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ENANTIOSEPARATION BY CAPILLARY ELECTROPHORESIS USING IONIC LIQUIDS AS CHIRAL SELECTORS

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Abbreviations: L-UCPB, undecenoxycarbonyl-L-pryrrolidinol bromide; **L-UCLB**, undecenoxycarbonyl-L-leucinol bromide; **[EtChol][NTf_2]**, (R)-N,N,N-trimethyl-2-aminobutanol-bis(trifluoromethane-sulfon)imidate; **[DMP][NTf_2]**, (+)-N,N-dimethylephedrinium-bis(trifluoromethanesulfon)imidate; **[HPTMA-β-CD][BF_4]**, 6-O-2-hydroxypropyltrimethylammonium-β-cyclodextrin tetrafluoroborate; **L-AlaC$_1$Lac**, L-alanine methyl ester lactate; **L-AlaC$_2$Lac**, L-alanine ethyl ester lactate, **L-AlaC$_4$Lac**, L-alanine tert butyl ester lactate, **D-AlaC$_4$Lac**, D-alanine tert butyl ester lactate; **L-AlaC$_4$NTf_2**, L-alanine tert butyl ester bis(trifluromethane)sulfonamide; **[TMA]$^+$[LA]$^-$**, tetramethylammonium-lactobionate; **(S)-[CHTA][NTf_2]**, S-[3-(chloro-2-hydroxypropyl)trimethylammonium][bis((trifluoro-methyl)sulfonyl)amide; **[L-ValC$_4$][NTf_2]**, L-valine tert butyl ester bis(trifluoromethanesulfon)imidate; [**D-AlaC$_4$][NTf_2]**, D-alanine tert butyl ester bis(trifluoromethanesulfon)imidate; **[EMIm][L-Lactate]**, 1-ethyl-3-methylimidazolium L-lactate; **L-UCAB**, N-undecenoxy-carbonyl-L-alaninol bromide, **[BMIm][BLHvB]**, (1-butyl-3-methylimidazolium(T-4)-bis[(2S)-2-(hydroxy-κO)-3-methyl-butanoato-κO]borate; **[BMIm][BSMB]**, 1-butyl-3-methylimidazolium(T-4)-bis[(αS)-α-(hydroxy-κO)-4-methyl-benzeneacetato-κO]borate; [**C$_6$mim][L-Pro]**, 1-hexyl-3-methylimidazolium L-proline; **[TMA][L-OH-Pro]**, tetramethylammonium L-hydroxyproline; **[L-Phn][CF_3COO]**, L-phenylalaninamide trifluoroacetate; **[L-Prn][$CF_3COO]_2$**, L-prolinamide trifluoroacetate; **[L-Aln][$CF_3COO]_2$**, L-alaninamide trifluoroacetate; **[BMIm][L-Ala]**, 1-butyl-3-methylimidazolium L-alanine; **[EMIm][L-Ala],** 1-ethyl-3-methylimidazolium L-alanine; **[HMIm][L-Ala]**, 1-hexyl-3-methylimidazolium L-alanine; **[C$_6$mim][L-Lys]**, 1-hexyl-3-methylimidazolium L-lysine; **[Epy][L-Lys]**, 1-ethylpyridinium L-lysine; **[Bpy][L-Lys]**, 1-butylpyridinium L-lysine; **[Hpy][L-Lys]**, 1-hexylpyridinium L-lysine; **[Opy][L-Lys]**, 1-octylpyridinium L-lysine; [**EMIm][L-Tar]**, 1-ethyl-3-methylimidazolium L-tartrate.

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Abstract

Capillary electrophoresis is one of the most widely employed analytical techniques to achieve enantiomeric separations. In spite of the fact that there are many chiral selectors commercially available to perform enantioseparations by CE, one of the most relevant topics in this field is the search for new selectors capable of providing high enantiomeric resolutions. Chiral ionic liquids have interesting characteristics conferring them a high potential in chiral separations although only some of them are commercially available. The aim of this article is to review all the works published on the use of chiral ionic liquids as chiral selectors in the development of enantioselective methodologies by CE, covering the period of time from 2006 (when the first research work on this topic was published) to 2017. The use of chiral ionic liquids as sole chiral selectors, as chiral selectors in dual systems or as chiral ligands will be considered. This review also provides detailed analytical information on the experimental conditions used to carry out enantioseparations in different fields as well as on the separation mechanism involved.

Keywords: Chiral ionic liquids, capillary electrophoresis, chiral analysis, enantioseparation, chiral selector.

1. Introduction

Capillary electrophoresis (CE) has already demonstrated its high potential to face different challenges in the field of chiral separations. In fact, it is probably one of the most employed separation techniques in analytical enantioseparations due to different reasons such as its high separation efficiency, versatility, and feasibility to use different chiral selectors to obtain high enantiomeric resolutions. Among the great variety of compounds employed as chiral selectors (monomeric and polymeric surfactants, antibiotics, chiral crown ethers, polysaccharides), cyclodextrins continue being by far the most frequently used in CE (Zhu and Scriba, 2016). Even though all these kinds of selectors have been effectively employed, different parameters such as low solubility, high UV absorptivity, instability at high temperature, complicated synthesis and high cost, may limit their use (Kapnissi-Christodoulou et al., 2014). For this reason, the search for new compounds offering high chiral resolution to carry out enantioseparations by CE continues being nowadays one of the most relevant challenges that researchers have to face. In this sense, a significant attention has been devoted to chiral ionic liquids (CILs).

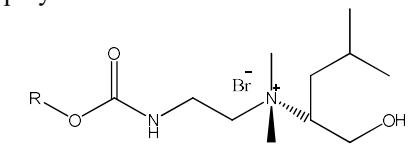
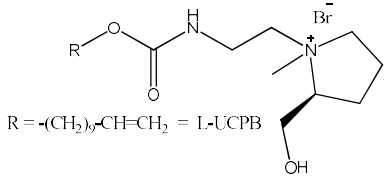
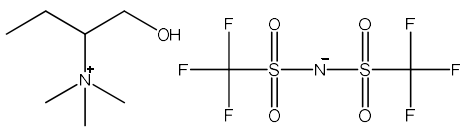
Ionic liquids (ILs) have been widely used in different areas of chemistry since their discovery in 1914 (Ho et al., 2014). In particular, within the scope of analytical chemistry, ILs have been applied in the extraction, characterization, detection and separation of different analytes (Tan et al., 2012). The word "ionic liquids" refers to salts with melting points below 100 ºC. These liquids are formed by bulky organic cations (ammonium, alkylimidazolium, pyridinium) and organic or inorganic anions (hexafluorophosphate (PF_6), tetrafluoroborate (TFB), etc.) (Kartsova et al., 2016). The type and size of cations and anions influence the unique physicochemical properties of ILs: high conductivity, low volatility and vapor pressure, good thermal stability, high miscibility in water and

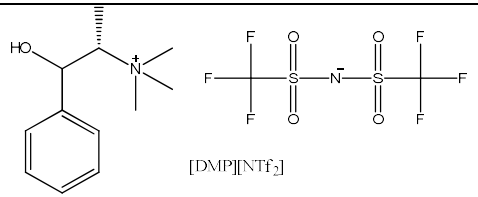
organic solvents, etc. In the last years, ILs have shown a great potential as stationary phases, selectors, additives in BGE, ligands or coating materials in separation techniques such as GC, LC, and CE (Kapnissi-Christodoulou et al., 2014; Tan et al., 2012; Kartsova et al., 2016; Huang et al., 2013; Boon et al., 2017; Ali et al., 2017). There is a subtype of ILs known as CILs which have a chiral moiety in their structure, i.e. the anion, the cation or both may be chiral. Whereas the chiral cation is often an imidazolium, pyridinium, ammonium or azole group, the anion could include an amino acid, lactic acid, borate, or camphorsulfonate. Resolution abilities and liquid properties of CILs give them a dual functionality since they may be used as chiral selectors, as chiral solvents, or both simultaneously. This means that CILs can, at the same time, show chiral selectivity and dissolve compounds of a broad range of polarity. All these characteristics confer CILs a high potential to play a key role in chemistry (Li et al., 2010). In the field of chiral separations, CILs have been used in chromatographic and electrophoretic techniques (Kapnissi-Christodoulou et al., 2014; Kartsova et al., 2016; Huang et al., 2013; Boon et al., 2017; Ali et al., 2017) as well as in chiral spectroscopy discrimination by NMR (Bwambok et al., 2008; de Rooy et al., 2011; Foreiter et al., 2014), NIR (Tran et al., 2006) or fluorescence (Bwambok et al., 2008; Tran and Oliveira, 2006). In spite of the fact that these designable properties of CILs make them particularly attractive to achieve enantiomeric separations, one of the main reason that hinders their application in this field is that only a few CILs are commercially available. In principle, the synthesis of these liquids is simple although it sometimes needs rather expensive reagents and elaborated schemes. Readers interested on gaining a deeper knowledge on the synthesis of CILs are referred to an excellent review article published by Payagala and Armstrong (2012).

