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Enantiomer discrimination in Absorption Spectroscopy and in Voltammetry: highlighting fascinating similarities and connections --Manuscript Draft--

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Enantiomer discrimination in Absorption Spectroscopy and in Voltammetry: highlighting fascinating similarities and connections

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Abstract. Absorption spectroscopy and voltammetry, of known analogies and connections, share even more fascinating similarities and connections at a higher complexity level, when “upgrading” them with the ability to discriminate between enantiomers by chiral selector implementation. In both techniques either “molecular” selectors or “electromagnetic” ones (L- vs R- circularly polarized light components for spectroscopy, α - vs β - spin electrons for voltammetry) can be considered; moreover, external magnetic field application can replace a truly chiral actor. A tentative schematization is provided. Analogies and connections also concern molecular features of the enantiodiscrimination actors. In both techniques outstanding performances are obtained with inherently chiral molecules, in which a conjugated backbone with tailored torsion is source of chirality as well as spectroscopic and electrochemical activity, in an attractive three-fold interconnection. Their outstanding effects can be justified by a combination of chemical and electromagnetic properties (excellent potential molecular spin filters), a fascinating challenge for future developments.

1. Well known analogies and connections between Voltammetry and Electronic Absorption Spectroscopy in the study of active molecules and molecular materials

The steadily growing search for molecules and molecular materials with advanced functional properties often involves systems that include sites with interesting electronic features, making them at the same time spectroscopically and electrochemically active, *i.e.* both chromophores and redox sites. To experimentally investigate and rationalize such electronic properties, electronic absorption spectroscopy and voltammetry are usually applied in synergy, with well-known reciprocal connections. The first one accounts for intramolecular electronic transitions driven by increasing energy in terms of decreasing wavelength of incident light; the second one accounts for electron transfer processes to/from electrode (oxidations/reductions) driven by increasing energy in terms of increasingly positive/negative electrode potentials. In turn, measured quantities, *i.e.* absorbance in the first case and current intensity in the second case, share dependency on (i) chromophore/redox site concentration, (ii) geometric parameters (optical path length, electrode surface), as well as (iii) molecular parameters accounting for the process mechanism (molar extinction coefficient, accounting for light-matter interaction, in the first case; energy barrier symmetry factor, number of exchanged electrons etc. in the second case). Accordingly, molecular identification/discrimination together with information about molecular energy levels can be achieved considering absorption wavelengths/potentials for electron transfer, while quantification is feasible by considering absorption/current intensities.

Actually the information obtained from the two approaches about energy levels is not expected to coincide, considering the significantly different conditions (homogeneous phase, organic solvent, even apolar, with no electrolyte, no net charge formation... in the first case; heterogeneous conditions, electrolyte medium, net charge formation... in the second case); nor is expected to coincide with values obtained by other approaches such as theoretical computations (usually in vacuum) or, for molecular solids, photoelectron spectroscopies (aggregation effects...).[1-3] However, for example, HOMO-LUMO energy gaps obtained (in eV) from first absorption wavelengths (maxima or onset ones [4]) according to

$$h \text{ (J s)} \times c \text{ (m s}^{-1}\text{)} / (\lambda_{\text{max/onset}} \text{ (m)} \times q_e \text{ (C e}^{-1}\text{)})$$

are often similar to those obtained from first oxidation and first reduction potentials (formal, or peak, or onset ones [4]) in voltammetry experiments, according to

$$1e \times [E_{Ia} - E_{Ic}]V$$

Notably, however, only electrochemical experiments make it possible to estimate single HOMO or LUMO levels,

$$E_{LUMO} \text{ (eV)} \approx -1e \times [(E_{Ic} / V(\text{Fc}^+|\text{Fc}) + 4.8 \text{ V (Fc}^+|\text{Fc vs zero})]$$

$$E_{HOMO} \text{ (eV)} \approx -1e \times [(E_{Ia} / V(\text{Fc}^+|\text{Fc}) + 4.8 \text{ V (Fc}^+|\text{Fc vs zero})]$$

on the basis of the estimation of the energy level of the reference intersolvental reference couple $\text{Fc}^+|\text{Fc}$ respect to vacuum (here considered as 4.8 eV, but for which actually there is a range of proposed literature values, being an extrathermodynamic quantity [5]).

Moreover, there can be exceptions in which the two approaches yield remarkably different results, particularly if first oxidation and/or first reduction in the voltammetry experiment do not involve the same HOMO and LUMO energy levels as in the spectroscopic experiments, like *e.g.* when in

large molecules easiest oxidation and easiest reduction involve different sites that are reciprocally distant and not communicating.

2. The two techniques at a higher selectivity level: discriminating enantiomers of chiral advanced molecules and molecular materials

Many optically and electrochemically active molecules of high relevance, for example among natural or synthetic active pharmaceutical ingredients/nutrients, catalysts, materials for optics and spintronics..., are chiral. Endowing spectroscopy and voltammetry with the ability to discriminate between their enantiomers is important, as an alternative or at least a complement to expensive and destructive separation by enantioselective chromatographic techniques.

In achiral environments the enantiomers of chiral electroactive molecules have identical physico-chemical properties and therefore result in identical absorption spectra or voltammetry patterns. Therefore, achieving enantiomer recognition, thus upgrading spectroscopy or voltammetry to chiral spectroscopy or chiral voltammetry, requires implementation of a suitable chiral selector able to significantly interact with the chiral probe, resulting in diastereomeric and therefore energetically distinguishable situations.

As we will discuss further on, the selector can be either a “molecular” one, *i.e.* the (*R*)- or (*S*)-enantiomer of a second chiral molecular species besides the chiral probe, or an “electromagnetic”, one, also truly chiral: in particular, the L- and R- circularly polarized light components, or the α - and β -spin electrons in rototranslational motion across the electrochemical interphase.

Of course, in order to achieve transduction of the recognition event, at least one chromophore or/and redox site, respectively for chiral spectroscopy or/and chiral voltammetry, must either be present in the probe and/or in the selector, or, if necessary, provided by a third, possibly achiral, co-actor [6]. In any case, such active sites should be possibly strictly related to (*e.g.* located close to, coupled with, or, best of all, coincident with) the stereogenic element which enables chiral recognition. In such perspective, particularly attractive are “inherently chiral” molecular selectors in which the main molecular backbone, based on a conjugated (hetero)aromatic system featuring an helical or axial stereogenic element, is the source of both chirality and key electron absorption/electron transfer properties.[7-9]

In summary, at least two chiral actors (probe/selector, although it should be remarked that discriminating between probe and selector is only a matter of perspective...) and at least one chromophore/redox site must be present in the environment were the enantio-recognition event has to be achieved and detected. A tentative comparative schematization of possible cases is provided in **Scheme 1**.

Scheme 1. (*following page*) A tentative schematization of possible enantiodiscrimination strategies in chiral electronic absorption spectroscopy or chiral voltammetry, with related implications.

Required for enantiomer discrimination:
at least two chiral actors («probe» and «selector») and one active site for the desired transduction mode.

Transduction of enantio-recognition event
for R vs S probe at constant selector, or vice versa

	Chiral probe	Chiral selector	Active site for transduction	Electronic intramolecular transitions (UV-Vis: $\Delta\lambda$, ΔA)	Molecule-to/from-electrode electron transfers (voltammetry: ΔE , ΔI)
I	TWO "MOLECULAR" CHIRAL ACTORS		In probe or/and selector, or in auxiliary achiral molecule	[Performed with unpolarized light] Critical requirement of bulk probe coordination with specific chiral selector Expensive/probe-destructive	Chiral selector can be implemented as a very thin layer modifying the electrode surface → minimum quantity required, non probe-destructive. Possible enhancing effects from local cage/structuring/field effects. α- vs β-spin electrons also involved, → possible additional electromagnetic effect besides the molecular one!
	Chiral molecule 1	Chiral molecule 2			
"MOLECULAR" + "ELECTROMAGNETIC" CHIRAL ACTORS					
IIa	Chiral molecule	L- vs R- circularly polarized light components	In probe or in auxiliary	[Performed with polarized light] Evaluating absorption difference between L- and R- polarized light components (electronic circular dichroism). No specific chiral molecular selector required, non probe-destructive	
IIb	Chiral molecule	α- vs β-spin electrons	In probe or in auxiliary		Evaluation of α- vs β electron spin ratio so far critical. Opting to evaluate changes in a spin-specific/spin-enriched current, the latter can be generated at a ferromagnetic electrode under magnetic field (which adds a further, «false chirality», actor, see below) or at a chiral electrode surface by CISS effect (which implies a chiral molecular selector, former case, unless the chiral layer be the probe itself). A device based on the Hall effect has also been proposed
Replacement of a chiral actor by magnetic field application (false chirality)					
ELECTROMAGNETIC TRULY CHIRAL ACTOR + ELECTROMAGNETIC FALSELY CHIRAL ACTOR					
IIIa	Achiral molecule	Magnetic field	L- vs R- circularly polarized light components	Active site for transduction in the achiral molecule	Magnetic circular dichroism, based on energy level perturbation due to static magnetic field
IIIb	Achiral molecule	Magnetic field	α- vs β-spin electrons (S)- vs (R)- Chiral electrode surface (implying α- vs β unbalance)	Active site for transduction in the achiral molecule	Impressive potential differences observed when combining the external and internal magnetic field!
MOLECULAR TRULY CHIRAL ACTOR + ELECTROMAGNETIC FALSELY CHIRAL ACTOR					
IV	Chiral molecule	Magnetic field		Active site for transduction in chiral molecule or auxiliary	[Performed with unpolarized light] Magneto-chiral dichroism Same case as above, regarded from a different perspective? (i.e. with the achiral molecule being the auxiliary, and the chiral surface being the probe)

