rapid, selective and effective analytical methods has aroused a considerable need to verify the enantiomeric purity of chiral drugs. Recently, applications of capillary electrophoresis (CE) in chiral separation have been increasing owing to its simplicity, high efficiency and low cost, as well as its high flexibility in selecting types of chiral selectors [1–5]. A variety of compounds including native β-cyclodextrins (β-CDs) and their derivatives [6], polysaccharides [7–9], antibiotics [10–13] and polymeric surfactants [14,15] have been effectively used as chiral selectors in CE. In some cases, however, utility of one single chiral selector to establish enantioseparation system is not enough to achieve satisfactory separation results. Consequently, the combination of more than one chiral reagent to improve chiral separation has drawn increasing attention in recent years [4,6].

Ionic liquids (ILs) are a group of organic salts with melting points (mp) below 100 °C or more often even close to room temperature [16]. They present unique physical and chemical properties, including lack of measurable vapor pressure, high thermal stability, strong solubility power and non-toxicity or relatively lower toxicity [17,18]. ILs have successfully been applied to various areas, such as replacing conventional organic solvent in organic or inorganic synthesis, solvent extractions, electrochemical reactions, liquid–liquid extractions, as a medium in enzyme reaction [19–21], stationary phases in gas chromatography [22,23], mobile phases additive in liquid chromatography [24,25] and buffer electrolytes [26] or additives [27–29] in CE. Development of ILs opens the way of evaluation of novel potential chiral ILs as chiral reagents for enantiomeric separation. Chiral ILs have chiral pools and unique properties, which make themselves suitable to participate in chiral separation processes; however, only a few kinds of chiral ILs have been synthesized and used as chiral selectors or as additives to form synergistic systems for CE chiral separation [30–34].

Compared to other chiral ILs, amino acid derived chiral ILs have many advantages, such as week UV absorption, stable chirality, high biocompatibility and easy availability. In this study, two amino acid

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http://dx.doi.org/10.1016/j.chroma.2013.09.064

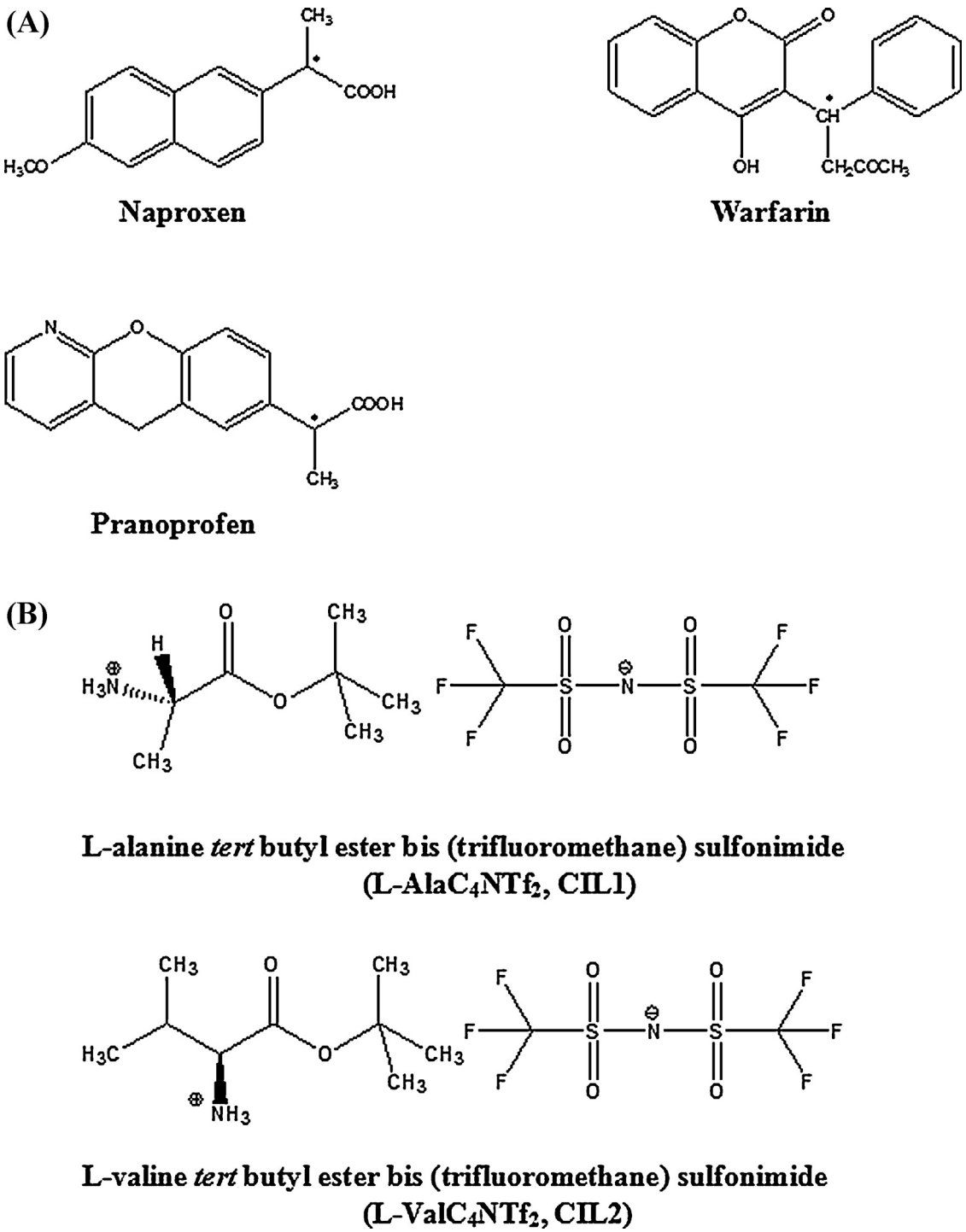

Fig. 1. Structures of (A) racemic drugs and (B) chiral ionic liquids L-alanine and L-valine *tert* butyl ester bis (trifluoromethane) sulfonimide (L-$AlaC_4NTf_2$ (CIL1) and L-$ValC_4NTf_2$ (CIL2)).

derived chiral ILs (L-alanine and L-valine *tert* butyl ester bis (trifluoromethane) sulfonimide, L-$AlaC_4NTf_2$ and L-$ValC_4NTf_2$, structures as Fig. 1) were applied for the first time in CE to evaluate their potential synergistic effects with classical chiral selectors (β-cyclodextrin derivatives) for enantiomeric separations. Methyl-β-cyclodextrin (Me-β-CD), hydropropyl-β-cyclodextrin (HP-β-CD) and glucose-β-cyclodextrin (Glu-β-CD) were chosen to act as chiral selector in the separation systems. Six anionic racemic drugs (naproxen, pranoprofen, warfarin, carprofen, ibuprofen and ketoprofen) were selected as model drugs, and among them, significant synergistic effect was observed for naproxen, pranoprofen and warfarin. We presented details of the synergistic systems for enantioseparation by CE.

2. Experimental

2.1. Chemicals and reagents

L-Alanine *tert* butyl ester hydrochloride (L-$AlaC_4Cl$, >98.5%) and L-valine *tert* butyl ester hydrochloride (L-$ValC_4Cl$, >98.5%)