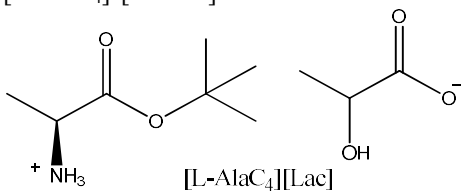
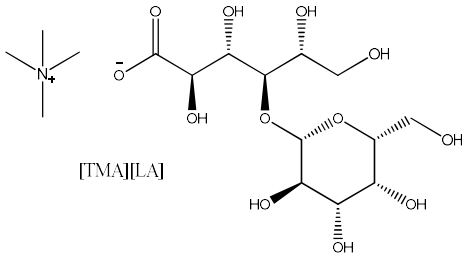
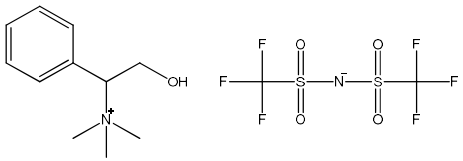
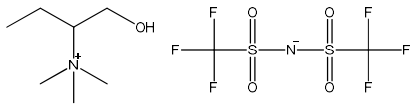
111 In chiral CE, CILs can be used in three different ways to achieve a enantioseparation: as
112 sole chiral selectors in the background electrolyte, as chiral selectors in dual systems, and
113 as chiral ligands. In the period of time covered by this article, several reviews were
114 published in the literature dealing with the general use of ionic liquids in analytical
115 chemistry or separation techniques, such as HPLC or GC, including some brief sections
116 to describe the application of CILs to chiral analysis by CE (Kapnissi-Christodoulou et
117 al., 2014; Ho et al., 2014; Kartsova et al., 2016; Huang et al., 2013; Payagala and
118 Armstrong, 2012; Yuanhong and Wang, 2009; Sun and Armstrong, 2010; Tang et al.,
119 2014; Boon et al., 2017; Ali et al., 2017). Although this fact reflects the interest in the use
120 of these compounds in separation techniques, until now, only a review (published in 2015)
121 has been exclusively focused on electrophoretic separations using CILs (Stanescu et al.,
122 2015).

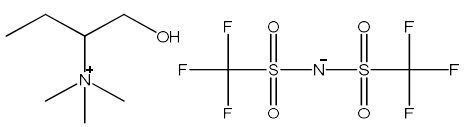
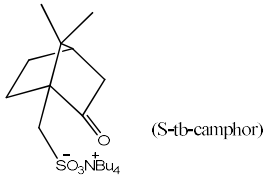
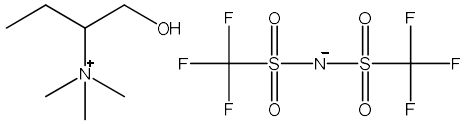
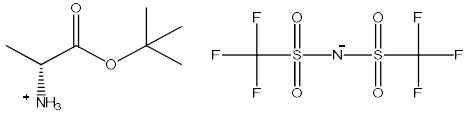
123 The goal of this review is to provide a critical view on the potential of CILs as chiral
124 selectors in the development of enantioselective methodologies by CE covering the
125 literature from 2006 to 2017. The structures of all CILs employed as well as the detailed
126 experimental conditions used to achieve the enantiomeric separation of a variety of
127 analytes by CE are shown in **Table 1**. The use of CILs as sole chiral selectors, as chiral
128 selectors in dual systems, and as chiral ligands, is described in the three following
129 sections. In this way, the particularities and separation mechanism of each approach is
130 appropriately discussed.

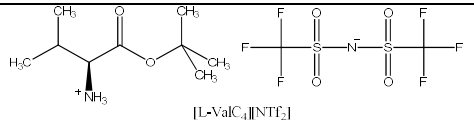
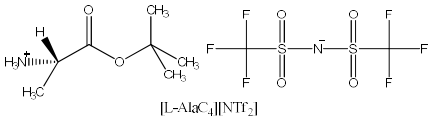
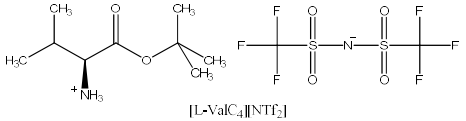
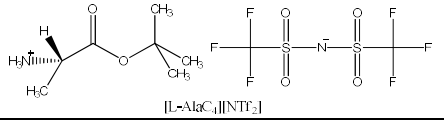
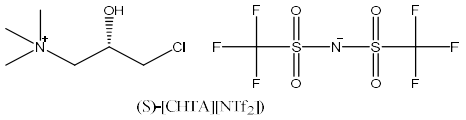
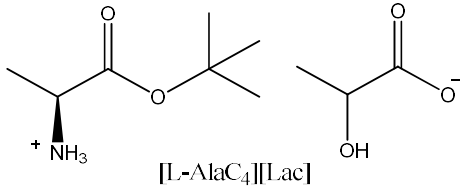
131 **Table 1.** Chiral ionic liquids and experimental conditions employed in the enantiomeric separations by CE.

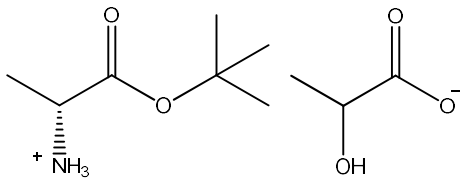
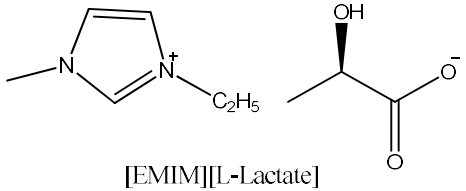
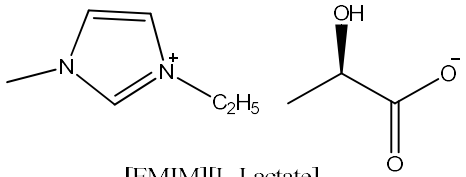
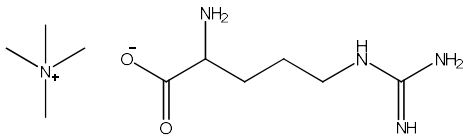
Classification	CIL	CE mode/ Optimal Separation conditions*	Analyte	Samples	Ref.
CILs as sole chiral selectors	L-UCPB L-UCLB poly-L-SUCLS poly-L-SUCL  R = -$(CH_2)_9$-CH=CH_2 = L-UCLB  R = -$(CH_2)_9$-CH=CH_2 = L-UCPB	MEKC-UV (214 nm) 25 mM L-UCPB or L-UCLB in 25 mM phosphate (pH 7.5) Capillary, 50 µm × 56.0 cm; -20 kV, 20°C	(±)- α-bromophenylacetic acid, (±)-2-(2-chlorophenoxy)propanoic acid	Standards	Rizvi and Shamsi, 2006
	$[EtChol]^+[NTf_2]^-$  $[EtChol][NTf_2]$	CE-UV (254 nm) 5 or 10 mM $[EtChol]^+[NTf_2]^-$ in 20 mM phosphate or 20 mM borate (pH 4.0-12.5) Capillary, 75 µm × 45.0 cm; 9-17 kV	α-methylbenzylamine, tryptophan, α-phenylglycine, 1-phenyl-1,2-ethanediol, phenylalanine, 2-phenyl-1-propanol, 3-benzyloxy-1,2-propane diol, tyrosine, propranolol, 1-(1-naphthyl)ethanol, Di-O,O`p-toluyl tartaric acid, 1-indanol, trans-2-phenyl-1-cyclohexanol, 2,3-o-benzylidene-threitol, 1,1,2-triphenyl-1,2-ethane diol	Standards	Yuan et al., 2006
	$[DMP]^+[NTf_2]^-$	NACE-UV (295 nm) 60 mM $[DMP]^+[NTf_2]^-$ in AcN-MeOH 60:40 (v/v) Capillary, 50 µm × 40 cm; 10 kV	Raberprazol, omeprazole	Standards	Ma et al., 2010

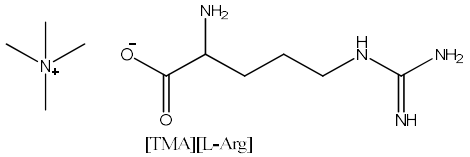
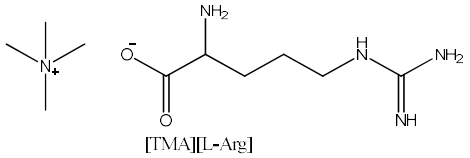
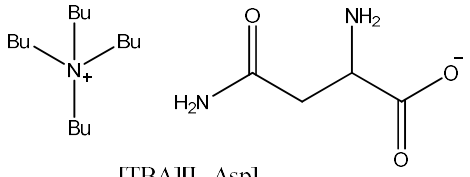
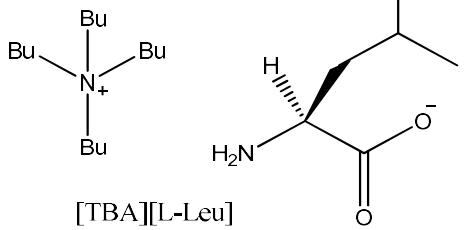
	 [DMP][NTf_2]				
	[HPTMA-β-CD]$^+$[BF_4]$^-$	CE-UV (254 or 249 nm) 13 mg/mL [HPTMA-β-CD]$^+$[BF_4]$^-$ in 30 mM phosphate (pH between 4 and 8 depending on the compound analyzed) Capillary, 50 µm × 40 cm; 20 kV, 25 ºC	Chlorpheniramine, tropicamide, bifonazole, promethazine, warfarin, liarozole, brompheniramine, pheniramine	Standards	Yu et al., 2013

