Chirality

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"Inherently Chiral" Ionic-Liquid Media: Effective Chiral Electroanalysis on Achiral Electrodes

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Abstract: *To achieve enantioselective electroanalysis either chiral electrodes or chiral media are needed. High enantiodiscrimination properties can be granted by the "inherent chirality" strategy of developing molecular materials in which the stereogenic element responsible for chirality coincides with the molecular portion responsible for their specific properties, an approach recently yielding outstanding performances as electrode surfaces. Inherently chiral ionic liquids (ICILs) have now been prepared starting from atropisomeric 3,3′-bicollidine, synthesized from inexpensive reagents, resolved into antipodes without need of chiral HPLC and converted into long-chain dialkyl salts with melting points below room temperature. Both the new ICILs and shorter family terms, solid at room temperature, employed as low-concentration additives in achiral ILs, afford impressive enantioselection for the enantiomers of different probes on achiral electrodes, regularly increasing with additive concentration.*

Impressive chirality manifestations and enantiorecognition ability have been recently obtained with "inherently chiral" polyconjugated thiophene-based electroactive films **1**, in which the electroactivity source and the stereogenic element responsible for chirality coincide: intercalated 3,3′-bithianaphthene scaffolds induce a left- or right-handed torsion of the conjugated backbone.[1] Coating electrodes with these materials has been proposed as a tool opening the way to chiral voltammetry.[2]

By analogy, high enantioselectivity could be achieved by implementing inherent chirality in the working medium, an interesting alternative to the use of a chiral active surface. Ionic liquids (ILs) look ideal candidate media, being intrinsically much more ordered than organic solvents, somehow resembling "liquid polymers" and bordering with liquid crystals.[3] This could be relevant for application in stereoselective reactions in general, and, in particular, in chiral electrochemistry, where no resolutive■?■ achievements have been obtained so far with traditional chiral solvents and supporting electrolytes.[4] In this context, we considered to apply the inherent chirality strategy to develop "inherently chiral" ionic liquids (ICILs).

The traditional design of "chiral ionic liquids" implies either the use of chiral anions, or the decoration of the onium cation (most ILs feature heterocyclic onium cations) with chiral pendants characterized by carbon stereocenters.[5] A stereogenic plane,[6] or a stereogenic axis related to *E*/*Z* double bonds,[7] or to spiranic stereogenic carbons,[8] were used in very few cases. We envisaged that bis-onium salts of atropisomeric bi-heteroaromatic nitrogen-containing scaffolds, with the interconnected aryl units providing the material both with dissymmetry and IL properties, could satisfy the "inherent chirality" requirements. Furthermore, high intrinsic order associated to C_2 symmetry could afford full exploitation of the enantioselectivity potential.

We recently presented the family of the 3,3′-dialkyl salts (all high melting solids) of atropisomeric 2,2′-dialkyl-1,1′-bibenzimidazoles, obtained in an enantiopure state by chiral HPLC, showing slight but perceivable CV asymmetric effects when used as additives in stereoselective electrooligomerization tests.[9]

Now we introduce a new family of inherently chiral salts **2**, based on the 3,3′-bipyridine scaffold, in particular the 3,3′-(2,2′,4,4′,6,6′-hexamethyl)bipyridine **3** (3,3′-bicollidine), which provides a turning point offering a unique pool of useful features (Scheme 1).

For **3**, DFT calculations indicate a very high enantiomerization barrier of approximately 42.0 kcal mol^{-1} (Figure S1 in the Supporting Information) implying a remarkable configurational stability of the enantiomers.

3,3′-Bicollidine **3** was already known, but its synthesis (pyrocondensation of collidine on white hot platinum coil at 200 °C for 7 days) was considered impracticable.[10] We prepared **3** in satisfactory yields by oxidative coupling of the 3-collidyl anion, produced by reaction of *n*-BuLi with the 3-