SCHEME 1

2.a Achieving enantiodiscrimination in electronic spectroscopy with truly chiral actors

In principle, enantiodiscrimination could be achieved in absorption or emission spectroscopy with both chiral actors being “molecular” ones, provided that their combination results in significant variation in absorption wavelength or/and intensity for at least one chromophore belonging to one or both chiral actors (or to a third auxiliary achiral co-actor).

Although a significant number of such cases have been studied, especially for colorimetric/visual readout of the recognition event (like *e.g.* [10,11]), this approach does not look very popular, possibly since it requires development, preparation and bulk consumption of specific, powerful chiral molecular selectors, and is probe-destructive.

Such onerous requirement is instead not necessary working with **polarized light**, in the well-established technique of **circular dichroism** [12-21,23].

Plane polarized light PL can be regarded (**Figure 1**) as the sum of two helix-like left-handed and right-handed circularly polarized light components, L-CPL and R-CPL (which in turn can be regarded as the sum of two perpendicular PLs with $\pm \pi/2$ phase difference). When PL passes through a chiral sample, its L-CPL and R-CPL components proceed at different speed; as a result,

- if the wavelength is such that no absorption can take place, the light exiting the chiral sample is still *plane* polarized, but rotated by a given α angle (the observed quantity in the popular *polarimetry* technique). Such rotation depends on the light wavelength, which is the object of the *optical rotation dispersion* ORD technique, analyzing L-CPL vs R-CPL propagation speed differences [21,22];
- if the light wavelength λ is such that it can be also absorbed by the sample, the light exiting the sample is *elliptically* polarized, as a consequence of the two CPL components being absorbed with different molar extinction coefficients ϵ_L and ϵ_R , resulting in different A_L and A_R absorbances (“Cotton effect”). Recording the ellipticity ϑ , or its proportional quantities $\epsilon_R - \epsilon_L$ or $A_R - A_L$, as a function of incident PL wavelength, provides *circular dichroism* CD spectra [12,15,23] or, more precisely, E[lectronic]CD spectra, to distinguish them from V[ibrational]CD spectra, which can be obtained in the infrared range [24,25].

ECD signals are located in correspondence of UV-Vis absorption ones, but, unlike them, being differential quantities they can be either positive or negative, and are perfectly specular for the enantiomers of a given chiral molecule.

It is worthwhile recalling that extinction coefficient ϵ , accounting for efficiency of photon/matter interaction, depends on both electric and magnetic transition dipole moments, accounting for electron density redistribution (translational and rotational displacement, respectively) in transition between different energy levels implying different orbital (electron density) shapes. In achiral UV-Vis absorption spectroscopy the electric transition dipole moment is usually the prevailing one, and allowed and forbidden transitions are defined considering it only. Instead, in chiral spectroscopy both dipole moments are important, involving *chiral* charge displacement along *e.g.* a helical path (in the asymmetric chiral magnetic field corresponding to the chiral sample) [12]

Simulation of CD spectra with theoretical computations enables to assign absolute configuration to the two enantiomers. [15,19,26]

Conformation [13], supramolecular [14] and solid-state effects [17,20,27-29] can result in significant modulation of ECD spectra. The ECD technique is particularly useful when studying chiral macromolecules (including both natural and synthetic ones), to account for the presence of a regular "secondary" chiral structure [13,30] (**Figure 1**). In particular, the more regular and stable the "secondary" helical/foldamer chiral structure of the macromolecule, the more evident its ECD response, which can instead nearly cancel for chiral polymers with "random coil" features and/or resulting from non-regioregular oligomerization. [28,31] Accordingly, the ECD of a given chiral macromolecule remarkably changes if the latter conformation changes (at constant configuration) *e.g.* as a function of pH, solvent, light, electric charge etc..[29]

Symmetrically to ECD, in **emission** spectroscopy with PL excitation, chiral samples can fluoresce with PL, consisting of **two circularly polarized components of different intensity (Circularly polarized luminescence, CPL)**. [32-35]

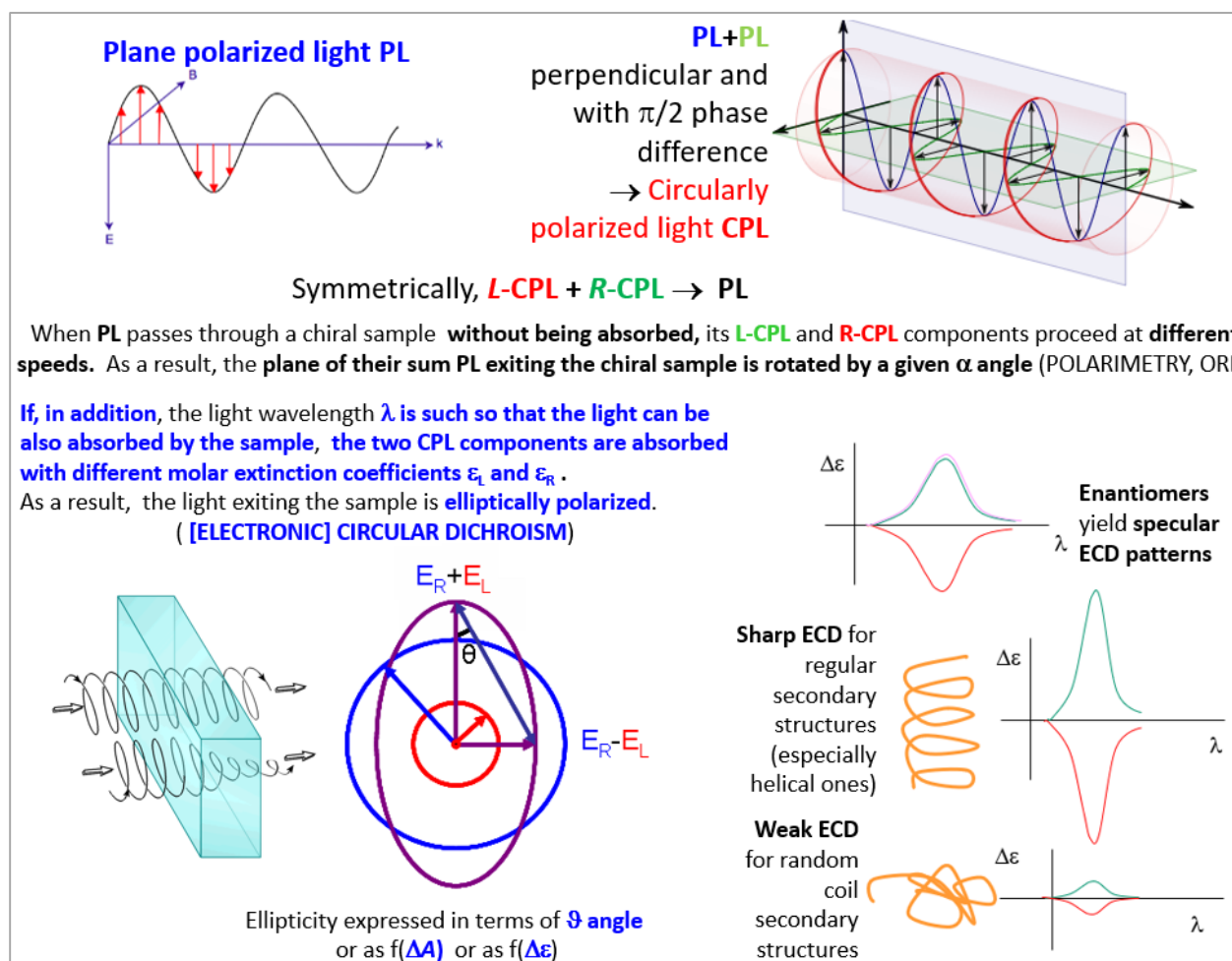


Figure 1. Polarized light and electronic circular dichroism basic features.

