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EVALUATION OF CHIRAL IONIC LIQUIDS AS ADDITIVES TO CYCLODEXTRINS FOR
ENANTIOMERIC SEPARATIONS BY CAPILLARY ELECTROPHORESIS

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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.

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 twenty years. Since the pioneering works by Zare et al. [1] and Fanali et al. [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 binaphthyl derivatives was produced by a polymeric surfactant, whereas the presence of the ILs only modified the 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 et al. [41] realized the first chiral separation of several anionic compounds by micellar

electrokinetic chromatography using two new synthetic chiral ionic liquids, undecenoxycarbonyl-L-proline bromide and undecenoxycarbonyl-L-leucine 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 (LiNTf₂) ($\geq 99\%$) was a gift from Institut Français du Pétrole (Solaize, France). (R)(-) 2-hydroxy-N,N,N-trimethyl-1-phenylethanaminium (PhChol NTf₂) and (R)(-) 1-hydroxy-N,N,N-trimethylbutan-2-aminium bis(trifluoromethylsulfonyl)imide (EtChol NTf₂) 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 synthesis 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 (0.5g, 3.6 mmol)] and the iodomethane (2.13 g, 15 mmol) were refluxed in diethyl ether (30 ml) under argon atmosphere and was protected from the light. After six 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 x 5 mL) with CH₂Cl₂. The aqueous phase was evaporated 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(trifluoromethanesulfonyl)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 x 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 :

(R)(-) 1-hydroxy-N,N,N-trimethylbutan-2-aminium bis(trifluoromethanesulfonyl)imide (EtChol NTf₂).

Colorless oil, ^1H NMR (400 MHz, MeOD) CD₃CN/TMS δ (ppm): 0.97 (t, $^3J_{\text{HH}} = 7\text{ Hz}$, 3H, CH₃-CH₂), 1.93 (quint, $^3J_{\text{HH}} = 2\text{ Hz}$, 2H, CH₃-CH₂-CH), 3.24 (s, 10H, CH₃-CH₂-CH-(N-(CH₃)₃)-CH₂-OH), 3.73 (dq, $^3J_{\text{HH}} = 14\text{ Hz}$, $^4J_{\text{HH}} = 4\text{ Hz}$, 1H, CH₃-CH₂-CH-(N-(CH₃)₃)-CH₂-OH), 3.95 (d, $^3J_{\text{HH}} = 14\text{ Hz}$, 1H, CH₃-CH₂-CH-(N-(CH₃)₃)-CH₂-OH), 4.68 (s, 1H, CH₃-CH₂-CH-(N-(CH₃)₃)-CH₂-OH); ^{13}C NMR (62.9 MHz, MeOD) CD₃CN/TMS δ (ppm): 11.93 (s, 1C, CH₃), 19.38 (s, 1C, CH₃-CH₂-CH), 53.55 (s, 3C, N-(CH₃)₃), 58.36 (s, 1C, CH-CH₂-OH), 78.77 (s, 1C, CH₃-CH₂-CH-(N-(CH₃)₃)-CH₂-OH), 121.60 (quad, $^1J_{\text{CF}} = 1273\text{ Hz}$, 2C, N-(SO₂-CF₃)₂); ^{19}F NMR (235.3 MHz, MeOD), CD₃CN/CCl₃F δ (ppm): -81.08 (s, 6F, N-(SO₂-CF₃)₂)

(R)(-) 2-hydroxy-N,N,N-trimethyl-1-phenylethanaminium bis(trifluoromethanesulfonyl)imide (PhChol NTf₂).