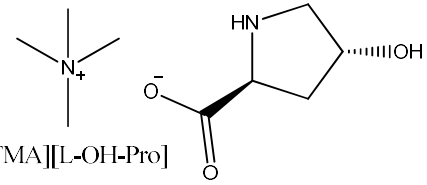
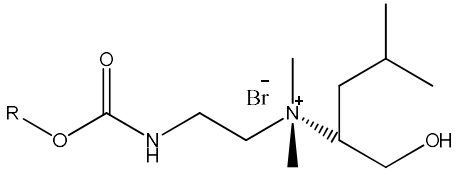
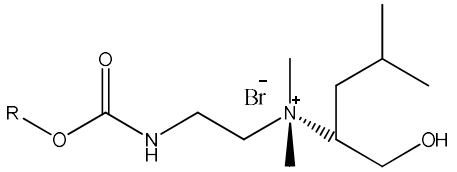
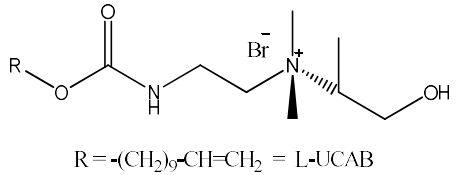
	$[L\text{-}AlaC_4]^+[Lactate]^-$  $[L\text{-}AlaC_4][Lac]$	CE-UV (214 nm) 60 mM $[L\text{-}AlaC_4]^+[Lac]^-$ in 100 mM Tris/10 mM borate (pH 8.0) Capillary 50 µm × 55.5 cm; 30 kV, 25 ºC	1,1-binaphthyl-2,2-diylhydrogenphosphate (BNP)	Standards	Stavrou and Kapnissi-Christodoulou, 201
	$[TMA]^+[LA]^-$  [TMA][LA]	CE-UV (215nm, 220 nm, 230 nm) 200 mM $[TMA]^+[LA]^-$ in 40 mM borate 40% v/v MeOH (pH 7.6) Capillary, 50 µm × 38.5 cm; 20 kV, 15ºC	Atenolol, metoprolol, nefopam, duloxetine, bisoprolol, propanolol	Standards	Zhang et al., 2015
CILs as chiral selectors in dual systems	$[EtChol]^+[NTf_2]^-$ $[PhChol]^+[NTf_2]^-$  $[PhChol][NTf_2]$  $[EtChol][NTf_2]$	CE-UV (200, 230, 240, 254, or 300 nm) 10 mM $[EtChol]^+[NTf_2]^-$ or $[PhChol]^+[NTf_2]^-$ + 30 mM DM-β-CD or TM-β-CD in 5 or 60 mM acetate (pH 5.0) containing 0, 10 or 25 % MeOH Capillary, 50 µm × 26.5 cm; 25 kV, 25 ºC	Carprofen, suprofen, naproxen, ketoprofen, indoprofen, ibuprofen	Standards	François et al., 2007
	$[EtChol]^+[NTf_2]^-$	CE-UV (214 nm)	Binapthol	Standards	Mofaddel et al., 2008

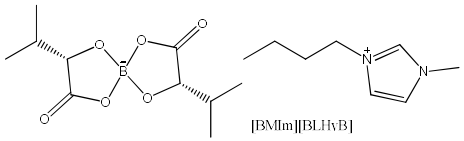
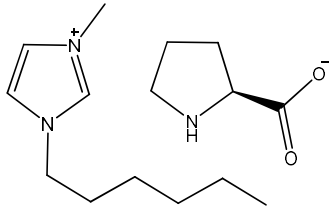
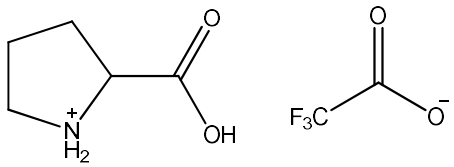
	(S)(+)-tetrabutylammonium camphorsulfonate  [EtChol][NTf_2]  (S-tb-camphor)	0-30 mM γ-CD + 0-20 mM CIL in 80 mM phosphate (pH 11.5) Capillary, 50 µm × 30 cm; 10 kV, 20 ºC			
	[EtChol]$^+$[NTf_2]$^-$  [EtChol][NTf_2]	NACE-UV (250 nm) 1.5 mM HDMS-β-CD + 5 mM CIL and 10 mM formate in MeOH (acidified with 0.75 M formic acid) Capillary, 50 µm × 40 cm; 30 kV, 15 ºC	4-amino-2,2-dimethyl-6-ethoxycarbonylamino-3,4-dihydro-2H-1-benzopyran	Standards	Rousseau et al., 2010
	[D-AlaC_4]$^+$[NTf_2]$^-$  [D-AlaC_4][NTf_2]	MEKC-UV (214) 10 mM CIL + 30 mM β-CD + 30 mM SDS + 15% IPA in 40 mM borate Capillary, 50 µm × 50.0 cm; 25 kV, 15 ºC	FMOC-Pipecolic acid	Standards	Hadjistasi et al., 2013
	[L-AlaC_4]$^+$[NTf_2]$^-$ [L-ValC_4]$^+$[NTf_2]$^-$	CE-UV (210, 215, or 235 nm) 15 mM CIL + 20 mM Me-β-CD in 30 mM citrate with 20 % EtOH or ACN (pH 5.0) Capillary 50 µm × 24.5 cm; 20 kV, 25 ºC	Naproxen, pranoprofen, warfarin	Standards	Zhang et al., 2013a

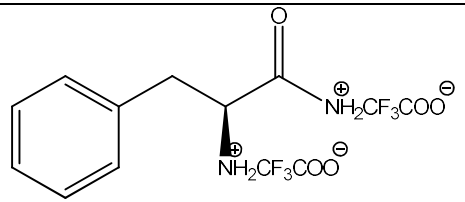
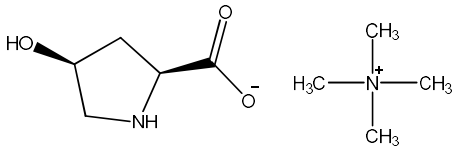
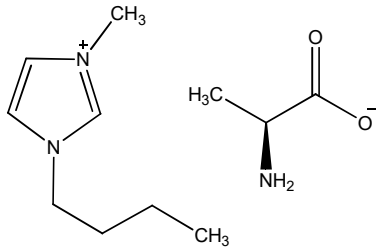
	 [L-ValC$_4$][NTf$_2$]  [L-AlaC$_4$][NTf$_2$]				
	[L-AlaC$_4$]$^+$[NTf$_2$]$^-$ [L-ValC$_4$]$^+$[NTf$_2$]$^-$  [L-ValC$_4$][NTf$_2$]  [L-AlaC$_4$][NTf$_2$]	CE-UV (210, 225, 230, or 235 nm) 15 mM CIL + 2 mM vancomycin in 50 mM phosphate + 20 % MeOH (pH 7.0) Capillary, 50 µm × 24.5 cm; 20 kV, 25 ºC	Naproxen, carprofen, ibuprofen, pranoprofen, ketoprofen	Standards and naproxen bulk sample	Zhang et al., 2014
	(S)-[CHTA]$^+$[NTf$_2$]$^-$  (S)-[CHTA][NTf$_2$])	CE-UV (214 nm) 20 mM CIL 30 mM sodium cholate (ibuprofen) 10 mM 1-S-octyl-β-D-thioglucopyranoside OTG (flurbiprofen) Capillary, 50 µm × 37 cm; 10-30 kV	Ibuprofen, flurbiprofen	Standards	Tran and Mejac, 2008
	[L-AlaC$_4$]$^+$[Lactate]$^-$  [L-AlaC$_4$][Lac]	CE-UV (200 or 230 nm) 15 or 20 mM CIL + 10-35 mM TM-β-CD in 5 mM acetate (pH 5.0) Capillary, 50 µm × 50 cm; 30 kV, 20 ºC	Ibuprofen, ketoprofen, carprofen, indoprofen, flurbiprofen, naproxen, fenoprofen	Standards	Mavroudi and Kapnissi-Christodoulou, 2015

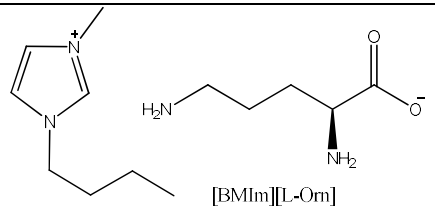
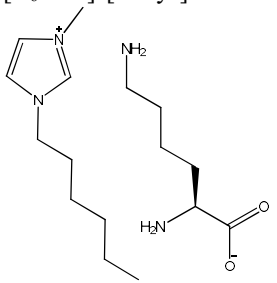
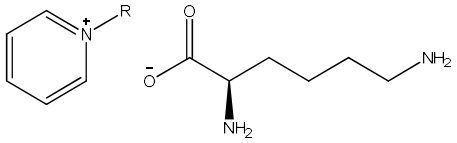
	[D-AlaC$_4$]$^+$[Lactate]$^-$  [D-AlaC$_4$][Lac]	CE-UV (230 nm) Huperazine A: 40 mM CIL + 2 mM SCF-7 in 4 mM acetato de amonio/5% MeOH (pH 4.0) Warfarin: 20 mM CIL +40 mM IPCF-6 in 4 mM acetate/20 % MeOH Coumachlor: 40 mM CIL + 40 mM IPCF-6 in 4 mM acetate/20% MeOH Capillary, 50 µm × 30 cm; 20 kV, 20 ºC	Huperazine A, warfarin, coumachlor	Standards	Stavrou et al., 2015
	[EMIm]$^+$[L-Lactate]$^-$  [EMIM][L-Lactate]	CE-UV 20 mM CIL + 10 mM β-CD in 30 mM Tris/phospahte (pH 2.5, except for homatropine methylbromide, pH 2.0) Capillary, 50 µm × 40 cm; 20 kV, 25 ºC	Zopiclone, repaglinide, chlorphenamine, brompheniramine , dioxopromethazine, promethazine, liarozole, carvedilol, homatropine hydrobromide, homatropine methylbromide, venlafaxine, sibutramine	Standards and Eszopiclone tablets	Zuo et al., 2013
	[EMIm]$^+$[L-lactate]$^-$  [EMIM][L-Lactate]	CE-UV 30 mM CIL + 40 mM HP-β-CD in 50 mM phosphate (pH 2.75) Capillary, 50 µm × 41 cm; 20 kV	Ofloxacin, propranolol, dioxopromethazine, isoprenaline, chlorpheniramine, liarozole, tropicamide, amlodipine benzenesulfonate, brompheniramine, homatropine methylbromide	Standards and Ofloxacin bulk sample	Cui et al., 2013
	[TMA]$^+$[L-Arg]$^-$  [TMA][L-Arg]	CE-UV (220, 230, or 237 nm) 60 mM CIL + 2.5 % glycogen in 36.67 mM Tris/phosphate (pH 3.0) Capillary, 50 µm × 41.5 cm; 18.9 kV, 19.2 ºC	Nefopam, citalopram, duloxetine	Standards	Zhang and Du, 2013