2.b Achieving enantiodiscrimination at the electrochemical interphase with truly chiral actors

In chiral voltammetry the most desirable transduction mode of the enantiomer recognition event is in terms of a significant, possibly wide, potential difference for the two electroactive probe enantiomers in the presence of the chiral enantiopure selector. (**Figure 2**) In fact, a potential difference can enable direct enantiomer recognition (also combined with quantitative estimation from peak currents) and/or selective enantiomer activation, [7] from the microscopic scale up to, fascinatingly, the macroscopic one, in many smart device architectures [36-40]

The most favourable circumstance is when a neat potential difference between two well-defined peaks with linear dynamic range for currents is observed for the two enantiomers simultaneously present, enabling to estimate enantiomeric excesses. [41,42] This optimal situation can be easier achieved for chemically reversible electron transfer processes, which result in little or no surface conditioning by the first enantiomer electrode process with respect to the second one. [41,42]

It must be underlined that there is obviously no *a priori* relationship between the combination of probe/enantiomer absolute configurations and the peak sequence, being the (*R*)- and (*S*)-descriptors assigned according to an abstract convention. Instead, specular potential differences *must* be obtained upon inverting either probe or selector configuration (**Figure 2**); such double inversion test provides the soundest reliability test for the enantiodiscrimination protocol, enabling to rule out possible other causes for the observed potential differences. [41]

Actually many cases have been recently presented of significant and even wide potential differences, obtained for various probe enantiomers by implementing molecular chiral selectors at the electrochemical interphase, either as confined solid selector layer/network, modifying the electrode surface with suitable chiral selector films [41-51], or as expanded semisolid selector network, exploiting media of high local order at the interphase with a charged achiral electrode implemented with chirality, like ionic liquids or deep eutectic solvents [52-57].

Since in the voltammetry case the enantiodiscrimination process is intrinsically heterogeneous, taking place at the interphase rather than in the bulk, only minimal quantities of the molecular selector can be employed, *e.g.* modifying the electrode surface by electrodeposition of a very thin chiral selector layer [41-51] or working with screen-printed cells with a thin layer of ionic liquid modified with a chiral additive (or itself chiral).[53-55,57] Moreover, the modified surface could be recycled (at least in favourable cases with no filming/conditioning products) and in any case the experiment is non-destructive for the bulk probe. Furthermore, local cage/structuring/electromagnetic effects can enhance probe/selector interactions respect to bulk conditions.

Notably, the observed potential shifts (up to some hundreds mVs) are consistent with mild coordination, considering *e.g.* the well known Kolthoff and Lingane treatment for ligand effect on electrochemically reversible species [58], or the significant peak potential differences that are often observed for a given electroactive molecule upon changing the supporting electrolyte, on account of different tendency to ionic couple formation.

Remarkably, when considering the study cases provided in the above cited papers, the selectors can be considered “multipurpose”, because a given selector is effective with even very different

probes, and a given probe can be discriminated by various selectors, although with different efficiency. This can be explained by the good number of elements available for probe/selector coordination (heteroatoms, (hetero)aromatic rings and π conjugated systems) in the reported examples.

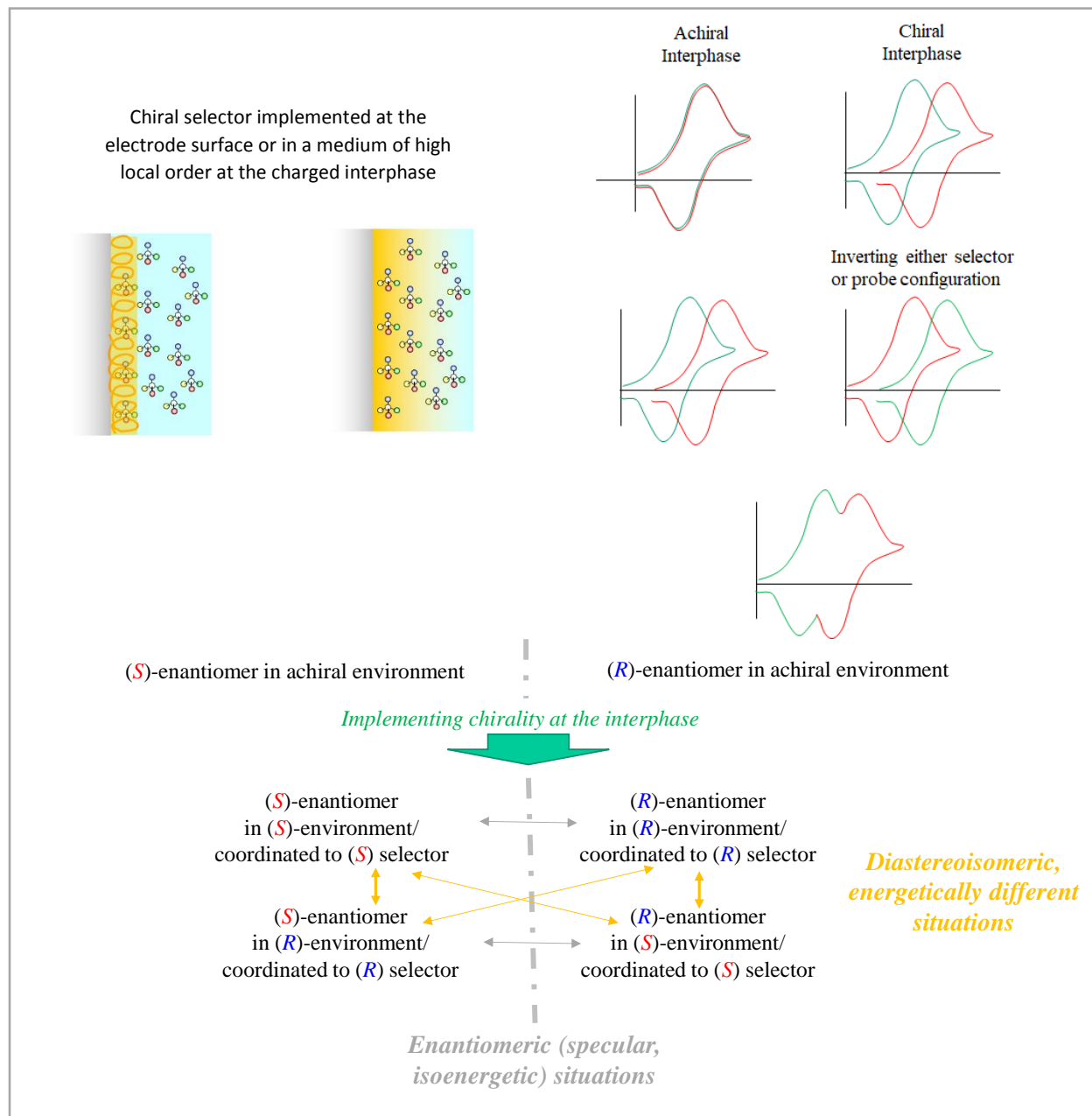


Figure 2. Chiral voltammetry basic features.

However, besides such “molecular interaction” effect, an “electromagnetic” effect should be considered, too [59], related to the α - vs β - spin electrons in rototranslational motion across the chiral interphase being promoted or hampered by the latter’s chiral magnetic field, in turn modulated by the presence of a second chiral magnetic field corresponding to the chiral probe. Indeed, referring to **Scheme 1**, voltammetry case (I) must also include voltammetry case (IIb), and

the concurrent presence of *two* chiral selectors should be considered, resulting in *two* contributions. It is worthwhile noticing that such considerations are possible on account of the electron flux being intrinsically unidirectional, *i.e.* perpendicular to the electrochemical interphase, while the parallel spectroscopic case (I), involving unpolarized light, implies infinite planes.

Of course a key issue is to evaluate the extent of such “electromagnetic” contribution.

The different interaction of α - vs β - spin electrons with a chiral magnetic field corresponding to a chiral molecular layer of (*R*)- or (*S*)- configuration, particularly modifying an electrode surface across which the chiral rototranslational motion of electrons takes place, is a fascinating subject that has been the object of extensive investigations (*e.g.* [59-85]), particularly by Naaman and colleagues [59-80], who termed it CISS (“chiral-induced spin selectivity”).

