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Evaluation of chiral ionic liquids as additives to cyclodextrins for enantiomeric separations by capillary electrophoresis

Yannis François [a], Anne Varenne [a], Emilie Juillerat [a], Didier Villemin [b], Pierre Gareil [a,*]

[a] *Laboratory of Electrochemistry and Analytical Chemistry, UMR CNRS 7575, ENSCP, 11 rue Pierre et Marie Curie, 75231 Paris Cedex 05, France*
[b] *Laboratory of Molecular and Thio-organic Chemistry, UMR CNRS 6507, ENSI Caen, 6, Boulevard du Maréchal Juin, 14050 Caen Cedex, France*

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Abstract

A great interest has been drawn these last years towards ionic liquids in analytical chemistry, especially for separation methods. Recent synthesis of chiral ILs opened the way of the evaluation of new potential selectors for enantiomeric separations. This work focused on the evaluation of two chiral ILs (ethyl- and phenylcholine of bis(trifluoromethylsulfonyl)imide) by CE. Particular selectivities are awaited by exploiting unique ion–ion or ion–dipole interactions and by tailoring the nature of the cation and the anion. To evaluate such phenomena, a study was carried out with anti-inflammatory drugs 2-arylpropionic acids as model compounds. The results show that these chiral ILs did not present direct enantioselectivity with regard to these model analytes. The influence of chiral ILs in the electrolytes was then studied in the presence of classical chiral selectors (di- or trimethyl-β-cyclodextrin). Although no general trend could be established, an increase in separation selectivity and resolution was observed in some cases, suggesting synergistic effects. The complementary determination of apparent inclusion constant values of these IL cations in the used cyclodextrins by affinity CE provided support to the understanding of the phenomena involved.

Keywords: Ionic liquids; Capillary electrophoresis; Chiral separations; Choline-based ionic liquids; Neutral cyclodextrins; Arylpropionic acids

1. Introduction

The high proportion of chiral compounds of biological or pharmacological interest has aroused a considerable need for the determination of the enantiomeric purities in the last 20 years. Since the pioneering works by Zare and co-workers [1] and Fanali [2] and as testified by the very important amount of literature and a number of comprehensive reviews [3–11], capillary electrophoresis (CE) has proven to be an excellent alternative to classical chromatographic techniques in this field. The use in very small quantity and in free form of the chiral selector makes it possible to compare the effects of various selectors and afterwards perform routine analyses at lower cost.

A great interest is being triggered by ionic liquids (IL) as alternatives for conventional molecular solvents used in organic synthesis and catalytic reactions [12]. They supplement the family of "green solvents" including water and supercritical fluids. Among these, room temperature ionic liquids are defined as materials containing only ionic species and having a melting point lower than 298 K. They exhibit many interesting properties such as negligible vapor pressure, low melting point, large liquid range, unique solvation ability and overall, the versatility of their physico-chemical properties makes them really attractive. They have been proposed as solvents for chemical reactions [13–15], multiphase bioprocess operations [16] and liquid–liquid separations [17,18], as electrolytes for batteries and fuel cells [19], stationary phases in gas chromatography [20–23] and mobile phase additives in liquid chromatography [24–26].

During these last years, a great attention has been paid to the relevance of these new media for capillary electrophoresis (CE) [27–37] and many efforts have been directed toward the understanding of the separation mechanisms involved in IL-containing background electrolytes (BGE). Concerning chiral separations, two applications only have been reported so far. The first one was with achiral ILs [38], 1-ethyl- and 1-butyl-3-methylimidazolium cations, associated with BF_4^- or PF_6^- anions. The enantioselectivity for binaphtyl derivatives was produced by a polymeric surfactant, whereas the presence of the ILs only modified the

* Corresponding author. Tel.: +33 1 55 42 63 71; fax: +33 1 44 27 67 50.
E-mail address: pierre-gareil@enscp.fr (P. Gareil).

