



An “inherently chiral” 1,1′-bibenzimidazolium additive for enantioselective voltammetry in ionic liquid media

Simona Rizzo^a, Serena Arnaboldi^{b,*}, Roberto Cirilli^c, Armando Gennaro^d, Abdirisak Ahmed Isse^d, Francesco Sannicolò^b, Patrizia Romana Mussini^{b,*}

^a Istituto di Scienze e Tecnologie Molecolari, C.N.R., Via Venezian 21, 20133 Milano, Italy

^b Università degli Studi di Milano, Dipartimento di Chimica, Via Golgi 19, 20133 Milano, Italy

^c Istituto Superiore di Sanità, Centro Nazionale per l'Analisi e il Controllo dei Farmaci, Viale Regina Elena 299, 00161 Roma, Italy

^d Università degli Studi di Padova, Dipartimento di Scienze Chimiche, via Marzolo 1, 35131 Padova, Italy

ARTICLE INFO

Keywords:

Chiral electrochemistry and electroanalysis
Ionic liquids
Chiral additives
Inherent chirality
Enantioselective recognition

ABSTRACT

A dialkyl-1,1′-bibenzimidazolium salt, consisting of an atropisomeric dication (*i.e.* featuring a stereogenic axis and thus “inherently chiral”) and an achiral counteranion, is employed as a chiral additive in three commercial ionic liquids, providing successful enantiodiscrimination in voltammetry experiments on screen-printed electrodes (SPEs) with the enantiomers of *N,N′*-dimethyl-1-ferrocenyl-ethylamine as model chiral probes. Significant differences in redox potentials are observed for the probe enantiomers despite the low concentration (0.01 M) of the chiral additive. The nature of the achiral ionic liquid in which the additive is employed significantly affects the peak potentials and potential differences, but does not alter the enantiomer sequence.

1. Introduction

The search for chiral media affording effective enantioselection in analytical and preparative electron transfer processes on achiral electrodes is an important issue in electrochemistry. Greater order at the chiral medium|electrode interface should result in a more efficient transmission of chiral information, with chiral supporting electrolytes appearing to perform better than chiral cosolvents in early preparative experiments, although enantiomeric excesses were not very high [1]. In this respect, chiral ionic liquids appear ideal candidate media on account of their very well-ordered structure at the interface with a charged electrode, which extends over many layers [2], even in the presence of a considerable amount of water [3]. On the other hand, the unprecedented enantiodiscrimination recently achieved on electrode surfaces consisting of “inherently chiral” molecular materials (*i.e.* in which the stereogenic element responsible for chirality coincides with the functional group responsible for the specific property of the material) [4–7], suggests that it is worth looking for “inherently chiral” media. Combining the two strategies, two inherently chiral ionic liquids (ICILs) consisting of atropisomeric dialkyl-bipyridinium salts have recently been reported [8]. It was observed that these ICILs result in outstanding discrimination of probe enantiomers in terms of peak potentials in cyclic voltammetry experiments, even when these are employed as low-concentration additives. Furthermore, similar results

were obtained with smaller members of the same chemical family (mono and diethyl-bipyridinium salts), which are solid at room temperature [8]. This is extremely interesting, since highly enantioselective working conditions can be obtained with a very small amount of the inherently chiral compound; moreover, a melting point below room temperature is no longer necessary, which greatly widens the range of inherently chiral additives to be explored as chiral inductors, including *e.g.* some which may be easily synthesized and/or belong to different chemical families.

This prompted us to test for this task our recently introduced family of inherently chiral 1,1′-bibenzimidazolium double salts [9], which could not be synthesized with a sufficient number of long alkyl chains to be liquid at room temperature, but which feature very high torsional barriers in their atropisomeric cations, and therefore should exhibit huge chirality effects. In particular, in this work we test the smallest member of the family, with the highest melting point (208–210 °C), the *C*₂ symmetric dimethyl dimethanesulfonate salt **1**, which has been characterized previously [9], and is available as stable (*R*)-**1** and (*S*)-**1** enantiomers (Fig. 1a).

In this test we also wish to confirm the general validity of the inherent chirality strategy, by employing a chemically different, albeit inherently chiral, molecular backbone.

* Corresponding authors.