They observed that α - vs β - spin polarization induced by a molecular chiral electrode surface can be impressive, even surpassing common inorganic spin-filters [60], pointing to competitive applications such as molecular spin filters or giant magnetoresistive molecular spin valves [86-88] in spintronics, a field of great current applicative interest [89-92]. They also pointed out that to justify such high spin polarizations an unusually high spin-orbit coupling should be considered, of several orders of magnitude greater than normal cases of organic molecules [60]. To justify it, spin transport has been modelled in the electromagnetic field of an *helical* molecular structure [60,63,71,81,82] resulting in estimated energy splittings of even several hundreds of meV [60] between the two spin states. Also the tunneling probability for the favoured spin has been estimated to be enhanced with respect to normal cases by even 1-2 orders of magnitude [63]. The importance of electron correlation has also been pointed out [84], with the estimated spin polarization increasing in molecular chains with the number of ionic sites and laps.

To study the CISS effect, spin-specific/enriched currents were typically generated using a magnetic electrode under magnetic field [61,62] (which actually adds a further actor, although a “false”, *i.e.* non time-invariant [93-95], chirality one), then evaluating their variations upon crossing the chiral layer under study [62]. More recently, however, a protocol based on a working electrode modified with a circuit implementing Hall effect has been proposed to avoid the presence of the magnetic field. [59] Actually spin-specific currents can also be produced by the CISS effect itself, at an electrode modified with a chiral molecular layer [93]. Very recently, spin-dependent charge transfer at chiral electrodes has been probed by magnetic resonance [69]. Moreover, Kelvin-probe experiments resulted in potential differences up to about one hundred mV. The CISS effect has been shown to be applicable to enhance water splitting [66,78], to achieve asymmetric reactions [75] enantiomer separation [70] and enantiomer bio-recognition [63], and to propagate along achiral low-resistance molecular wires [72].

Fascinatingly, the CISS effect has also been related to the intriguing subject of biological homochirality [96].

Returning to the present issue, in principle the spin electron polarization upon interaction with the chiral probe could be sufficient as a selector for enantiomer discrimination, even without a molecular one, and would represent the electrochemical parallel of the ECD experiment. However unlike the spectroscopic case, (a) the approach based on two molecular actors has so far been very

successful (it would be however interesting to evaluate how much is the spin polarization contribution) and (b) at least so far, evaluation of α - vs β - spin ratio is still critical/not trivial respect to evaluation of L-CPL to R-CPL ratio in spectroscopy. Were it to become easily accessible, an “electrochemical spin dichroism” could be developed for electrochemical enantiomer discrimination in the absence of molecular selectors!

2.c Substituting a “truly” chiral actor with a “falsely” chiral one: application of an external magnetic field

Achiral polarizable substrates can also give circular dichroism response under magnetic field application, proportionally to magnetic field intensity and presenting mirror image spectra upon inverting magnetic field orientation. Such “magnetic circular dichroism” (MCD) has been explained in terms of perturbation of electronic energy levels by an external static magnetic field and can be the sum of three contributions [97-99]: a first one, temperature-independent, of sigmoidal shape, related to loss of degeneration in excited states; a weak second one, also temperature-independent, bell-shaped, related to mixing of close excited states; and a third one, also bell-shaped and more intense, related to loss of degeneration in ground state, dominant especially at low temperatures, being linked to population distribution in α - vs β - ground sublevels. MCD is a well-established technique, exploited for molecular property elucidation (for example it has been widely applied to property elucidation of porphyrin and phthalocyanins properties since the ‘70s [100]) *e.g.* to resolve degenerate levels.

In a certain way, one might consider the combination achiral molecule+magnetic field as a [false] chirality probe substituting the [true] chirality molecular one. It must however be remarked that, as it was clearly pointed out by Barron [94,95], an external applied magnetic field can only result in “false”, *i.e.* non time-invariant, chirality, unlike the “true”, *i.e.* time-invariant, chirality of a chiral molecular magnetic field..

Simmetrically, mirror image spectra can be also obtained when working on chiral molecules with unpolarized light, by application of a magnetic field (“magneto-chiral dichroism” [101,102]). In this case the polarized light chiral actor is substituted by the combination of normal light+magnetic field.

Do similar considerations also apply to chiral voltammetry?

Magnetochemistry phenomena have been studied in the last two centuries since the first Faraday experiments (who incidentally in such context discovered the polarized light rotation under magnetic field, “Faraday effect”), encompassing magnetic field effects on electron transport (*e.g.* Lorentz force as well as Hall and spin Hall [90] effects) and on electrode processes, (involving interphase capacitance and electron transfer as well reactant diffusion/diffusion issues [103-107]). For example, chiral surfaces have been successfully prepared by electrodeposition exploiting magnetodynamic effects [105], and autonomous Janus swimmers driven by Lorentz force have been recently presented [108].

In the present context, performing voltammetry of an *achiral* molecule *under magnetic field*, a Zeeman effect must take place, resulting in loss of degeneration of α - vs β - spin levels and α - vs

β - electron unbalance; and, of course, upon inverting the magnetic field orientation the opposite situation must be obtained. However, the two situations are enantiomeric, *i.e.* energetically coincident and undistinguishable from the voltammetry “scalar” point of view.

Simmetrically, performing voltammetry of the *achiral* probe on a *chiral electrode*, a Zeeman effect must take place (as already above discussed); in this case the effect is a true chirality one, originating from a magnetic field of chiral molecular origin, and therefore time-invariant. Again, however, the situations obtained with (*R*)- vs (*S*)- layers are enantiomeric and undistinguishable from the voltammetry point of view.

A ”scalar” energy difference can be obtained by applying both magnetic fields, *e.g.* the molecular and the external one. In fact this implies a double splitting effect, modifying the couple of enantiomeric and therefore energetically equivalent combinations into two couples of diastereomeric and therefore energetically different ones). (**Figure 3** bottom)

Actually, very successful “pseudochiral voltammetry” experiments were recently obtained with achiral Fe(II)|Fe(III) redox couples (ferrocyanide|ferricyanide or ferrocene|ferricinium) working on chiral electrodes under magnetic field [93,46-48]. Potential differences were observed of hundreds of mVs, symmetrically upon inverting either magnetic field orientation or chiral surface configuration. A further analogy with MCD [97] is the dependence on the applied magnetic field strength (the observed potential differences regularly decrease with increasing magnet distance) and also, possibly, the temperature effect [93]. Importantly, while a similar phenomenon was observed with different chiral oligomer layers, it was entirely absent when the electrode was modified with an oligomer film of similar molecular properties but achiral.[93]

Looking at **Scheme 1**, this striking experiment, which implies spin-resolved electron energy levels (or, from the electrochemical perspective, spin-resolved electrochemical potentials), could correspond to either situations (IIIb) (considering the achiral probe+magnetic field combination to replace the chiral probe) or (IV) (regarding the chiral surface as probe, and the combination of α - / β - electron + magnetic field to replace the chiral selector).

From a further different perspective, application of the external magnetic field can enable to highlight the molecular spin filter properties of the chiral film on the electrode surface, and to discriminate its configuration; moreover, modulating the magnetic field can enable to modulate spin polarization and energy difference. In this light, it has been proposed that such setup could be looked at as a solution-based equivalent of magnetoresistance determination in all-solid devices (except for the distinction between electron transfer and electron transport) [93]