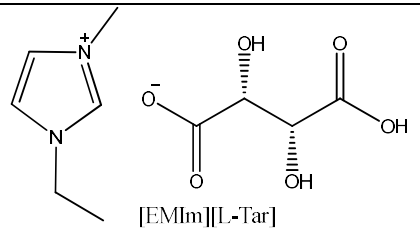
	[TMA]$^+$[L-Arg]$^-$  [TMA][L-Arg]	CE-UV (220, 215, 237, or 230 nm) 60 mM CIL + 7.0 % maltodextrin in 50 mM Tris-H_3PO_4 (pH 3.0) Capillary, 50 µm x 41.5 cm; 18 kV, 25 °C	Nefopam, duloxetine, ketoconazole, cetirizine, citalopram	Standars	Chen et al., 2017
	[TMA]$^+$[L-Arg]$^-$  [TMA][L-Arg]	CE-UV (237, 230, 220, or 225 nm) 30 mM CIL + 20 mM HP-β-CD in 40 mM Tris/H_3PO_4 (pH 2.6) Capillary 50 µm × 41.5 cm; 20 kV, 15 ºC	Amlodipine besylate, duloxetine, nefopam, propranolol	Standards	Zhang et al., 2016a
	[TBA]$^+$[L-Asp]$^-$  [TBA][L-Asp]	CE-UV (214 nm) 4 mM [TBA]$^+$[L-Asp]$^-$ + 5 mM β-CD in 15 mM borate (pH 9.5) Capillary, 50 µm × 50.2 cm; 10 kV, 25 ºC	phenylalanine, tryptophan	Amino acids injections	Wu et al., 2014
	[TBA]$^+$[Leu]$^-$  [TBA][L-Leu]	CE-UV (216.4, 226.4, or 279 nm) 15 mM HP-β-CD + 15 mM [TBA]$^+$[Leu]$^-$ in 50 mM citrate (pH 3.0) Capillary, 50 µm x 40 cm; 10, 15, 20 kV, 16-20 ºC	Ondansetron, ofloxacin, mianserin	Standars	Stanescu et al., 2017

	[TMA]$^+$[L-OH-Hyp]$^-$  [TMA][L-OH-Pro]	CE-UV (230, 237, 265, or 289 nm) 30 mM CIL+ 80 mM clindamicyn in 40 mM borate + 20 % MeOH (pH 7.6) Capillary 50 µm × 41.5 cm; 20 kV, 20 ºC	Propranolol, nefopam, citalopram, chlorphenamine	Standards	Xu et al., 2015
	L-UCLB  R = -$(CH_2)_9$-CH=CH_2 = L-UCLB	MEKC-UV (214 nm) 2.0 mM CIL + 35 mM TM-β-CD in 5 mM acetate (pH 5.0) Capillary, 50 µm × 56.0 cm; 30 kV, 16 ºC	Ibuprofen, fenoprofen, ketoprofen, suprofen, indoprofen	Standards and ibuprofen tablets	Wang et al., 2009
	L-UCLB L-UCAB  R = -$(CH_2)_9$-CH=CH_2 = L-UCLB  R = -$(CH_2)_9$-CH=CH_2 = L-UCAB	MEKC-UV BOH: 5 mM L-UCLB + 30 mM TM-β-CD in 10 mM acetate (pH 5.0) THBP: 3 mM L-UCLB + 30 mM TM-β-CD in 10 mM acetate (pH 5.0) TFAE: 5 mM L-UCLB + 30 mM TM-β-CD in 10 mM acetate (pH 5.0) TSO: 5 mM L-UCAB + 30 mM TM-β-CD in 10 mM phosphate (pH 7.0) Capillary 50 µm × 56 cm; 30 kV, 16 ºC	1,1`-bi-2-naphthol (BOH), 7,8,9,10-tetrahydro-benzo[a]pyren-7-ol (THBP), 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE), trans-stilbene oxide (TSO)	Standards	Liu and Shamsi, 2014

	$[BMIm]^+[BLHvB]^-$ $[BMIm]^+[BSMB]^-$  [BMIm][BLHvB]	CE-UV (289 nm, 230 nm, 237 nm, 205 nm, or 250 nm) 30 mM $[BMIm]^+[BLHvB]^-$ + 20 mM HP-β-CD in 20 mM Tris/H_3PO_4 (pH 2.5) Capillary 50 µm × 41.5 cm; 25 kV, 20 ºC	Propanolol, duloxetine, amlodipine besylate, nefopam, tropicamide,	Standards	Zhang et al., 2016b
CILs as chiral ligands	$[C6mim]^+[L\text{-}Pro]^-$  $[C_6mim][L\text{-}Pro]$	LE-CE-UV (200 nm) 30 mM $[C_6mim]^+[L\text{-}Pro]^-$ + 15 mM Cu(II) + 30 % MeOH (pH 4.0) Capillary, 50 µm × 40 cm; 30 kV, 25 ºC	His, Phe, Trp, Tyr	Standards	Liu et al., 2009
	$[L\text{-}Pro]^+[CF3COO]^-$  $[L\text{-}Pro][CF_3COO]$	LE-CE-UV (254 nm) 50.0 mM $[L\text{-}Pro]^+[CF_3COO]^-$ + 25.0 mM Cu(II) + 20% MeOH (pH 4) Capillay, 75 µm × 45 cm; 20 kV; 25 ºC	Ala, Asn, Asp, Ile, Met, Ser, Phe, Thr, Tyr (all derivatized with Dns)	Standards	Mu et al., 2012a
	$[L\text{-}Phn]^+[CF_3COO]_2^-$	LE-CE-UV (254 nm) 20 mM $[L\text{-}Phn]^+[CF_3COO]_2^-$ + 10 mM Cu(II) in 15 mM ammonium acetate (pH 5.0) Capillary, 75 µm x 45 cm; 16 kV, 25 °C	Ile, Tyr, Ala, Gln, Ser, Met, Asn, Phe (all derivatized with Dns)	Standars	Jiang et al., 2017

	 [L-Phn][CF_3COO]$_2$				
	[TMA]$^+$[L-OH-Pro]$^-$  [TMA][L-OH-Pro]	LE-CE-UV (200 nm) 60 mM [TMA]$^+$[L-OH-Pro]$^-$ + 30 mM Cu(II) (pH 4.5) Capillary, 50 µm × 41.5 cm; 25 kV, 25 ºC LE-MEKC-UV (200 nm) 10 mM SDS 60 mM [TMA]$^+$[L-OH-Pro]$^-$ + 30 mM Cu(II) (pH 4.5) Capillary, 50 µm × 41.5 cm; 25 kV, 25 ºC	LE-CE-UV: Phe, His, Trp, DOPA LE-MEKC-UV: Trp and DOPA	Standards	Liu et al., 2015
	[BMIm]$^+$[L-Ala]$^-$  [BMim][L-Ala]	LE-CE-UV (254 nm) 5.0 mM [BMIm]$^+$[L-Ala]$^-$ + 5.0 mM β-CD + 2.5 mM Mn(II) in 100 mM borate + 5.0 mM acetate (pH 8.3) Capillary, 75 µm × 45 cm; - 23 kV, 25 ºC	Thr, Val, Tyr, Leu, Ile, Pro, Met, Ser, His, Phe, Ala, Asn, Trp, Gln, Orn, Glu, Arg, Asp, Cys, Lys (all derivatized with Dns)	Standards	Su et al., 2015
	[BMIm]$^+$[Orn]$^-$	LE-CE-UV (254 nm) 15 mM [BMIm]$^+$[Orn]$^-$ + 3.0 mM Zn(II) in 100 mM borate + 5.0 mM acetate (pH 8.4) Capillary, 75 µm × 45 cm; 21 kV, 25	Ser, Met, Ile, Phe, Tyr, Cys, Asn, Arg, Ala, His, Thr, Asp, Leu, Lys (all derivatized with Dns)	Standards	Mu et al., 2012b

	 [BMIm][L-Orn]				
	$[C_6mim]^+[L\text{-}Lys]^-$  [C_6mim][L-Lys]	LE-CE-UV (254 nm) 6.0 mM $[C_6mim]^+[L\text{-}Lys]^-$ + 3.0 mM Zn(II) in 100 mM boric acid + 5.0 mM acetate (pH 8.2) Capillary, 50 µm × 50 cm; -20 kV, 25 ºC	Ser, Met, Ile (all derivatized with Dns)	Standards	Zhang et al., 2013b
	$[Epy]^+[L\text{-}Lys]^-$  [1-ethylpyridinium][L-lysine]	LE-CE-UV (254 nm) 6.0 mM $[Epy]^+[L\text{-}Lys]^-$ + 3.0 mM Zn(II) in 100 mM boric acid + 5.0 mM acetate Capillary, 75 µm × 60 cm; -21 kV	Ala, Asn, Asp, Ile, Leu, Met, Phe, Ser, Thr, Trp, Tyr (all derivatized with Dns)	Standards	Sun et al., 2014
	$[EMIm]^+[L\text{-}Tar]^-$	LE-CE-UV (200 nm) 54 mM $[EMIm]^+[L\text{-}Tar]^-$ + 9 mM Ni(II) + 5 mM SDS in 10 mM borate (pH 8.5) Capillary, 50 µm × 52 cm; 25 kV, 20 ºC	Trp, Tyr, Phe	Standards	Huang et al., 2016

	 [EMIm][L-Tar]				