E-mail addresses: serena.arnaboldi@unimi.it (S. Arnaboldi), patrizia.mussini@unimi.it (P.R. Mussini).

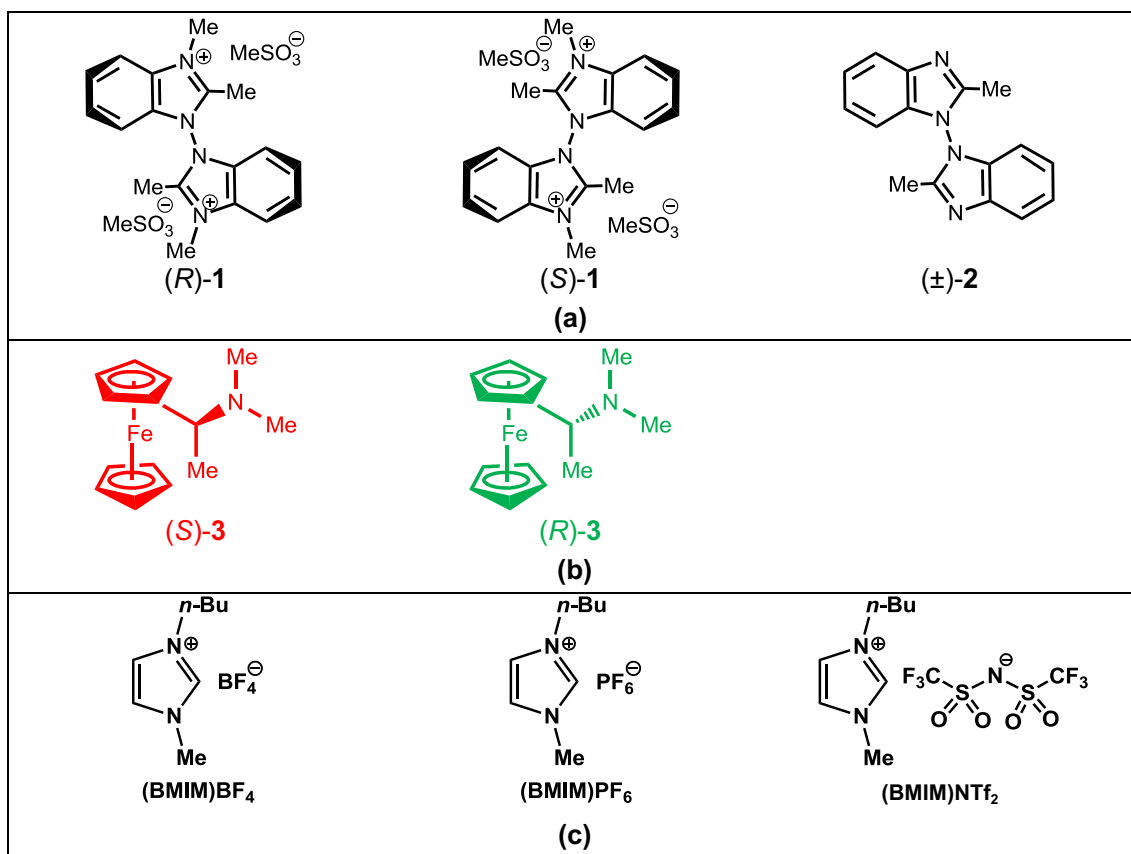


Fig. 1. (a) The inherently chiral additives (R)-1, (S)-1 and the racemic neutral precursor 2; (b) (S)-(+)-3 and (R)-(–)-3 *N,N'*-dimethyl-1-ferrocenylethylamine employed as chiral probes; (c) 1-butyl-3-methylimidazolium tetrafluoroborate (BMIM)BF₄, 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM)PF₆ and 1-butyl-3-methylimidazolium bis(trifluoromethylsulfonyl)imide (BMIM)NTf₂ employed as achiral bulk media.

2. Materials and methods

Enantiopure (R)- and (S)-2,2',3,3'-tetramethyl-bi[1,1'-(1*H*,1'*H*-benzimidazolium)] dimethanesulfonate salts, (R)-1 and (S)-1 (Fig. 1a), were obtained according to the protocol described in [9] from the corresponding enantiopure enantiomers of 2,2'-dimethyl-bi[1,1'-(1*H*,1'*H*-benzimidazole)] 2, synthesized as a racemic mixture (Fig. 1a) and resolved by semi-preparative HPLC on a chiral stationary phase [10].