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retention times and peak efficiency. Nevertheless, little was elucidated about the separation mechanism. Recent synthesis of chiral ILs [39,40] opened the way of the evaluation of new potential selectors for enantiomeric separations. Rizvi and Shamsi [41] realized the first chiral separation of several anionic compounds by micellar electrokinetic chromatography using two new synthetic chiral ionic liquids, undecenoxycarbonyl-L-pyrrolidinol bromide and undecenoxycarbonyl-L-leucinol bromide.

This work was focused on the separation performances of two chiral ILs (ethyl- and phenylcholine of bis(trifluoromethylsulfonyl)imide) by CE. In a previous work, a nonaqueous capillary electrophoresis (NACE) study on the electrophoretic behavior of 2-arylpropionic acids (profens), which were often selected as model chiral anionic compounds [42] in the presence of an achiral imidazolium-based IL evidenced peculiar ion-pairing interactions between these analytes and the achiral IL [43]. In the present work, the electrophoretic behavior of the same model analytes was first studied in the presence of one of both chiral choline-based ILs in nonaqueous media. As these chiral ILs alone did not present any enantioselectivity with regard to these model analytes under the conditions tested, the influence of the chiral ILs was then studied in aqueous and hydro-organic electrolytes containing classical chiral cyclodextrin selectors (di- or trimethyl-β-cyclodextrin). The figures of merit (effective enantioselectivity and resolution) of the chiral separations of the six arylpropionic acids were systematically determined, depending on the nature and the concentration of the chiral IL and cyclodextrin, ionic strength and hydro-organic composition of the electrolyte, to investigate for possible synergistic effects between the two chiral selectors. In addition to this study, apparent inclusion constant values for the used chiral ILs cations and neutral cyclodextrin derivatives were determined by affinity CE to provide support to the understanding of phenomena involved.

2. Experimental

2.1. Chemicals and reagents

Lithium bis(trifluoromethylsulfonyl)imide ($LiNTf_2$) (≥99%) was a gift from Institut Français du Pétrole (Solaize, France). (*R*)(−)2-Hydroxy-*N*,*N*,*N*-trimethyl-1-phenylethanaminium (PhChol NTf_2) and (*R*)(−)1-hydroxy-*N*,*N*,*N*-trimethylbutan-2-aminium bis(trifluoromethylsulfonyl)imide (EtChol NTf_2) were synthesized (see Section 2.2) in Villemin's group (Caen, France). Methanol (GC grade, 99.9% purity) and sodium acetate were purchased from Prolabo (Fontenay-sous-Bois, France). Formamide (>99%) and hexadimethrin bromide (polybrene) were supplied by Aldrich (St. Louis, MO, USA). Glacial acetic acid (>99%), heptakis-(2,6-di-*O*-methyl)-β-cyclodextrin (DM-β-CD) (>90%) and heptakis-(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TM-β-CD) (>90%) were obtained from Sigma (St. Louis, MO, USA). 2-Arylpropionic acids (carprofen, suprofen, naproxen, ketoprofen, indoprofen and ibuprofen) were donated by Rhone-Poulenc-Rorer (Vitry-sur-Seine, France).

2.2. Synthesis of chiral ionic liquids

Wasserscheid et al. have been the first to propose the use of choline derivatives as chiral ionic liquid [44]. These chiral ammonium ions can be easily obtained from pure enantiomeric aminoalcohol coming from the "chiral pool" as starting product.

The syntheses of the chiral ionic liquids were achieved in two steps: (i) permethylation of amine group into ammonium group and (ii) the metathesis exchange of anion.

In a typical procedure of permethylation, the *R*(−)2-aminobutan-1-ol (0.44 g, 5 mmol) [respectively, *R*(−) or *S*(+) phenylglycin-1-ol (0.5 g, 3.6 mmol)] and the iodomethane (2.13 g, 15 mmol) were refluxed in diethyl ether (30 ml) under argon atmosphere and were protected from the light. After 6 days' reflux, the solvent was removed by distillation under reduced pressure. The reactional mixture was solubilized in water (6 mL) and extracted three times (3 × 5 mL) with CH_2Cl_2. The aqueous phase was evapored under vacuum.