* Capillary dimension expressed as internal diameter × effective length (cm to the detector).
poly-L-SUCLS, polysodium N-undecenoxycarbonyl-L-leucine sulfate; **poly-L-SUCL**, polysodium N-undecenoxycarbonyl-L-leucinate; **[PhChol]$^+$[NTf$_2$]$^-$**, (R)-2-hydroxy, N,N, N- trimethyl-1-phenylethanaminium-bis(trifluoromethylsulfonyl)imide; **DM-β-CD**, heptakis(2,6-di-O-methyl)-β-CD; **TM-β-CD**, heptakis(2,3,6-tri-O-methyl)-beta-cyclodextrin; **HDMS-β-CD**, heptakis(2,3-di-O-methyl-6-O-sulfo)-β-CD; **FMOC-Cl,** 9-fluorenylmethoxycarbonyl chloride; **SDS**, sodium dodecyl sulfate; **Me-β-CD**, methyl-β-CD; **SCF-7,** sodium sulfated cyclofructan 7; **IPCF-6**, isopropyl cyclofructan-6; **HP-β-CD**, 2-hydroxypropil-β-CD; [**TMA**]$^+$[**L-Arg**]$^-$, tetramethylammonium L-arginine; **[TBA]$^+$[L-Asp]$^-$**, tetrabutylammonium L-aspartic acid; **[TBA]$^+$[L-Leu]$^-$,** tetramethylammonium L-leucinate; **[L-Pro]$^+$[CF$_3$COO]$^-$,** L-proline trifluoroacetate; **Dns**, 5-(dimethylamino)naphthalene-1-sulfonyl chloride; [**BMIm**]$^+$[**Orn**]$^-$, 1-butyl-3-methylimidazolium ornithine. *Others are listed in abbreviation section.

2. CILs as sole chiral selectors

There are very few examples where CILs have been used as the sole chiral selector in the background electrolyte in CE (see **Table 1**). The first enantioseparations obtained using CILs were reported in 2006. On the one hand, Rizvi and Shamsi (2006) synthesized the monomeric and polymeric forms of two amino acid CILs surfactants (undecenoxycarbonyl-L-pyrrolidinol bromide (L-UCPB) and undecenoxycarbonyl-L-leucinol (L- UCLB)) for the separation of two acidic analytes. The comparison between the chiral separations achieved using both the monomers and the polymers revealed that the factor affecting analyte-micelle interactions was the presence of opposite charges so that the chiral recognition was due to the interaction of the acidic analytes with the cationic group of the selector. The structural compatibility between analyte and selector was also an important factor (Rizvi and Shamsi, 2006). On the other hand, Yuan et al. (2006) demonstrated the discrimination power of (R)-N,N,N-trimethyl-2-aminobutanol-bis(trifluoromethanesulfon)imidate ($[EtChol]^+[NTf_2]^-$) to perform the enantioseparation of fifteen different compounds including alcohols, amines, acids, and amino acids by CE, HPLC and GC. In CE, the CIL was added at concentrations of 5 or 10 mM to phosphate or borate buffer at different pHs depending on the analyzed compounds. Under the best conditions selected for each compound, resolution values between 0.6 and 6.8 were achieved, showing the effectiveness of this CIL as chiral selector (Yuan et al., 2006).

Later, an ephedrine-based CIL, whose anionic moiety was the same as that employed by Yuan et al. (2006), served as selector to achieve the enantioseparation of rabeprazole and omeprazole by NACE. Resolution values around 1 for both pharmaceuticals were reached using 60 mM of (+)-N,N-dimethylephedrinium-bis(trifluoromethanesulfon)imidate ($[DMP]^+[Tf_2N]^-$) in ACN:methanol (60:40 v/v). The experiments showed that DMP^+ cations play a key role in the separation mechanism. In

fact, the enantioseparation was based not only on the ion-pair formation between this cation and the negatively charged enantiomers but also on the hydrogen bonding (between the hydroxyl group of DMP^+ and the sulfoxide group of the analytes) which provided a supplementary interaction for stereoselectivity (Ma et al., 2010).

An interesting CIL functionalized with β-cyclodextrin (6-O-2-hydroxypropyltrimethylammonium-β-cyclodextrin tetrafluoroborate [HPTMA-β-CD]$^+$[BF_4]$^-$) was synthesized and used as chiral selector for the enantioseparation of eight drugs including chlorpheniramine, brompheniramine, pheniramine, tropicamide, bifonazole, promethazine, warfarin and liarozole. [HPTMA-β-CD][BF_4] showed a higher solubility in aqueous buffers than β-cyclodextrin, and produced a stable reversed EOF. Under optimal buffer pH and CIL concentration, the enantiomers of the eight compounds analyzed were separated with resolution values ranging from 1.00 to 2.90. The comparison between the chiral separation of chlorpheniramine and promethazine obtained using β-cyclodextrin or [HPTMA-β-CD][BF_4] as selectors showed that the CIL provided clearly a better enantioseparation than the native cyclodextrin. This fact was attributed to a higher stability of the inclusion complex and to a higher differentiation in the intermolecular interactions established between the CIL and the analyte (provided by the nonsymmetrical chemical environment generated by charge localization) (Yu et al., 2013).

Stavrou and Kapnissi-Christodoulou, (2013) demonstrated for the first time the potential of amino acid ester-based CILs, (L-alanine methyl ester lactate (L-AlaC_1Lac), L-alanine ethyl ester lactate (L-AlaC_2Lac), L-alanine tert butyl ester lactate (L-AlaC_4Lac), D-alanine tert butyl ester lactate (D-AlaC_4Lac) and L-alanine tert butyl ester bis(trifluromethane)sulfonamide L-AlaC_4NTf_2) as the sole chiral selectors in CE. The

189 authors performed a systematical and interesting study about how different parameters
190 concerning amino acid ester-based CILs affect the enantioseparation of 1-1´-binaphthyl-
191 2,2-diylhidrogenphosphate (BNP). Thus, the effect of the alkyl ester group, the anion
192 employed, the cation configuration, the CIL concentration and the buffer pH on the chiral
193 separation, was studied. The results obtained revealed that the determining factors to
194 separate BNP enantiomers were the presence of the tert butyl ester group in the cation
195 (which implies that steric hindrance is involved in the separation mechanism), the cation
196 configuration (the enantiomer migration order was based on the L or D configuration),
197 and the working pH (CILs tested were pH-dependent; the positive charge of the amino
198 group decreases when increasing the pH which results in fewer electrostatic interactions
199 between the CIL and BNP enantiomer). Under the optimal experimental conditions (see
200 **Table 1**), BNP enantiomers were well-separated (Rs = 1.94) in less than 13 min (Stavrou
201 and Kapnissi-Christodoulou, 2013).
202 Another promising trend to develop CILs was proposed by Zhang et al. (2015) who
203 transformed a conventional saccharide chiral selector into a CIL. They compared the
204 discrimination power of three separation systems (lactobionic acid, lactobionic acid +
205 tetramethylammonium-chloride, and the CIL tetramethylammonium-lactobionate (TMA-
206 LA)) to achieve the chiral separation of six basic model drugs. Taking into account that
207 the chiral separations obtained using the system lactobionic acid +
208 tetramethylammonium-chloride were less than those achieved employing TMA-LA, it
209 cannot be considered as a simple combination of lactobionic acid and the salt. **Figure 1**
210 depicts the chiral separation obtained for the six studied drugs using TMA-LA as the sole
211 chiral selector. In this case, the separation mechanism was not fully demonstrated
212 although it could be related with the CIL dissociation degree which could affect the ionic
213 strength of the running buffer (Zhang et al., 2015).

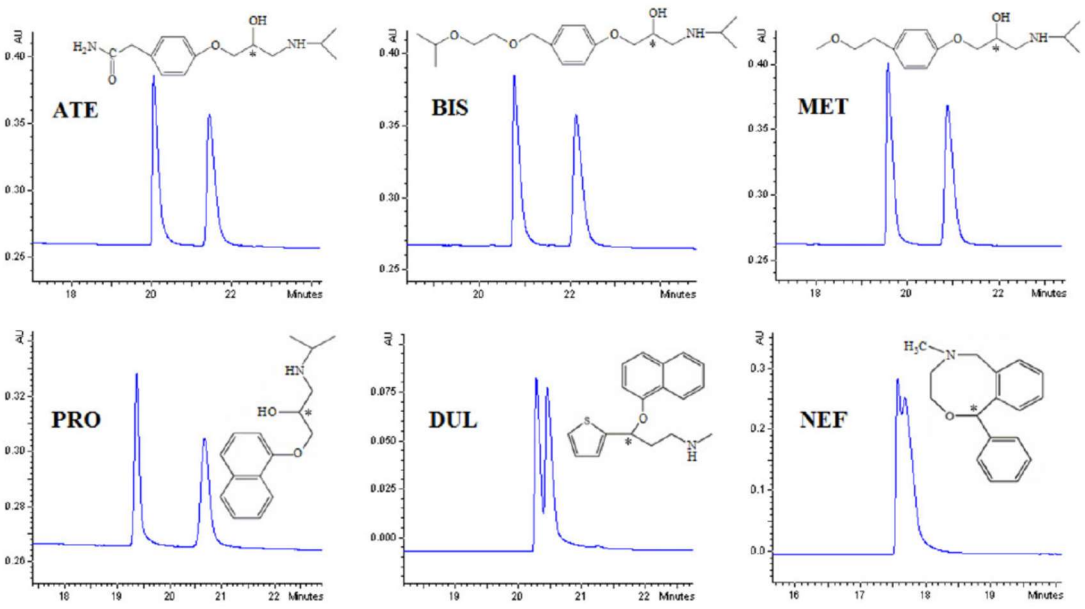


Figure 1. Electropherograms corresponding to the chiral separation of atenolol (ATE), bisoprolol (BIS), metoprolol (MET), propranolol (PRO), duloxetine (DUL) and nefopam (NEF) using TMA-LA as the sole chiral selector. Separation conditions: BGE, 200 mM TMA-LA in 40 mM borate containing 40 % methanol v/v (pH 7.6), voltage, 20 kV; temperature, 15 °C. Reprinted from (Zhang et al., 2015), copyright (2015) with permission from Wiley-VCH.