Colorless oil, ^1H NMR (400 MHz, MeOD) CD₃CN/TMS δ (ppm): 2.79 (s, 1H, OH), 3.19 (s, 9H, Ph-CH-(N-(CH₃)₃)-CH₂-OH), 4.22 (d, $^3J_{\text{HH}} = 13\text{ Hz}$, 1H, Ph-CH-(N-(CH₃)₃)-CH₂-OH), 4.45 (dd, $^3J_{\text{HH}} = 13\text{ Hz}$, $^3J_{\text{HH}} = 7\text{ Hz}$, 1H, Ph-CH-(N-(CH₃)₃)-CH₂-OH), 4.61 (dd, $^3J_{\text{HH}} = 7\text{ Hz}$, $^3J_{\text{HH}} = 4\text{ Hz}$, Ph-CH-(N-(CH₃)₃)-CH₂-OH), 7.49 to 7.56 (m, 3C, 1H para and 2H ortho), 7.62 to 7.65 (m, 2H, 2H meta); ^{13}C NMR (62.9 MHz, MeOD) CD₃CN/TMS δ (ppm): 53.90 (s, 3C, Ph-CH-(N-(CH₃)₃)-CH₂-OH), 62.04 (s, 1C, Ph-CH-(N-(CH₃)₃)-CH₂-OH), 80.35 (s, 1C, Ph-CH-(N-(CH₃)₃)-CH₂-OH), 121.64 (q, $^1J_{\text{CF}} = 1273\text{ Hz}$, 2C, N-(SO₂-CF₃)₂), 130.88 (s, 3C, 1C para, 2C meta), 132.35 (s, 2C, 2C ortho), 132.91 (s, 1C, C); ^{19}F NMR (235.3 MHz, MeOD), CD₃CN/CCl₃F δ (ppm): -81.06 (s, 6F, N-(SO₂-CF₃)₂).

2.4. Capillary electrophoresis and procedures

All experiments were performed with a HP^{3D}CE (Agilent Technologies, Waldbronn, Germany) capillary electrophoresis system. This apparatus automatically realized all the steps of the measurement protocols, including capillary conditioning, sample introduction, voltage application and diode array detection, and allows to run unattended method sequences. A CE Chemstation (Agilent Technologies, Waldbronn, Germany) was used for instrument control, data acquisition and data handling. Polymicro bare fused-silica capillaries of 50 μ m i.d. were obtained from Photonlines (Marly-le-Roi, France). They were used in 35 cm total length (26.5 cm to detection). Background electrolytes (BGE) were made up with acetic acid/sodium acetate at two different concentrations (5 and 60 mM) to a ^wpH of 5.0. The methanol-water mixtures were prepared by volumic mixing in 0, 10 and 25 % methanol proportions. Analytes were detected by UV absorbance at 200, 230, 240, 254 and 300 nm, according to cases. Formamide (0.001 % (v/v) in the BGE) was used as neutral marker to determine the electroosmotic mobility. The sample solutions were prepared by dissolving each analyte at a concentration of ca 0.5 mM in methanol. Samples were introduced hydrodynamically by successively applying a 30 mbar pressure for 3 s (approximately, 4 nL) to the neutral marker, BGE and sample vials. New capillaries were conditioned by successive flushes with 1 M and 0.1 M NaOH and then with water under a pressure of 935 mbar for 10 min each. The temperature in the capillary cartridge was set at 25 °C. The acquisition rate was 10 points / s. Capillaries were rinsed with water and dried by air when not in use.

2.5. Capillary coating

Capillaries were dynamically coated with polybrene as described in the literature [45-47]. Briefly, a new fused-silica capillary was first flushed with 1 M NaOH for 20 min and rinsed with water. Next, the capillary was flushed with a polybrene solution at 3 g/100 mL in water for 15 min. Finally, the capillary was rinsed with water for 5 min and conditioned with BGE for 5 min, all these steps being performed under a pressure of 935 mbar. Recoating of the capillary with the cationic polymer was accomplished by using a similar method.

2.6. Complexation constant determination

The apparent formation constant K for the inclusion complexes between chiral PhChol cations and neutral CDs of interest, was determined by mobility shift affinity capillary electrophoresis (ACE) according to a method similar to that developed for a series of imidazolium based ILs cations [48].