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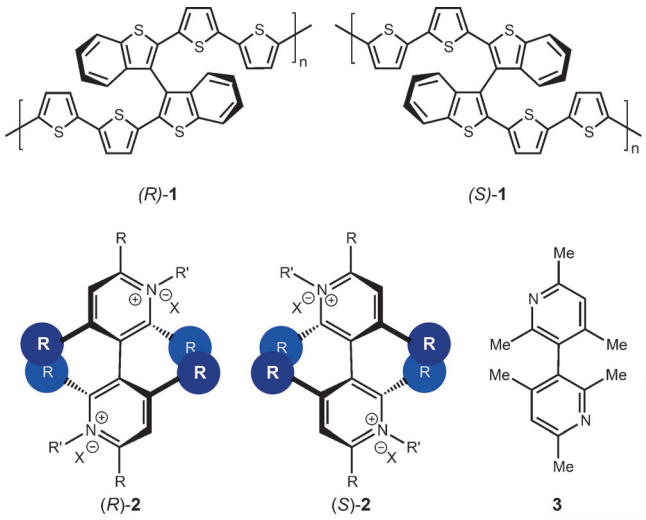


Scheme 1. Chemical structures of **1**–**3**.

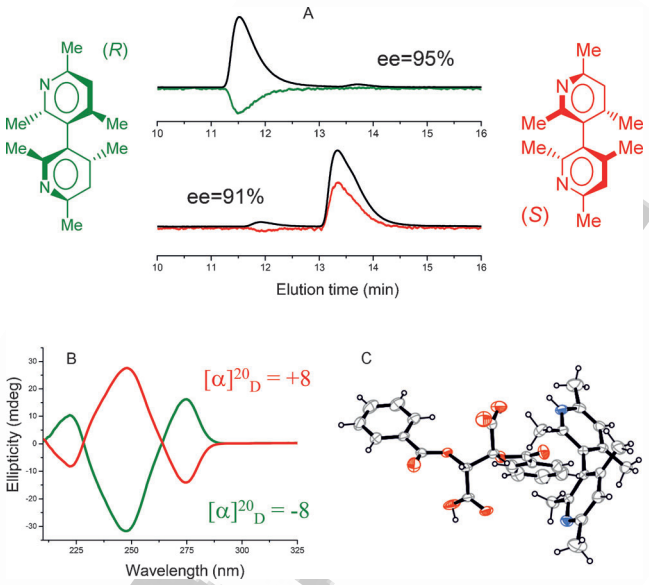


Figure 1. A) Chiral HPLC purity check of the resolved enantiomers of **3** (details in Supporting Information). B) Cyclic dichroism (CD) spectra (EtOH, $c = 0.3\ mg\,cm^{-3}$) and $[\alpha]_D^{20}$ (EtOH, $c = 0.1$). C) XRD structure of (*S*)-(+)-**3** (*R*,*R*)-*O*,*O*-dibenzoyl hydrogen tartrate (C gray, O red, N blue).[15]

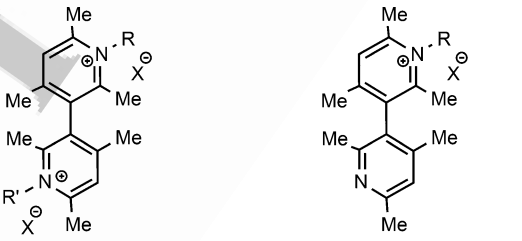
bromocollidine, obtained in turn by direct NBS bromination of collidine, a commercially available, inexpensive material.[11]

The calculated most stable conformation of **3** shows the pyridine rings in a nearly orthogonal arrangement (Figure S1), which hampers conjugation, as confirmed by the very wide free potential window in the cyclic voltammogram (CV) pattern of **3** (from −3.2 to +1.6 V vs. $Fc^+|Fc$, Figure S7; Fc = $[(\eta\text{-}C_5H_5)_2Fe]$) and by comparison of UV/Vis spectra of **3** and collidine (Figure S10).

Most attractively, successful resolution of racemic **3** was achieved at preparative scale level by fractional crystallization of the diastereomeric salts with *O*,*O*-dibenzoyltartaric acids from methanol. The enantiomeric purity of the antipodes was checked by analytical HPLC on CSP■please define CSP, thanks■ (Figure 1 A) and the absolute configuration was assigned to them through the single-crystal X-ray diffraction (XRD) of the diastereomerically pure salts (Figure 1 C).[15] Full chiroptical characterization was performed (Figure 1 B, Figures S2–S4).