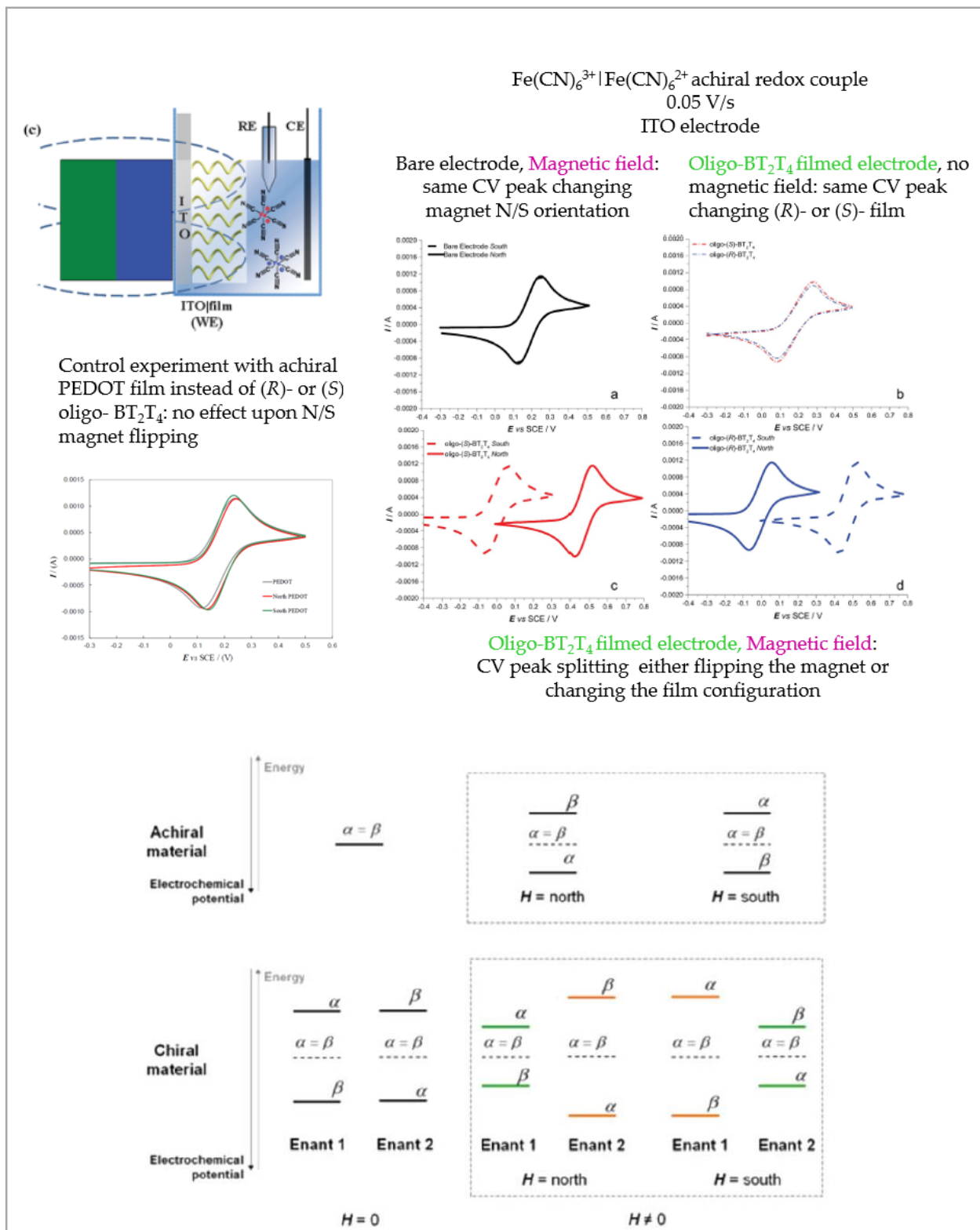


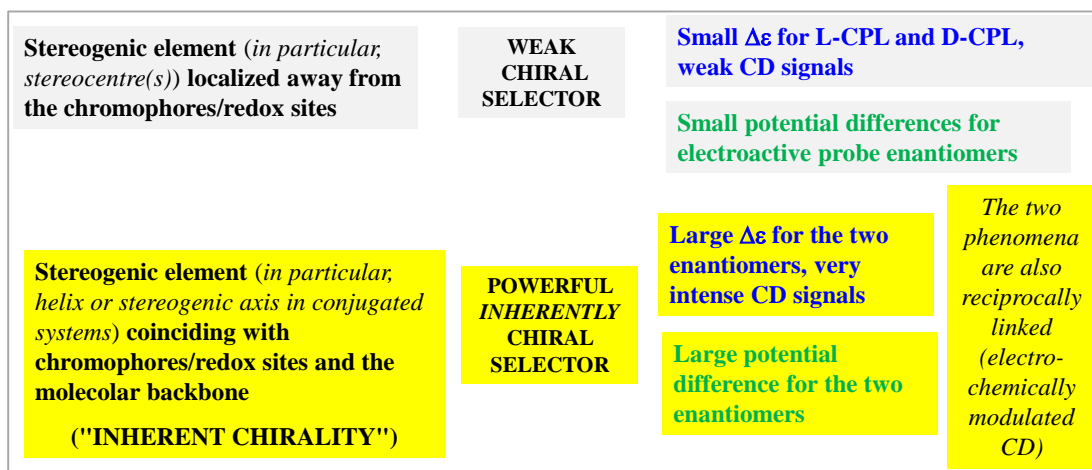
Figure 3 A “pseudochiral voltammetry” experiment obtained working on a chiral electrode with achiral probe under magnetic field. [93] Figure elements reproduced from Ref. 93 with permission from the Royal Society of Chemistry.

2.d Focusing on the molecular chiral actors involved: structure-activity relationship analogies

Beautiful analogies also concern the relationship between the structural features of the involved molecular actors and the observed chiroptical / chiral voltammetry effects.

i) Both techniques share the same ideal selector features: inherently chiral molecules

As mentioned above, the stereogenicity element should be as strictly related as possible to the optically/redox active site(s). In this light, chiral spectroscopy and chiral voltammetry share the same ideal chiral actor features. In particular, huge chirality manifestations are observed both in chiroptical spectroscopy ([12,15], following the old concept of “Inherently Dissymmetric Chromophores and Circular Dichroism” [110]) and in chiral voltammetry [41-51,53-55,57] with “inherently chiral” molecules, in which the source of both chirality and key functional properties coincides, while generally less effective discrimination is obtained when the stereogenic element is a localized, often peripheral, stereocentre (*e.g.* [111,112] vs [53-55,57] concerning chiral vs inherently chiral ionic liquid based media).



SCHEME 2

For example, very effective are inherently chiral selectors having as molecular backbone a conjugated electroactive (hetero)aromatic system featuring an helical or axial (atropisomeric) stereogenic element, their molecular design being also tailored to promote propagation/amplification of stereogenicity from monomer to oligomer and supramolecular structures. Such systems can give both intense, well defined ECD signals (as well as neat circularly polarized luminescence and VCD), and large potential differences (up to some hundreds of mVs) when employed as one of the chiral molecular actors in voltammetry [41,47,112,113].

Remarkably, a given selector appears highly effective with very different chiral probes; this can be justified by the presence of many heteroatoms and aromatic systems available for coordination, consistently with recent chiral voltammetry tests in systematic sequences of molecular probes or selectors (*e.g.* [45,49,51,56]); however, the helical or foldamer structure of the inherently chiral actor should also powerfully enhance the electron orbital-spin coupling and therefore the

“electromagnetic” contribution to the enantiomer discrimination. Actually with such selectors the above impressive magnetoelectrochemistry effect can also be observed [46-48,93].

ii) Both techniques highlight coupling effects of interacting chromophores/redox sites

Inherently chiral selectors with axial stereogenicity consisting of two equivalent and reciprocally interacting redox centres/chromophores (the two symmetrical moieties), like the biindole-based monomer described in [47], also provide very nice model cases to highlight similar energy splitting effects in spectroscopy and in voltammetry. (**Figure 4**)