Briefly, PhChol NTf₂ was dissolved at a concentration of 2 mM and electrophoresed in BGEs (ionic strength: 5 mM) containing increasing concentrations of DM- β -CD or TM- β -CD (0 to 100 mM). Each injection with a given electrolyte was repeated twice. Effective mobilities (μ_{ep}) of PhChol cation were calculated from migration time measurement at peak apex. The obtained values were corrected to compensate for change in electrolyte viscosity due to increasing CD concentrations. The corrected values $\mu_{ep,cor}$ were fitted to non-linear and linear forms (linearized isotherm, x-reciprocal, y-reciprocal, double reciprocal) of the 1:1 stoichiometry complexation isotherm [49,50] to determine the K value.

2.7. Calculation of the performance parameters for the chiral separations

The effective electrophoretic selectivity [51], α_{eff} , was calculated according to Eq. 1:

$$\alpha_{eff} = \frac{\mu_{ep1}}{\mu_{ep2}} \quad (1)$$

where μ_{ep1} , μ_{ep2} are the effective mobilities for enantiomers 1 and 2.

The chiral resolution, R_s , between two enantiomers, 1 and 2, was calculated according to:

$$R_s = 1.177 \frac{t_2 - t_1}{\delta_1 + \delta_2} \quad (3)$$

where t_1 , t_2 are the migration times and δ_1 , δ_2 are the temporal peak widths at half height.

3. Results and discussion

In a previous work, interactions between an achiral IL (1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide) and a series of 2-arylpropionic acids were studied in non aqueous capillary electrophoresis (NACE) [43]. The results indicated a quadratic effect of the

concentration of the achiral IL in the BGE on profen electrophoretic mobilities due to antagonistic interactions between anionic analytes and imidazolium cations either adsorbed to the capillary wall or free in the BGE electrolyte. With a view to evaluate a new family of chiral selectors, the same conditions have been investigated with two chiral choline-based ILs (ethyl- and phenylcholine bis(trifluoromethylsulfonyl)imide). No enantioselectivity has been shown in these conditions for this family of compounds. This work was then directed to the study of the association of a chiral IL to the best chiral selectors, reported previously for the enantiorecognition of profens, DM- β -CD and TM- β -CD [52,53], to search for possible synergistic effects. The use of CDs nevertheless is poorly compatible with that of nonaqueous BGEs, to preserve adequate CD solubilization and partial formation of inclusion complexes. This study was therefore realized in water and 90:10 and 75:25 (v/v) water-MeOH mixtures. The choice of MeOH as molecular solvent in hydro-organic mixtures was based on its favorable anion-solvating properties and ion-pairing and its ability to dissolve the tested CD.

The aim of this work was then to determine if a synergistic effect may exist between the chiral IL cation and the CD, and possibly to elucidate the interaction system bringing into play the three different entities: analyte, chiral IL and β -CD derivative (Figure 2). The main parameters expected to impact this complex system were the nature and concentration of the IL, the nature and concentration of the CD, the concentration of the buffer and the hydro-organic composition of the BGE. The influence of adding LiNTf₂ to the separation electrolyte in place of the chiral ILs was tested under the same conditions to discriminate specific chiral cation effect from a mere salt effect. Also, the study was conducted either with bare fused silica capillaries or polybrene-coated capillaries, to assess the influence of IL cation adsorbed to the capillary wall.

Owing to the number of parameters to be studied, only three model profens (naproxen, carprofen and suprofen (Figure 1)) were investigated for the part of the experiments realized with bare silica capillaries. For the experiments performed with polybrene-coated capillaries, which were only realized in aqueous media, the following six profens were selected: naproxen, carprofen, suprofen, ketoprofen, indoprofen and ibuprofen (Figure 1). The retained parameters for discussion were effective electrophoretic chiral selectivity, α_{eff} , (thermodynamic parameter, independent of electroosmotic flow variation) and chiral resolution, R_s , (global parameter). It is to note that no enantioselectivity was obtained for naproxen under all conditions tested and for suprofen under all DM- β -CD conditions. The results obtained for carprofen and suprofen with

bare silica capillaries are given in Table 1, while those obtained for the five profens showing enantioselectivity with polybrene-coated capillaries are presented in Table 2.

In a number of cases, an increase in resolution R_s and a decrease in selectivity α_{eff} were observed for the experiments with chiral ILs, as compared to the experiments without salt, but no general trend on the evolution of R_s and α_{eff} can be traced.