As for the alkylation of **3** to give onium salts, we found that alkyl iodides are the most effective alkylating agents, and that, as a rule, the reaction rate decreases with increasing the length of the alkyl chain. Furthermore, mono-alkylation generally develops in acceptable times, while double alkylation is much more difficult (months are required to obtain **2c** as a single reaction product). Fortunately, we developed a simple and efficient separation method for high-purity mono and double salts by column chromatography on neutral alumina (details in Supporting Information). Thus, we could obtain good quantities of pure double salts even with long alkyl chains, without having to wait for complete dialkylation. Moreover, the availability of long chain mono-alkyl salts **4a**,**c** in a pure state enabled us to accede to C_1 symmetric *N*,*N*′-dialkylbicollidinium salts by performing the second alkylation with a short chain alkyl iodide, requiring acceptable times for completion (preparation of **2e** from **4c**, Scheme 2).

Mono- and di-alkylated iodides **4a**,**c** and **2a**,**c**,**e** (Scheme 2) are solid or waxy solid at room temperature



a	R,R' = Et	X = I	**a**	R = Et	X = I
b	R,R' = Et	X = BF_4	**b**	R = Et	X = BF_4
c	R,R' = Oct	X = I	**c**	R = Oct	X = I
d	R,R' = Oct	X = $(CF_3SO_2)_2N$			
e	R = Oct,R' = Me	X = I			
f	R = Oct,R' = Me	X = $(CF_3SO_2)_2N$			

Scheme 2. *N*,*N*′-dialkyl-3,3′-bicollidinium salts **2** and *N*-alkyl-3,3′-bicollidinium salts **4**.

and, consequently, not suitable for use as reaction media. Furthermore, on account of the high reactivity of the iodide ion, they are not appropriate for use in electrochemical experiments (particularly oxidations). They, however, afford easy exchange with BF_4^- and PF_6^- anions, popular in electroanalysis, and bis(trifluoromethanesulfonyl) imidate, widely used in IL design for its relatively high stability and low toxicity and because it favors melting point lowering. Thus, we achieved (*R*)- and (*S*)-**2d** and (*R*)- and (*S*)-**2f** both liquid at room temperature; to our knowledge, they are the first RT ICILs with atropisomeric cation.

Alkylation makes pyridine rings electron poorer, and therefore more easily reducible than the parent scaffold: two

reduction peaks can be observed ($E_p = -1.79$ V and -2.05 V ($Fc^+|Fc$) for **2d**, Figure S8; -1.81 V and -2.13 V for **2f**) both monoelectronic and chemically and electrochemically reversible, in accordance with two equivalent, reciprocally interacting redox centers. The potential window is narrower than that of neutral scaffold **3** but still large and with the anodic side completely available.

We have performed preliminary enantioselectivity tests using **2d** and **2f** as low-concentration additives in achiral IL (BMIM)PF_6, with the commercial ferrocenyl probes (*R*)-FcA and (*S*)-FcA previously used to test inherently chiral electrode surfaces.[1,2] The tests were performed on screen-printed electrode (SPE) supports, depositing on the Au working electrode a drop of a solution of enantiopure **2d** and FcA in (BMIM)PF_6, testing all chiral probe-chiral additive combinations. While no discrimination occurs working in (BMIM)PF_6 (Figure 2A), the presence of chiral inductor **2d** results in a remarkable difference of approximately 170 mV between the CV peaks of the probe antipodes (Figure 2B). Specular results are obtained upon changing either additive or probe enantiomer. Lower, but still high, enantioselectivity (ca. 120 mV peak difference) is obtained with asymmetric **2f** as chiral additive (Figure 2C).

Repeating the experiment with enantiopure (*S*)- and (*R*)-**2b** as chiral inductors, having shorter alkyl chains and smaller BF_4^- anion, a spectacular difference of around 250 mV between the CV peaks of the two probe antipodes was observed, again specular upon changing either additive or probe enantiomer (Figure 2D). Interestingly, the peak potential difference regularly decreases employing as additives the enantiomers of the monoalkyl salt **4b** (Figure 2E) and of the neutral scaffold **3** (Figure 2F).