The enantioselectivity tests were performed by cyclic voltammetry at 0.05 V/s scan rate on screen-printed electrode (SPE) supports (Dropsens, custom-made without paint), with Au working and counter electrodes and an Ag pseudoreference electrode, resulting in good reproducibility at constant conditions with the present working protocol. The experiments were performed in air, depositing on the working electrode a drop of achiral ionic liquid with 0.01 M (R)-1 or (S)-1 as an additive and 0.002 M (R)-(+)- or (S)-(–)-*N,N'*-dimethyl-1-ferrocenylethylamine ((R)-3 and (S)-3, Fig. 1b; Aldrich, submitted to a further chromatographic purification step) as the enantiopure probe. (R)-3 and (S)-3 had been previously used as chemically and electrochemically reversible model chiral probes to test inherently chiral electrode surfaces [4–7].

The bulk achiral ionic liquids employed were either 1-butyl-3-methylimidazolium tetrafluoroborate (BMIM)BF₄ (CAS 174501-65-6; Aldrich for catalysis > 98.5%), or 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM)PF₆ (CAS 174501-64-5; Aldrich ≥ 98.5%) or 1-butyl-3-methylimidazolium bis(trifluoromethanesulfonyl)imide (BMIM)NTf₂ (CAS 174899-83-3; Aldrich ≥ 98%).

For the sake of comparison, the tests were also carried out with the same protocol, but in the absence of the chiral additives. Potentials were referred to the formal potential of the ferrocene/ferrocinium

intersolvent reference redox couple, obtained by recording its CV under the same conditions used in the enantioselection tests.

3. Results and discussion

The cyclic voltammograms (CVs) of the chiral ferrocenyl probes (R)-3 and (S)-3 recorded on screen-printed gold electrodes in each bulk ionic liquid are reported in Fig. 2 together with the CV of ferrocene, which is used as a reference for intersolvent comparison of potentials as well as currents. Key CV features are summarized in Table 1.

Chemically reversible CV peaks are obtained in all cases for ferrocene and the ferrocenyl probe enantiomers in the three tested ILs (Fig. 1b), making it possible to estimate *formal peak potentials* in terms of $E^{\circ'} = (E_{p,a} + E_{p,c}) / 2$. All $E^{\circ'}$ values reported in Table 1 for the ferrocenyl probes as well as all CVs shown in Fig. 2 are referred to the $E^{\circ'}$ of the ferrocene couple recorded under the same conditions. The ferrocene peak intensities may be explained by the viscosity of the medium (in terms of $I \propto D^{1/2} \propto \eta^{-1/2}$, with D = diffusion coefficient and η = solvent viscosity), considering the intrinsic ionic liquid viscosities (450, 219, 52 Cp for (BMIM)PF₆, (BMIM)BF₄, (BMIM)NTf₂ respectively [11]), which can be significantly modulated by the amount of trace water, resulting in a decrease in viscosity [12]; this is particularly relevant for (BMIM)BF₄, which is by far the most hydrophilic of the three ILs tested (in fact, the only one miscible with water [11]).

In the absence of inherently chiral additives, the enantiomers of the chiral ferrocenyl probes give, as expected, practically coincident CV peaks, in terms of potential, current, and shape (Fig. 2, left side). The inductive effect of the alkyl chain, according to Hammett parameters [13], should result in a very small negative or null potential shift with respect to ferrocene; however only in one case did the formal potentials of the chiral probes nearly coincide with the ferrocene one (in (BMIM)