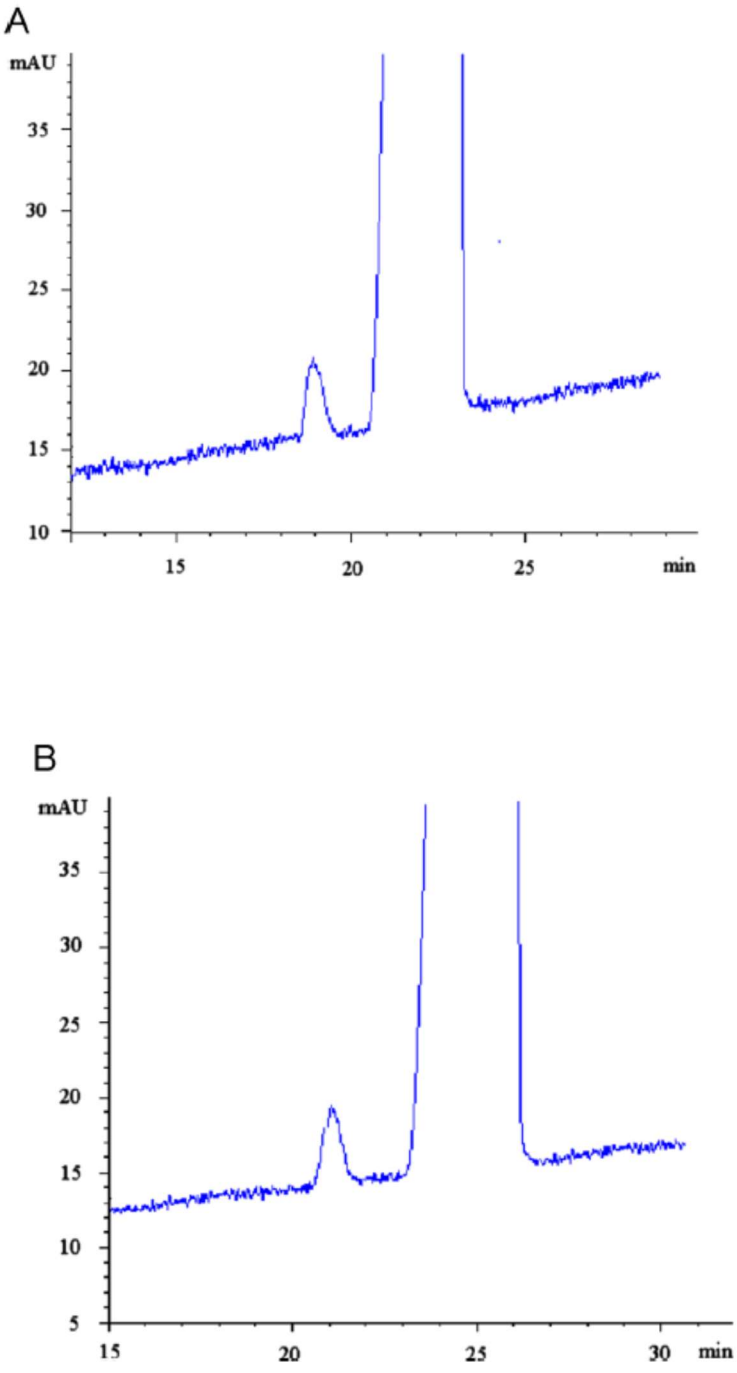
3. CILs as chiral selectors in dual separation systems.

During the period of time covered by this review, most of the applications of CILs in CE employed dual recognition systems based on the combination of a CIL and other chiral selectors such as cyclodextrins, antibiotics, cyclofructans, polysaccharides, or surfactants.

As it can be observed in **Table 1**, different works employed CILs based on a chiral cationic moiety with bis(trifluoromethanesulfon)imidate) as anion in combination with cyclodextrins (François et al., 2007; Mofaddel et al., 2008; Rousseau et al., 2010; Hadjistasi et al., 2013; Zhang et al., 2013a), antibiotics (Zhang et al., 2014) or chiral

surfactants (Tran and Mejac, 2008) to achieve the enantioseparation of a broad range of chiral compounds. Basically, three different types of chiral cationic moieties have been used. The first type includes choline derivatives such as ethylcholine (EtChol) and phenylcholine (PhChol) which were employed for instance in combination with dimethyl-β-CD and trimethyl-β-CD with the purpose of separating six arylpropionic acids. Parameters such as the nature and the concentration of the CIL and the cyclodextrin, buffer concentration, and hydro-organic composition of BGE were evaluated to investigate a possible synergistic effect between both selectors. In spite of the fact that a general trend was not established, the increase of resolution and selectivity in certain cases suggested that the synergistic effect could be due to ion-paring interactions between the cation of CILs and the analyte (François et al., 2007). The effect of $[EtChol]^+[NTf_2]^-$, and (S)(+)-tetrabutylammonium camphorsulfonate, in combination with γ-cyclodextrin for the enantioseparation of binaphthol was also investigated (Mofaddel et al., 2008). In this case, a central composite experimental design was achieved using as factors the concentrations of the cyclodextrin and the CIL. An improvement in the chiral resolution was not obtained by adding the CILs to the separation media. In fact, a neutral effect was observed when $[EtChol]^+[NTf_2]^-$ was employed whereas a weak antagonist effect was obtained employing (S)(+)-tetrabutylammonium camphorsulfonate. The discrimination potential of $[EtChol]^+[NTf_2]^-$ in combination with anionic cyclodextrins (heptakis(2,3-di-O-methyl-6-O-sulfo)-β-cyclodextrin) also allowed to determine the enantiomeric purity of an intermediate formed in the synthesis of a new benzopyran by NACE (Rousseau et al., 2010). The addition of the CIL to the separation system gave rise to an increase of resolution and selectivity that indicated a synergistic effect of both chiral selectors. Under the best experimental conditions, it was possible to determine percentages of 0.1 % of one enantiomer in presence of the other.

255 The second type of CIL based on the combination of a chiral cation with $[NTf_2]^-$ described
256 in the literature is S-[3-(chloro-2-hydroxypropyl)trimethylammonium]
257 [bis((trifluoromethyl)sulfonyl)amide] (S-$[CHTA]^+[NTf_2]^-$). Its combined use with a
258 second chiral selector (sodium cholate), and a third one (1-S-octyl-β-D-
259 thioglucopyranoside) allowed the chiral separation of ibuprofen and flurbiprofen,
260 respectively (Tran and Mejac, 2008). The need for these systems suggested that the chiral
261 cation of IL provided one or two of three interactions points needed for the chiral
262 separation. Finally, as it can be seen in **Table 1**, amino acids are the third type of chiral
263 cationic moiety employed (Hadjistasi et al., 2013; Zhang et al., 2013a; Zhang et al., 2014).
264 The potential synergistic effects of L-alanine and L-valine *tert* butyl esters (L-AlaC_4NTf_2,
265 L-ValC_4NTf_2) with β-CD derivatives or vancomycin for the enantioseparation of different
266 racemic drugs was evaluated by Zhang et al. (Zhang et al., 2013a; Zhang et al., 2014).
267 Compared to cyclodextrin or vancomycin alone, significant improvements in the
268 separation of all the analytes were observed when CILs were added to the separation
269 media. In both dual systems (CIL/cyclodextrin or CIL/vancomycin), the chiral
270 recognition process was based on hydrogen-bonding and ionic interactions. The addition
271 of an organic modifier caused a decrease in EOF which gave more chances for
272 interactions between the analyte and selectors improving the chiral resolution and
273 effective selectivity. It is worth noting that the dual systems vancomycin/L-AlaC_4NTf_2
274 and vancomycin/L-ValC_4NTf_2 were successfully applied to test the chiral impurity of
275 naproxen samples (Zhang et al., 2014). **Figure 2** shows the electropherogram obtained
276 for the optical purity test of (S)-naproxen (bulk drug) with both chiral systems. In both
277 cases, the content of (S)-naproxen as enantiomeric impurity was 1 %.
278
279



280

281 **Figure 2.** Optical purity test of (S)-naproxen sample with (A) vancomycin/L-AlaC4NTf2

282 and (B) vancomycin/L-ValC4NTf2 as chiral systems. Separation conditions: BGE, 15

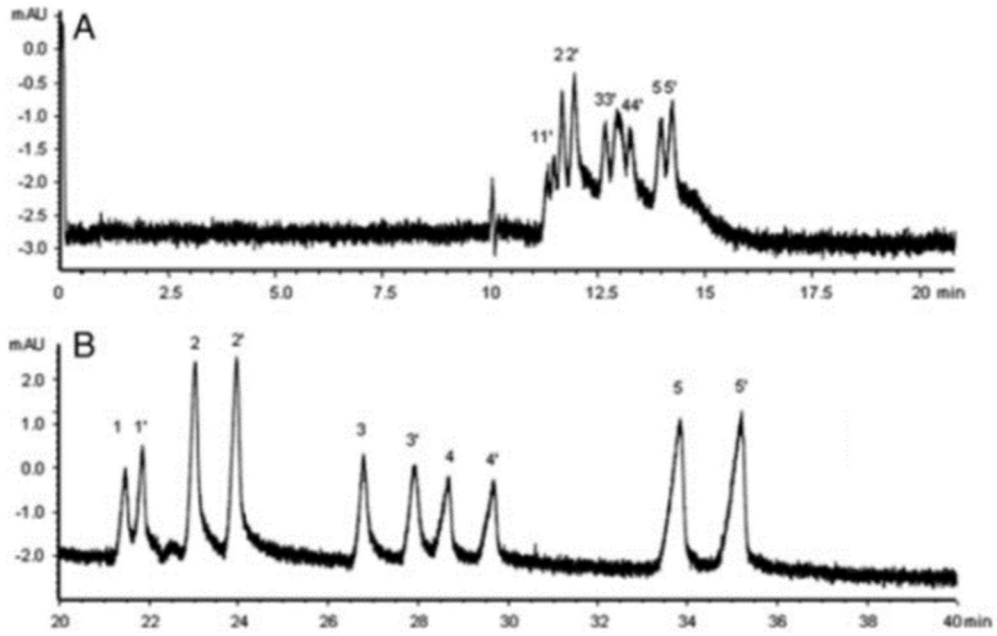
283 mM CIL 2 mM vancomycin in 50 mM phosphate buffer containing 10 % methanol v/v

(pH 7.0), voltage, 20 kV; temperature, 25 °C. Reprinted from (Zhang et al., 2014), copyright (2014) with permission from Elsevier.