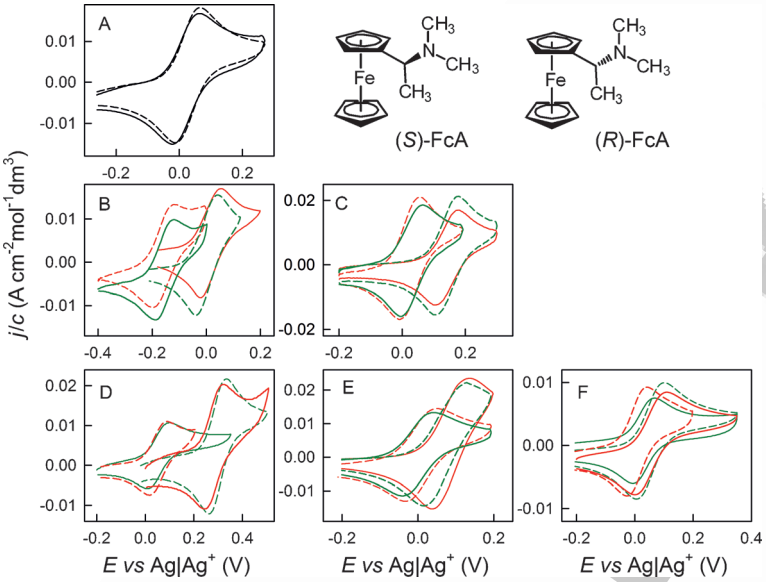


Figure 2. Enantiodiscrimination CV tests on A) (*R*)- and (*S*)-FcA antipodes (solid or dotted lines, respectively), on SPEs in (BMIM)PF_6^- (gray), or with addition of 0.01 M (*R*) or (*S*) enantiopure antipodes (green or red lines, respectively) of: B) dioctyl ICIL **2d**, C) methyl-octyl ICIL **2f**, D) diethyl salt **2b**, E) monoethyl salt **4b**, F) bicollidine **3**.

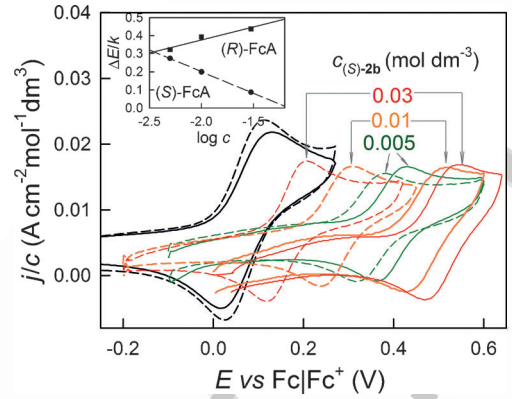


Figure 3. Enantiodiscrimination CV tests on (*R*) and (*S*) antipodes of FcA chiral probe (solid or dotted lines, respectively) on SPEs, in (BMIM)BF_4 and with increasing additions of (*S*)-**2b**. Inset: Relationship between $\Delta E_{1/2}$ shift and additive concentration; $\Delta E_{1/2} = E_{1/2} - E_{1/2}$ ($c_{(S)\text{-}2b} = 0$).

Repeating the tests with (*S*)-**2b** in commercial IL (BMIM)BF_4 with the same counteranion as the chiral additive, also resulted in outstanding discrimination (Figure 3). The enantiomer peak difference is significant (ca. 50 mV) even with 0.005 M chiral additive and regularly increases with additive concentration $c_{(S)\text{-}2b}$, apparently with a linear correlation between half-wave potential of each chiral FcA antipode and $\log c_{(S)\text{-}2b}$ (Figure 3 inset), reaching an amazing around 370 mV difference at a 0.03 M concentration.

A tentative explanation could be based on the high supramolecular order of ionic liquids at the interphase with a charged surface; even simple BMIMs have been shown to give self-assembling in a sort of nematic order,[12] modulated by the electrode charge and by size and nature of the IL ions.[13] A chiral additive could result in chiral reorganization of this peculiar interphase, as in the case of nematic-to-cholesteric transitions induced by chiral dopants in liquid crystals.[14] This reorganization would depend on both additive nature and concentration; our inherently chiral double salt additives could be particularly effective. Thus, the electron transfer process would take place within a highly ordered chiral interface. Some specific direct interaction between chiral additive and probe at the interphase could also be considered.

Enantioselection also holds for chemically and stereochemically different probes, as (*R*)- and (*S*)-BT_2T_4 monomer **1a**,[1,2] for which a ΔE_p of approximately 140 mV was obtained with 0.01 M **2b** (Figure 4A) and L- and D-DOPA methyl ester, for which an impressive ΔE_p of approximately 360 mV was achieved, both as separate enantiomers and as racemate (Figure 4B).