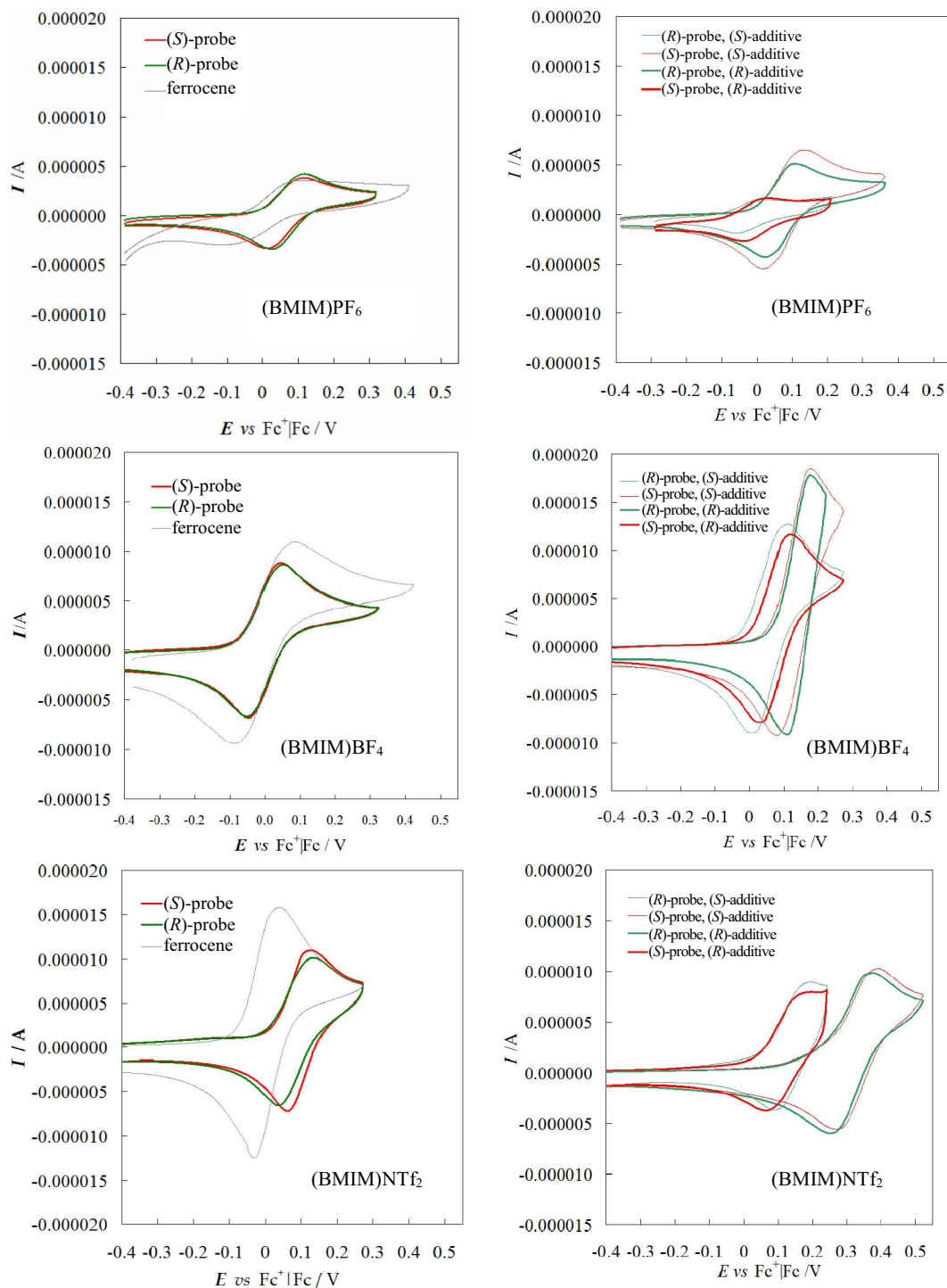


Fig. 2. CVs recorded on a screen-printed Au electrode at 0.05 V/s in three ionic liquid bulk media. Left: model ferrocenyl probes (R)-3 (green) and (S)-3 (red) as well as redox intersolvent standard ferrocene (grey) at a concentration of 0.002 M. Right: CVs of either (R)-3 (green) or (S)-3 (red) probe in the presence of either (R)-1 or (S)-1 0.01 M inherently chiral additives (thin or thick lines, respectively). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

BF_4), while in the other cases they are shifted to more positive potentials (particularly in (BMIM)NTf₂). This positive shift in the less hydrophilic ILs, as well as changes in peak height, might be explained by significantly different coordination and/or ionic coupling effects involving the ionic liquid anion and the ferrocene or the ferrocenyl probe couple.