Pipecolic acid was also separated by a MEKC methodology in which β-CD and D-AlaC_4NTf_2 were combined. To improve the sensitivity, 9-fluorenylmethoxycarbonyl chloride (FMOC-Cl) was employed as derivatizing agent. The addition of the CIL to the separation medium containing β-CD, SDS and isopropanol as organic modifier provided and increase in the resolution of pipecolic acid from 1.14 to 1.87 (Hadjistasi et al., 2013). Recently, a subtype of this kind of amino acid based CILs characterized by the use of L-Lactate as anion instead of NTf_2 was also employed along with cyclodextrins (Mavroudi and Kapnissi-Christodoulou, 2015) or cyclofructans (Stavrou et al., 2015) for the enantioseparation of different chiral drugs. Both studies showed that the use of binary systems (trimethyl-β-CD/L-AlaC_4Lac or cyclofructans/D-AlaC_4Lac) enabled to achieve values of resolution and peaks efficiencies higher than those obtained using the cyclodextrin or the cyclofructans alone. This fact clearly pointed out that the addition of the amino acids based CILs provided a synergistic effect needed to obtain a better enantioseparation of the studied compounds. Lactate was also used as anionic part in imidazolium CILs. Thus, researchers from Guo´s group investigated the combination of β-CDs with 1-alkyl-3-methylimidazolium-L-Lactate $[EMIm]^+[L\text{-Lactate}]^-$ which is commercially available (Zuo et al., 2013; Cui et al., 2013). On the one hand, they applied a dual system made up of $[EMIm]^+[L\text{-Lactate}]^-$ and β-CD which, under the optimal conditions, provided the separation of twelve drugs with values of resolution ranging from 1.26 to 5.20. In addition, they proved as longer alkyl (butyl instead of ethyl-) chains of the cationic part of CIL offered a slightly higher resolution, at the expense of longer analysis time. This observation was related to the fact that longer alkyl chains form a

309 stable bilayer inside the capillary which may provide a more stable environment for the
310 chiral separation (Zuo et al., 2013). On the other hand, the same research group also
311 demonstrated the synergistic effect between hydroxypropyl-β-CD and $[EMIm]^+[L$-
312 $Lactate]^-$ for the enantioseparation of ten different drugs. In this case, they illustrated the
313 low influence of the chirality and nature of the anionic part of CIL on the
314 enantioseparation (Cui et al., 2013). The two methods optimized by Gou et al. (see **Table**
315 **1**) were successfully applied to the chiral impurity determination of eszopiclone in
316 commercial tablets (Zuo et al., 2013) and ofloxacin in bulk samples (Cui et al., 2013).
317 The zwitterionic structure of amino acids allows their use not only as chiral cations to
318 obtain CILs but also as chiral anions. As it can be seen in **Table 1**, within the period of
319 time covered by this review, different studies were performed to explore the synergistic
320 effect of this kind of CILs using as amino acids L-Arg, L-Asp, L-Hyp, L-Ile, L-Leu, L-
321 His, L-Pro in combination with polysaccharides (Zhang and Du, 2013; Chen et al., 2017),
322 cyclodextrins (Zhang et al., 2016a; Wu et al., 2014; Stanescu et al., 2017), or antibiotics
323 (Xu et al., 2015). In these works, experimental parameters such as CIL and chiral selector
324 concentration, buffer pH, type and concentration of organic modifier, voltage and
325 temperature were systematically optimized. A relevant factor that deserves to be
326 highlighted is that the structure and properties of the chiral part of these CILs (i.e. the
327 amino acids) have a high influence on the separation process which may be attributed to
328 the hydrogen bonding interactions between basic analytes and CILs. Although these
329 amino acid based CILs were mainly applied to the chiral separation of model drugs
330 (Zhang and Du, 2013; Chen et al., 2017; Zhang et al., 2016a; Stanescu et al., 2017; Xu et
331 al., 2015), they have demonstrated to be adequate for the quantification of underivatized
332 phenylalanine and tryptophan in amino acids injections (Wu et al., 2014).
333

The same amino acid derived CIL (L-UCLB) employed by Rizvi and Shamsi (2006) as sole chiral selector was used also in dual systems with β-CD derivatives. On the one hand, Wang et al. (2009) carried out the enantiodiscrimination of five anionic drugs using 2,3,6-tri-O-methyl-β-cyclodextrin and L-UCLB (which forms micelles in aqueous separation media). As **Figure 3** shows, the use of the cyclodextrin alone resolved partially the enantiomeric mixture of the drugs whereas the addition of L-UCLB to the buffer containing the cyclodextrin provided the baseline separation for all of them except for ibuprofen (whose resolution value was 1.32). The effect was the result of the interaction between the CIL and the cyclodextrin which reduced the interaction of CIL with the capillary wall. The developed dual system was successfully applied to the quantitative analysis of ibuprofen racemate in commercial tablets. On the other hand, Liu and Shamsi, (2014) used the same CIL to resolve four neutral chiral compounds. In addition to L-UCLB, other cationic CIL surfactants with different head groups were evaluated in combination with 2,3,6-tri-O-methyl-β-cyclodextrin. A significant effect of the head group hydrophobicity on the resolution and migration time was observed so that both the optimum head group and CIL concentration must be screened for each compound. As **Table 1** shows, the most suitable dual system for 1,1´-bi-2-naphthol (BOH), 2,2,2-trifluoro-1-(9-anthryl)ethanol (TFAE) and 7,8,9,10-tetrahydro-benzo[a]pyren-7-ol (THBP) was 2,3,6-tri-O-methyl-β-cyclodextrin/L-UCLB, whereas for trans-stilbene oxide (TSO), the system 2,3,6-tri-O-methyl-β-cyclodextrin/ N-undecenoxy-carbonyl-L-alaninol bromide (L-UCAB), provided better enantioresolution.



359

360 **Figure 3.** Electropherograms corresponding to the chiral separation of ibuprofen,
361 fenoprofen, indoprofen, suprofen and ketoprofen with (A) absence and (B) presence of
362 L-UCLB. Separation conditions: BGE, 5 mM acetate containing (A) 35 mM TM-β-CD
363 and (B) 35 mM TM-β-CD and 1.5 L-UCLB, voltage 30 kV, temperature, 16 ºC. Reprinted
364 from (Wang et al., 2009), copyright (2009) with permission from Wiley-VCH

365

366 Finally, Zhang et al. (2016b), synthesized and applied for the first time two spirocyclic
367 chiral ionic liquids (1-butyl-3-methylimidazolium(T-4)-bis[(2S)-2-(hydroxy-κO)-3-
368 methyl-butanoato-κO]borate, $BMIm^{+}BLHvB^{-}$) and (1-butyl-3-methylimidazolium(T-4)-
369 bis[(αS)-α-(hydroxy-κO)-4-methyl-benzeneacetato-κO]borate, $BMIm^{+}BSMB^{-}$), as chiral
370 selectors in a dual separation system with β-cyclodextrin derivatives. The synergistic
371 effect established in the dual system consisting of $BMIm^{+}BLHvB^{-}$/ hydroxypropyl-β-CD
372 provided a significant improvement of the chiral separation for the five drugs analyzed.
373 The better enantioresolution exhibited by $BMIm^{+}BLHvB^{-}$ compared to $BMIm^{+}BSMB^{-}$
374 was attributed to the presence of an aromatic ring in $BSMB^{-}$ which may hinder the

recognition interactions. In addition, the results obtained by a molecular modeling study indicated that the associated state of CIL and hydrogen bonding interactions played an essential role in the chiral recognition process.