Influence of electroosmotic flow and total salt concentration on R_s

The two chiral choline IL derivatives, EtChol and PhChol, were used in this work at a concentration of 10 mM and at two buffer salt concentrations (5 mM and 60 mM), in keeping with the preliminary study realized with achiral imidazolium-based IL cation by NACE [38]. Indeed, the chiral IL addition in solution caused a change of system properties such as a possible variation of the electrolyte viscosity, a marked increase in the total salt concentration, especially when the buffer salt concentration is 5 mM, and a modification of the capillary wall. These three parameters could mask a specific effect of the chiral IL on the enantiomeric separation.

The viscosity of each solution was measured using CE instrumentation by the method described in the literature [54]. The results showed no difference upon adding an IL or LiNTf₂ salt to a solution already containing a CD. So, there was no viscosity effect due to the IL addition on enantiomeric separation.

As the addition of the chiral IL was changing the total salt concentration of the solution, the same experiments were realized with LiNTf₂ salt in place of chiral IL to discriminate between a mere salt effect and a specific effect due to the chiral nature of IL cations.

In effect, in a lot of cases, Table 1 shows an increase in R_s upon chiral IL addition, but also upon LiNTf₂ addition. Salt addition caused a decrease in electroosmotic mobility (μ_{eo}) and under these counter-electroosmotic flow condition an increase in R_s values [55]. As expected, a more important μ_{eo} variation and hence R_s increase was observed at the lower starting level of buffer salt concentration (5 mM), for which the relative variation in concentration was higher (Figure 3). It was also noted that, with bare silica capillaries, in the majority of cases the addition of a chiral IL caused a more important decrease in μ_{eo} than LiNTf₂ did. This decrease was likely due to the adsorption of the IL cation to the capillary wall, as already mentioned by Stalcup [27,28]. To further discriminate between IL cation wall adsorption and salt effect, the same experiments were

resumed with polybrene-coated capillaries which are anticipated to eliminate the IL cation interaction with capillary wall. Table 2 shows that in a majority of cases, an increase in R_s for the experiments with chiral IL and LiNTf₂ was still observed as compared to CD-alone experiments. In all these cases, a decrease in μ_{eo} was also observed, due to the increase in salt concentration. These experiments with positively charged capillaries highlighted the significance of salt effects on the chiral resolution of the five model profens.

Influence of chiral IL on α_{eff}

Finally, effective electrophoretic selectivity, α_{eff} , designed to be independent of electroosmotic mobility, was the only parameter able to indicate a possible synergistic effect between the two selectors. In some cases, when the initial buffer salt concentration was 5 mM, an increase in α_{eff} was observed upon adding 10 mM LiNTf₂ salt. This behavior can only be understood in considering that the apparent inclusion constants for profens into the CDs, which control α_{eff} , can be depending on electrolyte ionic strength. Apart from this, an increase in α_{eff} , with a difference of more than 3%, in the presence of a chiral IL additive as compared to the experiments with the same concentration of LiNTf₂ was noted in five cases with bare silica capillaries (Table 1) and in four cases with the polybrene-coated capillaries (Table 2). Such a relative difference was considered as the limit of significance based on a mean 3% error for experimental electrophoretic values of chiral compounds (Table 1 and Table 2). Among these nine cases, eight were obtained with 5 mM buffer salt concentration and all five cases identified in the experiments reported in Table 1 were obtained with aqueous and hydroorganic media. It is to note that the experiments with polybrene-coated capillaries were performed with both 5 mM (results shown in Table 2) and 60 mM (results not shown) buffer salt concentrations, but no case of synergy was observed at the higher concentration. In spite of the lack of general trend, this behavior suggests that the synergistic effect observed between the two selectors may be due to specific ion-pairing interaction between the analyte and the chiral IL cation.