Repeating the same experiments under the same conditions but with the addition of either the (R)-1 or the (S)-1 enantiopure additive enantiomer (electrochemically inactive in the potential window

considered here [9]) in a 5:1 ratio with respect to the chiral probe, the CV peak of either probe enantiomer undergoes significant modifications in peak potential and in many cases also in current and shape. Importantly, peak potential differences are observed for the two probe enantiomers (Fig. 2, right side) when inverting the additive configuration, as in the previously reported case of bicolindinium double salt additives [8].

Notably:

Table 1

Key CV parameters obtained for 0.002 M chiral probes (*S*)-3 and (*R*)-3 in three achiral ionic liquids, with and without either (*S*)-1 or (*R*)-1 0.01 M inherently chiral additive. Formal potentials are referred to the formal potential of the Fc^+/Fc couple. Parameters for the intersolvent standard ferrocene couple vs the screen printed silver pseudoreference electrode are also reported.

	Bulk achiral ionic liquid					
	(BMIM)PF ₆		(BMIM)BF ₄		(BMIM)NTf ₂	
	<i>E'</i> /V	10 ⁶ <i>I</i> _{pa} /A	<i>E'</i> /V	10 ⁶ <i>I</i> _{pa} /A	<i>E'</i> _a /V	10 ⁶ <i>I</i> _{pa} /A
Fc^+/Fc vs Ag/Ag^+	-0.011	2.5	0.078	10.9	0.128	15.2
(<i>S</i>)-3 vs Fc^+/Fc	0.062	3.6	0.000	8.3	0.094	11.0
(<i>R</i>)-3 vs Fc^+/Fc	0.070	3.9	0.003	8.2	0.082	10.1
Average^a	0.066		0.002		0.088	
(<i>S</i>)-3, (<i>R</i>)-1 vs Fc^+/Fc	-0.023	1.3	0.072	11.2	0.118	7.9
(<i>R</i>)-3, (<i>S</i>)-1 vs Fc^+/Fc	-0.008	1.9	0.060	11.9	0.137	8.7
Average^a	-0.016		0.066		0.128	
(<i>R</i>)-3, (<i>R</i>)-1 vs Fc^+/Fc	0.066	5.1	0.143	17.1	0.308	9.8
(<i>S</i>)-3, (<i>S</i>)-1 vs Fc^+/Fc	0.072	6.5	0.127	18.0	0.322	10.3
Average^a	0.069		0.135		0.315	
Average difference^b	0.085		0.069		0.187	

^a Average of the values reported in the preceding two entries.

^b Difference between the average values measured for (*R,S*)/(*S,R*) and (*R,R*)/(*S,S*) combinations.

- *Specular* additive/probe combinations (i.e. [(*R*)-1, (*R*)-2] vs [(*S*)-1, (*S*)-2]; or, [(*R*)-1, (*S*)-2] vs [(*S*)-1, (*R*)-2]), result in the *same CV peak* (within experimental error);
- By contrast, energetically different *diastereomeric* additive/probe combinations (i.e. [(*R*)-1, (*R*)-2] or [(*S*)-1, (*S*)-2] vs [(*R*)-1, (*S*)-2] or [(*S*)-1, (*R*)-2]) result in *significantly different CV peaks*;
- *The recognition sequence is the same in all ILs*, which is quite reasonable considering that enantioselectivity originates from the additive cation, which is the only chiral selector present;
- In particular, the potentials of the (*R,S*) or (*S,R*) combinations are consistently less positive than those of the (*R,R*) or (*S,S*) combinations. It should be noted that the opposite sequence was observed with bicolindinium double salts [8], but the additive was a chemically different one; and, although it might appear a bit trivial, it must be underlined that absolute configuration descriptors (*R,S*) do not in themselves account for chirality manifestations;
- *The bulk ionic liquid anion significantly influences the enantiomer peak potential shifts and difference*, although it does not alter the enantiomer sequence;
- In particular, the largest peak potential shifts of the chiral probe enantiomers (+0.13 V and +0.32 V, i.e. with the oxidation processes becoming much more unfavourable), as well as the largest enantiomer peak potential difference (~0.19 V), are observed in (BMIM)NTf₂. A much smaller peak potential difference between probe enantiomers, ~0.08 V, is observed in both (BMIM)PF₆ and (BMIM)BF₄; however, in the first case the difference originates from one peak undergoing a negative shift with the other remaining nearly unchanged, while in the second case both enantiomer peaks are shifted in the positive direction, although less than in the (BMIM)NTf₂ case;
- Concerning peak height and shape, the combinations coming first, i.e. [(*R*)-1, (*S*)-2] or [(*S*)-1, (*R*)-2] apparently result in smaller peaks compared to the following [(*R*)-1, (*R*)-2] or [(*S*)-1, (*S*)-2] ones, which might point e.g. to a significantly lower diffusion coefficient; the difference in peak heights actually decreases in the sequence (BMIM)PF₆ > (BMIM)BF₄ > (BMIM)NTf₂, which is also the sequence of decreasing viscosity of the bulk ionic liquid.