4. CILs as chiral ligands

A considerable number of works published showed that chiral amino acid ILs are promising alternatives as chiral ligands in Ligand-Exchange Capillary Electrophoresis (LE-CE). The first enantioseparation based on the use of this type of CIL was reported in 2009 by Liu et al. In that work, [1-hexyl-3-methylimidazolium][L-Pro] ($[C_6mim]^+[L\text{-}Pro]^-$), coordinated with Cu(II) was employed for the enantioseparation of phenylalanine (Phe), histidine (His), tryptophan (Trp) and tyrosine (Tyr). The results obtained in this study, in which the CIL was used as both chiral ligand and BGE, demonstrated that the cation part of CIL and the pH were the key factors in the separation mechanism. The former factor affected the separation due to the formation of ion pairs of alkylimidazolium cation and the CIL on the surface of the capillary, where the latter was relevant for the difference in charge-to-mass ratio between the amino acid-Cu complex and the uncomplexed amino acid. Subsequently, other Cu(II)-amino acid based CILs were also applied with success to the separation of other amino acids. Thus, the discrimination power of a CIL made up L-Proline as cation and $[CF_3COO]^-$ as anion was evaluated for the separation of nine pairs of enantiomers of amino acids (derivatized with dansyl chloride (Dns)) (Mu et al., 2012a). Under the optimal conditions of CIL concentration, pH and organic acid concentration (see **Table 1**) resolution values between 0.93-6.72 were achieved for the amino acids analyzed. The use of other anions (such as nitrate (NO_3^-), tetrafluoroborate (BF_4^-) or sulfate (SO_4^{2-})) in the CIL structure also provided the chiral separation of isoleucine which demonstrated the availability of this system for ligand

400 exchange separation. Liu et al. (2015), also evaluated the potential of other Cu(II)-amino
401 acid based CIL, namely tetramethylammonium L-hydroxyproline, $[TMA]^+[L\text{-}OH\text{-}Pro]^-$,
402 for the enantioseparation of different underivatized aromatic amino acids and 3,4
403 dihydroxyphenylalanine (DOPA) both in LE-CE and in LE-MEKC. The LE-CE system
404 enabled to achieve excellent separations for tryptophan and DOPA (resolution of 3.0 and
405 4.3, respectively) but no separation was observed for phenylalanine and histidine.
406 However, when SDS was added, the separation mechanism was based not only on the
407 differences in complex stability, but also in the differences of partition coefficients. In
408 this case, although the resolution of DOPA decreased (probably due to its catechol group
409 which prevents the interaction with the micellar phase), it was possible to reach the
410 separation of all the amino acids (even the R_S of tryptophan increased up to 3.8).
411 Recently, Jiang et al. (2017) have studied the effect of Cu(II)-amino amide ionic liquids
412 in the separation of Dns-D,L-amino acids. Among the CILs studied (L-
413 phenylalaninamide trifluoroacetate, $[L\text{-}Phn][CF_3COO]_2$, L-prolinamide trifluoroacetate,
414 $[L\text{-}Prn][CF_3COO]_2$, and L-alaninamide trifluoroacetate, $[L\text{-}Aln][CF_3COO]_2$), L-
415 phenylalaninamide based ionic liquid was chosen as it gave the highest resolution in the
416 shortest retention time. Parameters such as pH, buffer concentration or Cu(II) and CIL
417 ratio were evaluated and under the best conditions (see **Table 1**) 8 pairs of Dns-D,L-
418 amino acids enantiomers could be baseline separated. In order to stablish the recognition
419 mechanism that may involve the stabilization of the ternary complex formed between
420 Cu(II)-IL and the enantiomers, different experiments were carried out. In a first
421 experiment L-Phn was used as the chiral ligand and in a second one L-Phn and CF_3COOH
422 were used together as additives. However, the best resolution values were obtained with
423 the addition of the CIL. The method was also applied for the quantification of Dns-D,L-
424 amino acids and for the enantiomeric purity determination.

Besides Cu(II), other metal ions such as Zn(II) or Mn(II) were employed to form ligand selectors with amino acid based CILs (Su et al., 2015; Mu et al., 2012b; Zhang et al., 2013b; Sun et al., 2014). The baseline separation of twelve Dns-amino acids and the partial separation of six Dns-amino acids were obtained using a dual system made up of (Mn(II)-[1-butyl-3-methylimidazolium][L-alanine]), Mn(II)-[BMIm][L-Ala], and β-CD as chiral selectors in LE-CE (Su et al., 2015). This CIL was chosen among others with different alkyl chain length ([1-ethyl-3-methylimidazolium][L-Ala] ([EMIm][L-Ala]), [1-hexyl-3-methylimidazolium][L-Ala] ([HMIm][L-Ala])) in the imidazolium cation. Even though the resolution of three model amino acids improved when increasing the alkyl chain length, $[BMIm]^+$ was selected based on the principle of short migration time and high resolution. After the quantitative analysis of tyrosine (Tyr) which is the substrate of tyrosinase, the developed LE-CE methodology was successfully applied to study the inhibition efficiency of the tyrosinase inhibitors (Su et al., 2015). Regarding Zn(II), its coordination with an amino acid based CIL whose anion was L-ornithine gave rise to the baseline separation of eleven pairs of enantiomers of Dns-amino acids (Mu et al., 2012b). This ligand-exchange system was successfully applied in the screening of D-amino acid oxidase inhibitors based on the decrease of the concentration of D-methionine (Mu et al., 2012b). Zn(II) was also used along with CILs in which L-lysine was employed as anion (Zhang et al., 2013b; Sun et al., 2014). Zhang et al. (2013b) investigated CILs with different alkyl chain lengths in the imidazolium cation ($C_n$mim, from C_4 to C_8) for the enantioseparation of seven pairs of enantiomers of Dns-amino acids. Among them, the best chiral separation was achieved using [C_6mim][L-Lys]. **Figure 4** depicts the electropherograms obtained under optimal experimental conditions for the separation of the amino acids analyzed. On the other hand, Sun et al. (2014) developed a LE-CE methodology based on the use of CILs with pyridinium as cation and L-Lys as anion and

coordinated with Zn(II). 1-ethylpyridinium [Epy][L-Lys], 1-butylpyridinium [Bpy][L-Lys], 1-hexylpyridinium [Hpy][L-Lys] and 1-octylpyridinium [Opy][L-Lys] were synthesized and tested as ligand selectors for the separation of Dns-amino acids. The results obtained demonstrated that an increase in the alkyl chain length diminished the solubility of the CILs in the buffer which had a negative effect on the enantioseparation. Using [Epy][L-Lys]/Zn(II) and the appropriate experimental conditions (see **Table 1**) eight pairs of enantiomers of Dns-amino acids were baseline separated and three pairs partially separated. In addition, this LE-CE system was employed to study the kinetics of L-amino acid oxidase.

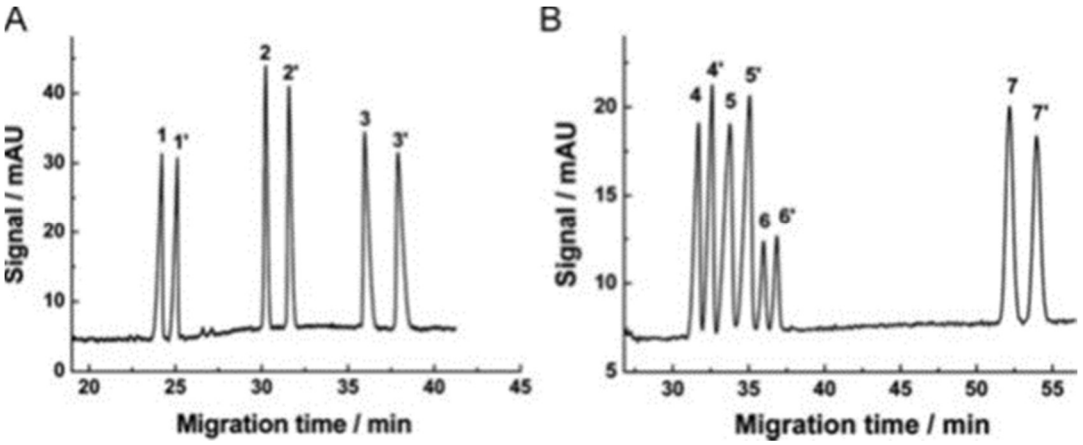


Figure 4. Electropherograms corresponding to the chiral separation of Dns-amino acids using [C_6mim][L-Lys] as chiral ligand. Separation conditions: BGE, 100 mM boric acid, 5 mM ammonium acetate, 3 mM $ZnSO_4$, 6 mM [C_6mim][L-Lys] (pH 8.2), voltage, -20 kV; temperature, 25 °C. Peak identity: (A) 1. Dns-D-Ile, 1'. Dns-L-Ile; 2. Dns-D-Met, 2'. Dns-L-Met; 3. Dns-D-Ser, 3'. Dns-L-Ser; (B) 4. Dns-D-Thr, 4'. Dns-L-Thr; 5. Dns-D-Phe, 5'. Dns-L-Phe; 6. Dns-D-Tyr, 6'. Dns-L-Tyr; 7. Dns-D-Asn, 7'. Dns-L-Asn. Reprinted from (Zhang et al. 2013b), copyright (2013) with permission from Wiley-VCH.

Even though most of the works described in the literature to carry out chiral separations by LE-CE employed an amino acid CIL, Huang et al. (2016) demonstrated the potential of [EMIM][L-Tar] as chiral ligand for the enantioseparation of tryptophan, tyrosine and phenylalanine enantiomers. Under alkaline conditions, the use of [EMIM][L-Tar] combined with Ni(II) gave rise to the best enantioseparations whereas the complexation with other metals such as Zn(II) or Co(II) provided only partial separation and no separation was observed with Cu(II). The study of the separation mechanism demonstrated that the effect of CIL in the separation is complex and it cannot be considered as simple superposition of the effect of cations and anions.

5. Concluding remarks

Despite many chiral selectors are available to carry out chiral separations by CE, the search for new selectors able to provide high enantiomeric resolutions is a relevant topic in this field. As it is shown in this review, over the last ten years different CE methodologies based on the use of CILs as sole chiral selectors, chiral selectors in dual systems, or chiral ligands have been developed for the enantioseparation of a broad range of chiral compounds (mainly pharmaceuticals and amino acids). From the positive results obtained in all these studies it is quite clear that CILs possess a high potential to carry out chiral analyses by CE. Among the different parameters that must be optimized to achieve with success the resolution of enantiomers using CILs, the type and concentration of CILs, the buffer pH and the chain length of the cationic part have demonstrated to be the most relevant. These parameters have a high influence on the adsorption of the cationic part of the CIL on the capillary wall which modifies the EOF as well as on the effective charge mobility of both the analytes and the CILs that influence their interactions. In spite

492 of the high discrimination power showed by CILs, till now their contribution in the chiral
493 analysis of real samples is scarce. Therefore, although CILs have received a significant
494 attention, their full potential as chiral selectors in CE has not yet achieved so that it is
495 expected that the development of new methodologies by CE using CILs as chiral selectors
496 will keep growing in the near future.
497
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504

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