The presence of the phenyl group in the chiral choline cation did not appear to be of importance in the observation of apparent synergistic effects, whereas most cases were observed with TM- β -CD. For a better understanding of the interactions brought into play and to assess a possible competition between the analyte and the IL cation for inclusion complex formation with the CD,

a study on possible inclusion complexation between chiral IL cation and β -CD derivatives was undertaken. Concerning EtChol NTf₂, a recent study realized by our group on inclusion constant determination between quite a large number of neutral CDs and alkyl(methyl)methylimidazolium cations [48], revealed that the inclusion of IL cation almost exclusively depends on the alkyl chain length. For 1-ethyl-3-methylimidazolium cation, no inclusion was measured with any tested CD. On analogy, it seems reasonable to conclude that there is no inclusion between EtChol cation and the two β -CD derivatives of the present study. The previously used mobility shift affinity CE method was adapted to determine the apparent inclusion constant for PhChol cation and DM- and TM- β -CD in a acetic acid/sodium acetate buffer at pH 5.0 (ionic strength, 30 mM) . The results obtained in this work showed that there was no inclusion of PhChol cation into TM- β -CD cavity but that this cation formed a complex with DM- β -CD having an apparent constant of 144 ± 3 at 25°C. This difference in behavior could be explained by the more important steric hindrance of TM- β -CD as compared to DM- β -CD. Eventually, the study of inclusion phenomena between chiral IL cations and used CDs showed that there was an influence of the CD nature on the competition between the analyte and the IL cation with the CD. Nevertheless, the two thirds of apparent synergistic cases were observed with TM- β -CD with respect to DM- β -CD for EtChol as well as PhChol ILs, which does not allow to further clarify which factor is the most influent.

4. Conclusion

This work focused on the evaluation of two chiral ILs (ethyl- and phenylcholine of bis(trifluoromethylsulfonyl)imide) by CE. No direct enantioselectivity was observed for these two chiral IL cations with respect to a series of arylpropionic acids, selected as model compounds, in various nonaqueous BGE conditions. BGEs containing both a chiral IL cation and a classical chiral selector (di- or trimethyl- β -cyclodextrin) in water and water-MeOH mixtures were subsequently investigated to look for a compromise between the selective formation of inclusion complexes, favored in aqueous electrolyte, and of ion-pairs, favored in nonaqueous media. In most cases, an increase in resolution was observed upon adding one of the chiral IL, but this variation was most often due to a decrease in electroosmotic flow, resulting from the increase in salt concentration and a possible wall adsorption. In nine cases, however, simultaneous increase in α_{eff} and R_s was observed as compared to a simple salt effect, which suggests a synergistic effect of the two selectors. Apparent inclusion constant for EtChol and PhChol cations and the used cyclodextrins were evaluated, demonstrating an influence of the CD nature on the competition between the analyte and the IL cation with respect to CD complexation. Nevertheless, the presence of the phenyl group in the IL cation appeared to be of less importance in promoting these synergistic effects than that of methanol and of a low salt concentration in the BGE, which suggests that specific ion-pairing interactions may be involved.

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Captions

Figure 1: Structures of (A) the studied arylpropionic acids and (B) ionic liquids ethylcholine and phenylcholine bis(trifluoromethanesulfonyl)imide (EtCholNTf₂, PhCholNTf₂). pK_a values at 26-27 °C from [53]

Figure 2: Schematic description of the interaction system between anionic profen, chiral IL cation, free in the BGE or adsorbed onto the capillary wall, and β -CD derivatives.

Figure 3: Enantioseparation of carprofen in the presence of TM- β -CD and chiral ILs. Fused silica capillary, 50 μ m i.d. 35 cm (effective length, 26.5 cm). Electrolyte: 2.63 mM acetic acid, 5.0 mM sodium acetate buffer, w_p pH 5.0 containing (a) 30 mM TM- β -CD, (b) 30 mM TM- β -CD + 10 mM EtCholNTf₂, (c) 30 mM TM- β -CD + 10 mM PhCholNTf₂ (d) 30 mM TM- β -CD + 10 mM LiNTf₂ in (90:10, v/v) H₂O-MeOH mixture. Applied voltage: 25 kV. Temperature: 25 °C. UV absorbance at 230 nm. Hydrodynamic injection (30 mbar, 3 s). EOF: electroosmotic flow.