Statistical tests on experiment repetitions with selected probe + selector combinations were carried out to check both the reproducibility and the significance of the potential differences observed

for (*R*)-3 and (*S*)-3 probe enantiomers. It must be underlined that from this perspective an even more important piece of evidence is the specularity of the results observed i.e. when inverting either probe or additive configurations.

Concerning rationalization of the phenomenon, bulk complexation should be ruled out [8], consistent with the fact that the bibenzimidazolium chiral cations have not been designed as specific ligands for the probes concerned (*inter alia*, benzimidazolium cations have no free N atom for coordination; instead, π interactions between aromatic rings are more likely). However, specific additive/probe interactions promoted by their simultaneous presence at the very compact and ordered electrode|ionic liquid interface cannot be excluded. We have assumed that, in analogy with the nematic to cholesteric transition that has recently been reported to be induced in a bulk liquid crystal by an inherently chiral additive [14], a similar “chiral domino effect” could take place at the very compact and ordered ionic liquid|electrode interface [2,3,15–19], i.e. a chain reorganization induced by small quantities of chiral additive, and modulated by the size and nature of the involved species, as well as by the electrode potential. Further studies are planned to investigate this possibility.

The results obtained so far are, however, important in themselves, since they appear fully consistent with those recently obtained with a different family of inherently chiral additives in the proof-of-concept study reported earlier [8]. Thus, the general validity of the inherent chirality strategy is supported, even when implemented in terms of inherently chiral salt additives with biheteroaromatic atropisomeric cations, employed at a low concentration in achiral ionic liquid media. The next step, apart from rationalization of the mechanism, should concern extension to different probes and, particularly, to preparative experiments.

Acknowledgement

The authors' inherent chirality work is financially supported by Fondazione Cariplo and Regione Lombardia (2016-0923 RST — Avviso congiunto FC-RL Sottomisura B) rafforzamento (Enhancing VINCE (Versatile INherently Chiral Electrochemistry)).