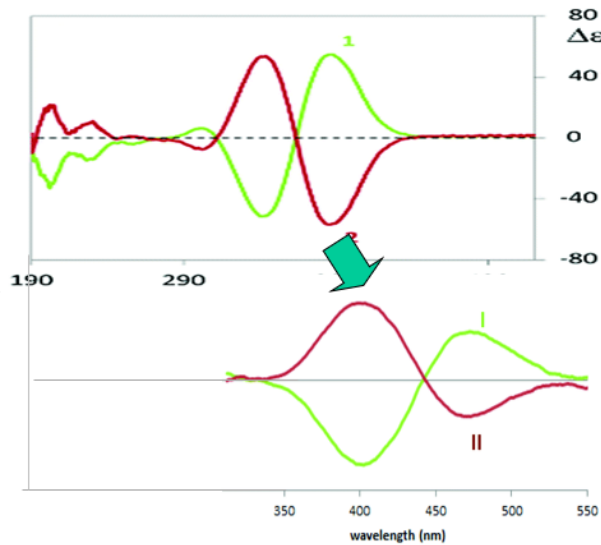
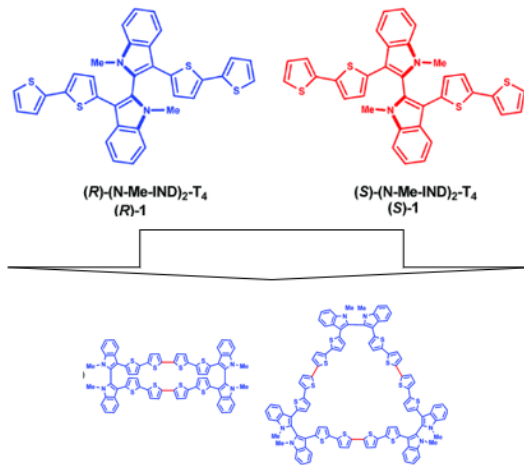
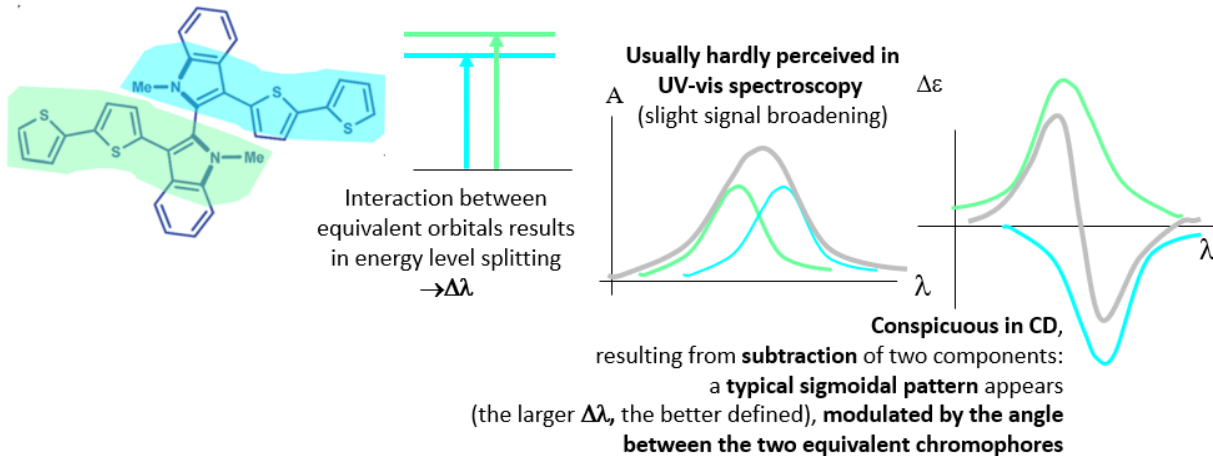
From the perspective of intramolecular electronic transitions, the interaction between the two equivalent chromophores results in an energy level degeneration removal and a wavelength splitting, which however is usually difficult to resolve in UV-vis spectroscopy, only corresponding to a slight signal broadening. Instead the same effect (“exciton coupling” resulting in “Davydov splitting”) becomes evident in CD, since in this case the two components have opposite sign: thus a typical sigmoidal pattern appears (the larger the $\Delta\lambda$, the better defined is such pattern) [12,15,26] (**Figure 4** top). The effect is modulated by the angle between the two equivalent chromophores, is affected by the chromophore environment and working conditions, and can provide important information about the molecule conformation [12,15] in case the magnetic dipole transition moment contribution can be well represented by two independent electric dipole transition moments dissymmetrically disposed [114]

The voltammetry pattern of the same molecule features a typical first oxidation twin peak system which is related to the presence of two equivalent, reciprocally interacting redox sites, mainly localized in the two moieties of the atropisomeric biindole core, which is the electron richest part of the molecule. (This is confirmed by the observation that oligomerization, requiring radical cation formation on the thiophene terminals, does not occur when limiting the potential in the range of the twin peak system, and can only be obtained at potentials corresponding to the subsequent oxidation peak system).

Also in this case the effect provides interesting information on the molecular properties (in particular, the peak splitting increases with the extent of reciprocal interaction/electronic communication [115]) and is affected from the redox site environment (for example the peak splitting decreases upon increasing the solvent polarity [47,115]).

Figure 4. (*following page*) A comparative study case of equivalent, reciprocally interacting chromophores/redox sites in ECD and in CV. Figure elements reproduced from Ref. 47 with permission from the Royal Society of Chemistry.

In spectroscopy: "Exciton coupling" → "Davidov splitting" → Typical bisignate CD pattern

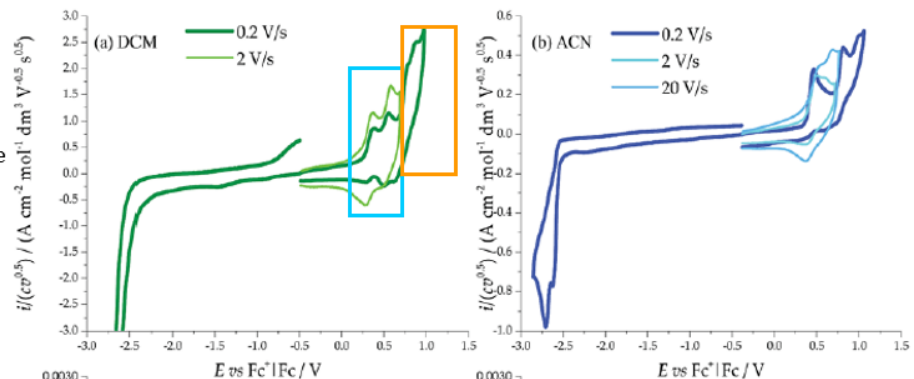


The effect is maintained upon electrooligomerization (open and cyclic oligomers of various dimensions, but all of them retaining the monomer configuration)

In voltammetry: twin peak system corresponding to equivalent interacting redox sites

- Electron richer core: oxidations mainly localized on the core, reductions on the terminals
- **First system of twin reversible oxidation peaks** (equivalent interacting redox centres, mainly localized on the two core moieties), better evidenced in the less polar solvent.
- Oligomerization requires to cycle the potential around the subsequent oxidation system

Peak splitting, increasing with efficiency of redox site interaction, decreasing with increasing solvent polarity



iii) Exploiting the intrinsic reciprocal connection of the three outstanding properties in inherently chiral molecules

Finally, an attractive property of the above inherently chiral molecules is that since chirality, optical activity and electrochemical activity all originate from the main backbone, they are reciprocally strictly linked. For example, chiroptical activity can be regularly and reversibly modulated by electrochemistry, as nicely demonstrated in CD spectroelectrochemistry experiments. [41,112]

3. Conclusions and perspectives

Absorption spectroscopy and voltammetry, having well known analogies and connections, share even more fascinating similarities and connections at a superior complexity level, when “upgrading” them with the ability to discriminate between enantiomer probes, which requires implementation of a chiral selector.

Both “molecular” selectors, having significantly different coordination ability for the probe enantiomers, and “electromagnetic” selectors (L- vs R- circularly polarized light components for spectroscopy, α - vs β - spin electrons in voltammetry) can be considered in both techniques.

In the more mature area of chiral spectroscopy, the technique of choice for enantiodiscrimination, electronic circular dichroism, is based on the second alternative, which requires no development/consumption of high-value reagents and is not probe-destructive, and is made possible by the commercial availability of instrumentation enabling to evaluate differential adsorption of the polarized light components. In the “younger” chiral voltammetry technique, very good results in terms of enantiomer potential differences have been so far obtained with molecular chiral selectors, which in voltammetry case is not critical concerning material quantity (for example, working with chirally modified electrodes requires very little selector quantities) and is not probe-destructive. However, recent evidence concerning the differential interactions of α - vs β - spin electrons with molecular chiral magnetic fields at the electrode surface (CISS effect) suggest that an additional contribution be present besides the molecular one, and could be even exploited alone, analogously to the dichroism technique, should it become reasonably feasible from a technical point of view.

Another analogy between spectroscopy and voltammetry is the possibility of applying an external magnetic field, which may be regarded as replacing a chiral actor (although with “false chirality”), as in the well established magnetic circular dichroism technique, and in intriguing recent magnetoelectrochemistry experiments.

Many analogies and connections also concern the molecular side of the enantiodiscrimination events. In both techniques – circular dichroism and voltammetric enantiomer discrimination – outstanding performances can be obtained with inherently chiral molecular actors. In this context, a helical or atropisomeric molecular structure, in which a conjugated molecular backbone with a tailored torsion is the source of both chirality and optical as well as electrochemical activity, offers a fascinating and useful reciprocal three-fold connection of functional properties. Such molecular design results *inter alia* in nice cases of equivalent and reciprocally interacting

chromophores/redox sites, evidenced both by sigmoidal patterns in CD and by twin peak splitting in CV.

The powerful chirality manifestations of inherently chiral molecules can be justified by both molecular considerations (many heteroatoms and aromatic rings available for molecular interactions) and electromagnetic ones (powerful molecular chiral magnetic field, for which they can be regarded as excellent potential molecular spin filters). Discriminating between the two contributions in order to rationalize and exploit the impressive observed phenomena represents a very desirable target as well as a fascinating challenge.