For the anion exchange step, the ammonium iodide (25 mmol) was dissolved in water (35 mL) and an aqueous saturated solution of lithium bis(trifluoromethylsulfonyl)imide (7.2 g, 25 mmol) was added. The liquid obtained was centrifuged and the ionic liquid and water were separated. The ionic liquid was washed with water (3 × 10 mL) and finally vacuum-dried.

2.3. Characterization of chiral ionic liquids

The structures of the chiral ionic liquids were characterized by ^1H, ^{13}C and ^{19}F NMR spectroscopy.

2.3.1. (R)(−)1-Hydroxy-N,N,N-trimethylbutan-2-aminium bis(trifluoromethylsulfonyl)imide (EtChol NTf_2)

Colorless oil; ^1H NMR (400 MHz, MeOD) CD_3CN/TMS δ (ppm): 0.97 (t, $^3J_{HH}$ = 7 Hz, 3H, C**H**$_3$-CH_2), 1.93 (quint, $^3J_{HH}$ = 2 Hz, 2H, CH_3-C**H**$_2$-CH), 3.24 (s, 10H, CH_3-CH_2-C**H**-(*N*-(C**H**$_3$)$_3$)-CH_2-OH), 3.73 (dq, $^3J_{HH}$ = 14 Hz, $^4J_{HH}$ = 4 Hz, 1H, CH_3-CH_2-CH-(*N*-$(CH_3)_3$)-C**H**$_2$-OH), 3.95 (d, $^3J_{HH}$ = 14 Hz, 1H, CH_3-CH_2-CH-(*N*-$(CH_3)_3$)-C**H**$_2$-OH), 4.68 (s, 1H, CH_3-CH_2-CH-(*N*-$(CH_3)_3$)-CH_2-O**H**); ^{13}C NMR (62.9 MHz, MeOD) CD_3CN/TMS δ (ppm): 11.93 (s, 1C, **C**H_3), 19.38 (s, 1C, CH_3-**C**H_2-CH), 53.55 (s, 3C, *N*-(**C**H_3)$_3$), 58.36 (s, 1C, CH-**C**H_2-OH), 78.77 (s, 1C, CH_3-CH_2-**C**H-(*N*-$(CH_3)_3$)-CH2-OH), 121.60 (quad, $^1J_{CF}$ = 1273 Hz, 2C, *N*-$(SO_2$-**C**$F_3)_2$); ^{19}F NMR (235.3 MHz, MeOD), CD_3CN/CCl_3F δ (ppm): −81.08 (s, 6F, *N*-$(SO_2$-C**F**$_3)_2$).

2.3.2. (R)(−) 2-Hydroxy-N,N,N-trimethyl-1-phenylethanaminium bis(trifluoromethylsulfonyl)imide (PhChol NTf_2)

Colorless oil; ^1H NMR (400 MHz, MeOD) CD_3CN/TMS δ (ppm): 2.79 (s, 1H, O**H**), 3.19 (s, 9H, Ph-CH-(*N*-(C**H**$_3$)$_3$)-CH_2-OH), 4.22 (d, $^3J_{HH}$ = 13 Hz, 1H, Ph-CH-(*N*-$(CH_3)_3$)-C**H**$_2$-OH), 4.45 (dd, $^3J_{HH}$ = 13 Hz, $^3J_{HH}$ = 7 Hz, 1H, Ph-C**H**-(*N*-$(CH_3)_3$)-CH_2-OH), 4.61 (dd, $^3J_{HH}$ = 7 Hz, $^3J_{HH}$ = 4 Hz, Ph-CH-(*N*-$(CH_3)_3$)-C**H**$_2$-OH), 7.49–7.56 (m, 3C, 1H para and 2H ortho), 7.62–7.65 (m, 2H, 2H meta); ^{13}C NMR (62.9 MHz, MeOD) CD_3CN/TMS δ (ppm): 53.90 (s, 3C, Ph-CH-(*N*-(**C**H_3)$_3$)-CH_2-