References

- [1] T. Fushigami, S. Inagi, Stereochemistry of organic electrode processes, in: O. Hammerich, B. Speiser (Eds.), Organic Electrochemistry, 5th ed., CRC Press, Boca Raton 2016, pp. 1489–1491 with cited literature, pp. 1506–1507.
- [2] K. Ma, R. Jarosova, G.M. Swain, G.J. Blanchard, Charge-induced long-range order in a room-temperature ionic liquid, *Langmuir* 32 (2016) 9507–9512.
- [3] A. Lahiri Cui, T. Carstens, N. Borisenko, G. Pulletikurthi, C. Kuhl, F. Endres, Influence of water on the electrified ionic liquid/solid interface: a direct observation of the transition from a multilayered structure to a double-layer structure, *J. Phys. Chem. C* 120 (2016) 9341–9349.
- [4] F. Sannicolò, S. Arnaboldi, T. Benincori, V. Bonometti, R. Cirilli, L. Dunsch, W. Kutner, G. Longhi, P.R. Mussini, M. Panigati, M. Pierini, S. Rizzo, Potential-driven chirality manifestations and impressive enantioselectivity by inherently chiral electroactive organic films, *Angew. Chem. Int. Ed.* 53 (2014) 2623–2627.
- [5] S. Arnaboldi, M. Magni, P.R. Mussini, Enantioselective selectors for chiral electrochemistry and electroanalysis: stereogenic elements and enantioselection performance, *Curr. Opin. Electrochem.* 8 (2018) 60–72.
- [6] F. Sannicolò, P.R. Mussini, T. Benincori, R. Cirilli, S. Abbate, S. Arnaboldi, S. Casolo, E. Castiglioni, G. Longhi, R. Martinazzo, M. Panigati, M. Pappini, E. Quartapelle Procopio, S. Rizzo, Inherently chiral macrocyclic oligothiophenes: easily accessible electroresponsive cavities with outstanding enantioselective performances, *Chem. Eur. J.* 20 (2014) 15261–15264.
- [7] S. Arnaboldi, T. Benincori, R. Cirilli, W. Kutner, M. Magni, P.R. Mussini, K. Noworyta, F. Sannicolò, Inherently chiral electrodes: the tool for chiral voltammetry, *Chem. Sci.* 6 (2015) 1706–1711.
- [8] S. Rizzo, S. Arnaboldi, V. Mihali, R. Cirilli, A. Forni, A. Gennaro, A.A. Isse, M. Pierini, P.R. Mussini, F. Sannicolò, “Inherently chiral” ionic-liquid media: effective chiral electroanalysis on achiral electrodes, *Angew. Chem. Int. Ed.* 56 (2017) 2079–2082.
- [9] S. Arnaboldi, R. Cirilli, A. Forni, A. Gennaro, A.A. Isse, V. Mihali, P.R. Mussini, M. Pierini, S. Rizzo, F. Sannicolò, Electrochemistry and chirality in bibenzimidazole systems, *Electrochim. Acta* 179 (2015) 250–262.
- [10] S. Rizzo, S. Menta, C. Faggi, M. Pierini, R. Cirilli, Influence of the nature of the alkyl substituents on the high-performance liquid chromatography enantioseparation and

- retention of new atropisomeric 1,1'-bibenzimidazole derivatives on amylose tris (3,5-dimethylphenylcarbamate) chiral stationary phase, *J. Chromatogr. A* 1363 (2014) 128–136.
- [11] J.G. Huddleston, A.E. Visser, W.M. Reichert, H.D. Willauer, G.A. Broker, R.D. Rogers, Characterization and comparison of hydrophilic and hydrophobic room temperature ionic liquids incorporating the imidazolium cation, *Green Chem.* 3 (2001) 156–164.
- [12] A.A.J. Torriero, Characterization of decamethylferrocene and ferrocene in ionic liquids: argon and vacuum effect on their electrochemical properties, *Electrochim. Acta* 137 (2014) 235–244.
- [13] C. Hansch, A. Leo, R.W. Taft, A survey of Hammett substituent constants and resonance and field parameters, *Chem. Rev.* 91 (1991) 165–195.
- [14] S. Matsushita, B. Yan, S. Yamamoto, Y.S. Jeong, K. Akagi, Helical carbon and graphite films prepared from helical poly(3,4-ethylenedioxythiophene) films synthesized by electrochemical polymerization in chiral nematic liquid crystals, *Angew. Chem. Int. Ed.* 53 (2014) 1659–1663.
- [15] M.Z. Bazant, B.D. Storey, A.A. Kornyshev, Double layer in ionic liquids. Overscreening versus crowding, *Phys. Rev. Lett.* 106 (2011) 046102.
- [16] S. Perkin, L. Crowhurst, H. Niedermeyer, T. Welton, A.M. Smith, N.N. Goswami, Self-assembly in the electrical double layer of ionic liquids, *Chem. Commun.* 47 (2011) 6572–6754.
- [17] V. Ivaništšev, K. Kirchner, M.V. Fedorov, Restructuring of the electrical double layer in ionic liquids upon charging, *J. Phys. Condens. Matter* 27 (2015) 102101.
- [18] T. Zhong, J. Yan, M. Li, L. Chen, B. Ma, The electric double layer in an ionic liquid incorporated with water molecules: atomic force microscopy force curve study, *ChemElectroChem* 3 (2016) 2221–2226.
- [19] V. Ivaništšev, S. O'Connor, M.V. Fedorov, Poly(a)morphic portrait of the electrical double layer in ionic liquids, *Electrochem. Commun.* 48 (2014) 61–64.