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Enantiomer discrimination in Absorption Spectroscopy and in Voltammetry: highlighting fascinating similarities and connections

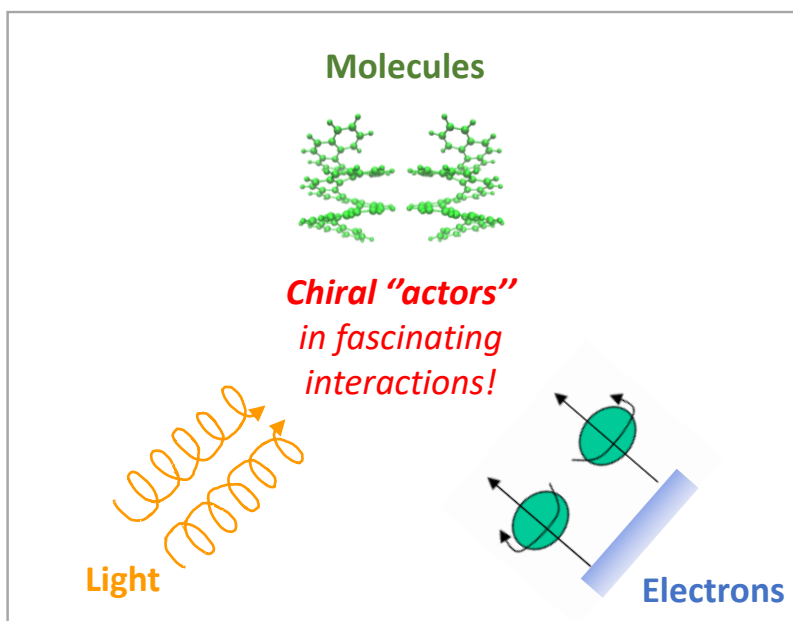
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Abstract. Absorption spectroscopy and voltammetry, of known analogies and connections, share even more fascinating similarities and connections at a higher complexity level, when “upgrading” them with the ability to discriminate between enantiomers by chiral selector implementation. In both techniques either “molecular” selectors or “electromagnetic” ones (L- vs R- circularly polarized light components for spectroscopy, α - vs β - spin electrons for voltammetry) can be considered; moreover, external magnetic field application can replace a truly chiral actor. A tentative schematization is provided. Analogies and connections also concern molecular features of the enantiodiscrimination actors. In both techniques outstanding performances are obtained with inherently chiral molecules, in which a conjugated backbone with tailored torsion is source of chirality as well as spectroscopic and electrochemical activity, in an attractive three-fold interconnection. Their outstanding effects can be justified by a combination of chemical and electromagnetic properties (excellent potential molecular spin filters), a fascinating challenge for future developments.

1. Well known analogies and connections between Voltammetry and Electronic Absorption Spectroscopy in the study of active molecules and molecular materials

The steadily growing search for molecules and molecular materials with advanced functional properties often involves systems that include sites with interesting electronic features, making them at the same time spectroscopically and electrochemically active, *i.e.* both chromophores and redox sites. To experimentally investigate and rationalize such electronic properties, electronic absorption spectroscopy and voltammetry are usually applied in synergy, with well-known reciprocal connections. The first one accounts for intramolecular electronic transitions driven by increasing energy in terms of decreasing wavelength of incident light; the second one accounts for electron transfer processes to/from electrode (oxidations/reductions) driven by increasing energy in terms of increasingly positive/negative electrode potentials. In turn, measured quantities, *i.e.* absorbance in the first case and current intensity in the second case, share dependency on (i) chromophore/redox site concentration, (ii) geometric parameters (optical path length, electrode surface), as well as (iii) molecular parameters accounting for the process mechanism (molar extinction coefficient, accounting for light-matter interaction, in the first case; energy barrier symmetry factor, number of exchanged electrons etc. in the second case). Accordingly, molecular identification/discrimination together with information about molecular energy levels can be achieved considering absorption wavelengths/potentials for electron transfer, while quantification is feasible by considering absorption/current intensities.

Actually the information obtained from the two approaches about energy levels is not expected to coincide, considering the significantly different conditions (homogeneous phase, organic solvent, even apolar, with no electrolyte, no net charge formation... in the first case; heterogeneous conditions, electrolyte medium, net charge formation... in the second case); nor is expected to coincide with values obtained by other approaches such as theoretical computations (usually in vacuum) or, for molecular solids, photoelectron spectroscopies (aggregation effects...).[1-3] However, for example, HOMO-LUMO energy gaps obtained (in eV) from first absorption wavelengths (maxima or onset ones [4]) according to

$$h \text{ (J s)} \times c \text{ (m s}^{-1}\text{)} / (\lambda_{\text{max/onset}} \text{ (m)} \times q_e \text{ (C e}^{-1}\text{)})$$

are often similar to those obtained from first oxidation and first reduction potentials (formal, or peak, or onset ones [4]) in voltammetry experiments, according to

$$1e \times [E_{Ia} - E_{Ic}]V$$

Notably, however, only electrochemical experiments make it possible to estimate single HOMO or LUMO levels,

$$E_{\text{LUMO}} \text{ (eV)} \approx -1e \times [(E_{Ic} / V(\text{Fc}^+|\text{Fc}) + 4.8 \text{ V (Fc}^+|\text{Fc vs zero})]$$

$$E_{\text{HOMO}} \text{ (eV)} \approx -1e \times [(E_{Ia} / V(\text{Fc}^+|\text{Fc}) + 4.8 \text{ V (Fc}^+|\text{Fc vs zero})]$$

on the basis of the estimation of the energy level of the reference intersolvental reference couple $\text{Fc}^+|\text{Fc}$ respect to vacuum (here considered as 4.8 eV, but for which actually there is a range of proposed literature values, being an extrathermodynamic quantity [5]).

Moreover, there can be exceptions in which the two approaches yield remarkably different results, particularly if first oxidation and/or first reduction in the voltammetry experiment do not involve the same HOMO and LUMO energy levels as in the spectroscopic experiments, like *e.g.* when in

large molecules easiest oxidation and easiest reduction involve different sites that are reciprocally distant and not communicating.

2. The two techniques at a higher selectivity level: discriminating enantiomers of chiral advanced molecules and molecular materials

Many optically and electrochemically active molecules of high relevance, for example among natural or synthetic active pharmaceutical ingredients/nutrients, catalysts, materials for optics and spintronics..., are chiral. Endowing spectroscopy and voltammetry with the ability to discriminate between their enantiomers is important, as an alternative or at least a complement to expensive and destructive separation by enantioselective chromatographic techniques.

In achiral environments the enantiomers of chiral electroactive molecules have identical physico-chemical properties and therefore result in identical absorption spectra or voltammetry patterns. Therefore, achieving enantiomer recognition, thus upgrading spectroscopy or voltammetry to chiral spectroscopy or chiral voltammetry, requires implementation of a suitable chiral selector able to significantly interact with the chiral probe, resulting in diastereomeric and therefore energetically distinguishable situations.

As we will discuss further on, the selector can be either a “molecular” one, *i.e.* the (*R*)- or (*S*)-enantiomer of a second chiral molecular species besides the chiral probe, or an “electromagnetic”, one, also truly chiral: in particular, the L- and R- circularly polarized light components, or the α - and β -spin electrons in rototranslational motion across the electrochemical interphase.

Of course, in order to achieve transduction of the recognition event, at least one chromophore or/and redox site, respectively for chiral spectroscopy or/and chiral voltammetry, must either be present in the probe and/or in the selector, or, if necessary, provided by a third, possibly achiral, co-actor [6]. In any case, such active sites should be possibly strictly related to (*e.g.* located close to, coupled with, or, best of all, coincident with) the stereogenic element which enables chiral recognition. In such perspective, particularly attractive are “inherently chiral” molecular selectors in which the main molecular backbone, based on a conjugated (hetero)aromatic system featuring an helical or axial stereogenic element, is the source of both chirality and key electron absorption/electron transfer properties.[7-9]

In summary, at least two chiral actors (probe/selector, although it should be remarked that discriminating between probe and selector is only a matter of perspective...) and at least one chromophore/redox site must be present in the environment where the enantio-recognition event has to be achieved and detected. A tentative comparative schematization of possible cases is provided in **Scheme 1**.

Scheme 1. (*following page*) A tentative schematization of possible enantiodiscrimination strategies in chiral electronic absorption spectroscopy or chiral voltammetry, with related implications.

Required for enantiomer discrimination:
at least two chiral actors («probe» and «selector») and one **active site** for the desired transduction mode.