The validity of the inherent chirality strategy was confirmed by the observation that peak difference was negligible performing the test on the FcA antipodes using enantiopure 1-ethyl-3-methylimidazolium (*S*)-2-aminopropionate or L-

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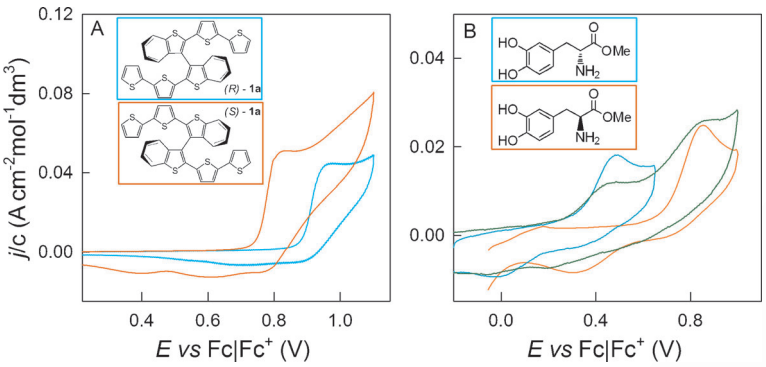

Figure 4. Enantiodiscrimination CV tests with 0.01 M (*R*)-**2b** in (BMIM)PF_6^-: A) 0.01 M (*S*)-(+) and (*R*)-(−) **1a** enantiopure monomers (orange and light blue, respectively); B) 0.002–0.004 M L- and D-DOPA methyl ester (*S*)- and (*R*)-enantiomers (orange and light blue, respectively) and racemate (green, normalized versus single enantiomer concentration).

lactate, commercially available CILs, as bulk media (Figure S9).

In conclusion, the family of the "inherently chiral" onium salts based on the atropisomeric 3,3′-bicollidine scaffold provides a breakthrough in the search for new CIL media. Outstanding stereoselection results even when employing them as minority components (additives or supporting electrolytes) in commercial achiral ILs. This appears indeed attractive on account of both the small chiral inductor consumption and for the possibility to employ species with short alkyl chains, that are solid at room temperature and that can be prepared by much easier and faster synthesis, with a large palette of possible counteranions.■ok? original wording unclear■

The new salts look particularly appealing for a wide scope of applications, owing to their good accessibility in an enantiopure state at a preparative scale level.

Work is in progress to elucidate the enantioselection mechanism, to explore a wider range of chiral inductors, and chiral probes in different achiral media and, overall, to scale up the synthesis of the new ICILs to test them as bulk media.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: bicollidinium salts · chiral electroanalysis · chiral ionic liquids · enantiodiscrimination · inherent chirality

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[15] CCDC 1458698, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via The Cambridge Crystallographic Data Centre.

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Communications

Chirality

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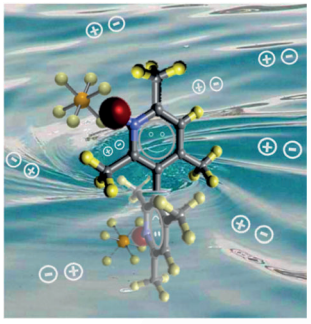

The right stuff: Dialkyl bicollidinium salts afford "inherently chiral" ionic liquids and grant outstanding enantioselection for different chiral probes on achiral electrodes even as low-concentration additives in achiral ionic liquids.

Chiralität

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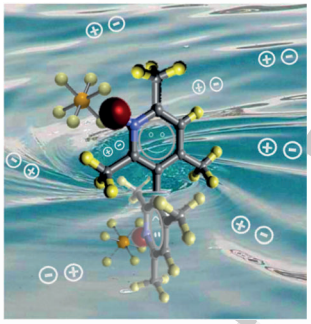

Dialkylbicollidinium-Salze ergeben „inhärent chirale" ionische Flüssigkeiten und ermöglichen eine herausragende Enantioselektion für verschiedene chirale Sonden auf achiralen Elektroden, selbst wenn sie als niedrig konzentrierte Additive in achiralen ionischen Flüssigkeiten eingesetzt werden.

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