Transduction of enantiorecognition event
for R vs S probe at constant selector, or vice versa

	Chiral probe	Chiral selector	Active site for transduction	Electronic intramolecular transitions (UV-Vis: $\Delta\lambda$, ΔA)	Molecule-to/from-electrode electron transfers (voltammetry: ΔE , ΔI)
I	Chiral molecule 1	Chiral molecule 2	In probe or/and selector, or in auxiliary achiral molecule	[Performed with unpolarized light] Critical requirement of bulk probe coordination with specific chiral selector Expensive/probe-destructive	Chiral selector can be implemented as a very thin layer modifying the electrode surface → minimum quantity required, non probe-destructive. Possible enhancing effects from local cage/structuring/field effects. α- vs β-spin electrons also involved, → possible additional electromagnetic effect besides the molecular one!
"MOLECULAR" + "ELECTROMAGNETIC" CHIRAL ACTORS					
IIa	Chiral molecule	L- vs R- circularly polarized light components	In probe or in auxiliary	[Performed with polarized light] Evaluating absorption difference between L- and R- polarized light components (electronic circular dichroism). No specific chiral molecular selector required, non probe-destructive	
IIb	Chiral molecule	α- vs β-spin electrons	In probe or in auxiliary		Evaluation of α- vs β electron spin ratio so far critical. Opting to evaluate changes in a spin-specific/spin-enriched current, the latter can be generated at a ferromagnetic electrode under magnetic field (which adds a further, «false chirality», actor, see below) or at a chiral electrode surface by CISS effect (which implies a chiral molecular selector, former case, unless the chiral layer be the probe itself). A device based on the Hall effect has also been proposed

Replacement of a chiral actor by magnetic field application (*false chirality*)

ELECTROMAGNETIC TRULY CHIRAL ACTOR + ELECTROMAGNETIC FALSELY CHIRAL ACTOR					
IIIa	Achiral molecule	Magnetic field	L- vs R- circularly polarized light components	Active site for transduction in the achiral molecule	Magnetic circular dichroism, based on energy level perturbation due to static magnetic field
IIIb	Achiral molecule	Magnetic field	α- vs β-spin electrons (S)- vs (R)- Chiral electrode surface (implying α- vs β unbalance)	Active site for transduction in the achiral molecule	Impressive potential differences observed when combining the external and internal magnetic field!
MOLECULAR TRULY CHIRAL ACTOR + ELECTROMAGNETIC FALSELY CHIRAL ACTOR					
IV	Chiral molecule	Magnetic field		Active site for transduction in chiral molecule or auxiliary	[Performed with unpolarized light] Magneto-chiral dichroism Same case as above, regarded from a different perspective? (i.e. with the achiral molecule being the auxiliary, and the chiral surface being the probe)

SCHEME 1

2.a Achieving enantiodiscrimination in electronic spectroscopy with truly chiral actors

In principle, enantiodiscrimination could be achieved in absorption or emission spectroscopy with both chiral actors being “molecular” ones, provided that their combination results in significant variation in absorption wavelength or/and intensity for at least one chromophore belonging to one or both chiral actors (or to a third auxiliary achiral co-actor).

Although a significant number of such cases have been studied, especially for colorimetric/visual readout of the recognition event (like *e.g.* [10,11]), this approach does not look very popular, possibly since it requires development, preparation and bulk consumption of specific, powerful chiral molecular selectors, and is probe-destructive.

Such onerous requirement is instead not necessary working with **polarized light**, in the well-established technique of **circular dichroism** [12-21,23].

Plane polarized light PL can be regarded (**Figure S1** in SI) as the sum of two helix-like left-handed and right-handed circularly polarized light components, L-CPL and R-CPL (which in turn can be regarded as the sum of two perpendicular PLs with $\pm \pi/2$ phase difference). When PL passes through a chiral sample, its L-CPL and R-CPL components proceed at different speed; as a result,

- if the wavelength is such that no absorption can take place, the light exiting the chiral sample is still *plane* polarized, but rotated by a given α angle (the observed quantity in the popular *polarimetry* technique). Such rotation depends on the light wavelength, which is the object of the *optical rotation dispersion* ORD technique, analyzing L-CPL vs R-CPL propagation speed differences [21,22];
- if the light wavelength λ is such that it can be also absorbed by the sample, the light exiting the sample is *elliptically* polarized, as a consequence of the two CPL components being absorbed with different molar extinction coefficients ϵ_L and ϵ_R , resulting in different A_L and A_R absorbances (“Cotton effect”). Recording the ellipticity ϑ , or its proportional quantities $\epsilon_R - \epsilon_L$ or $A_R - A_L$, as a function of incident PL wavelength, provides *circular dichroism* CD spectra [12,15,23] or, more precisely, E[lectronic]CD spectra, to distinguish them from V[ibrational]CD spectra, which can be obtained in the infrared range [24,25].

ECD signals are located in correspondence of UV-Vis absorption ones, but, unlike them, being differential quantities they can be either positive or negative, and are perfectly specular for the enantiomers of a given chiral molecule.

It is worthwhile recalling that extinction coefficient ϵ , accounting for efficiency of photon/matter interaction, depends on both electric and magnetic transition dipole moments, accounting for electron density redistribution (translational and rotational displacement, respectively) in transition between different energy levels implying different orbital (electron density) shapes. In achiral UV-Vis absorption spectroscopy the electric transition dipole moment is usually the prevailing one, and allowed and forbidden transitions are defined considering it only. Instead, in chiral spectroscopy both dipole moments are important, involving *chiral* charge displacement along *e.g.* a helical path (in the asymmetric chiral magnetic field corresponding to the chiral sample) [12]

Simulation of CD spectra with theoretical computations enables to assign absolute configuration to the two enantiomers. [15,19,26]

Conformation [13], supramolecular [14] and solid-state effects [17,20,27-29] can result in significant modulation of ECD spectra. The ECD technique is particularly useful when studying chiral macromolecules (including both natural and synthetic ones), to account for the presence of a regular "secondary" chiral structure [13,30] (**Figure S1** in SI). In particular, the more regular and stable the "secondary" helical/foldamer chiral structure of the macromolecule, the more evident its ECD response, which can instead nearly cancel for chiral polymers with "random coil" features and/or resulting from non-regioregular oligomerization. [28,31] Accordingly, the ECD of a given chiral macromolecule remarkably changes if the latter conformation changes (at constant configuration) *e.g.* as a function of pH, solvent, light, electric charge etc..[29]

Symmetrically to ECD, in **emission** spectroscopy with PL excitation, chiral samples can fluoresce with PL, consisting of **two circularly polarized components of different intensity (Circularly polarized luminescence, CPL)**. [32-35]

2.b Achieving enantiodiscrimination at the electrochemical interphase with truly chiral actors

In chiral voltammetry the most desirable transduction mode of the enantiomer recognition event is in terms of a significant, possibly wide, potential difference for the two electroactive probe enantiomers in the presence of the chiral enantiopure selector. (**Figure 1**) In fact, a potential difference can enable direct enantiomer recognition (also combined with quantitative estimation from peak currents) and/or selective enantiomer activation, [7] from the microscopic scale up to, fascinatingly, the macroscopic one, in many smart device architectures [36-40]

The most favourable circumstance is when a neat potential difference between two well-defined peaks with linear dynamic range for currents is observed for the two enantiomers simultaneously present, enabling to estimate enantiomeric excesses. [41,42] This optimal situation can be easier achieved for chemically reversible electron transfer processes, which result in little or no surface conditioning by the first enantiomer electrode process with respect to the second one. [41,42]

It must be underlined that there is obviously no *a priori* relationship between the combination of probe/enantiomer absolute configurations and the peak sequence, being the (*R*)- and (*S*)-descriptors assigned according to an abstract convention. Instead, specular potential differences *must* be obtained upon inverting either probe or selector configuration (**Figure 1**); such double inversion test provides the soundest reliability test for the enantiodiscrimination protocol, enabling to rule out possible other causes for the observed potential differences. [41]

Actually many cases have been recently presented of significant and even wide potential differences, obtained for various probe enantiomers by implementing molecular chiral selectors at the electrochemical interphase, either as confined solid selector layer/network, modifying the electrode surface with suitable chiral selector films [41-51], or as expanded semisolid selector network, exploiting media of high local order at the interphase with a charged achiral electrode like ionic liquids or deep eutectic solvents, implemented with chirality [52-57].

Since in the voltammetry case the enantiodiscrimination process is intrinsically heterogeneous, taking place at the interphase rather than in the bulk, only minimal quantities of the molecular selector can be employed, *e.g.* modifying the electrode surface by electrodeposition of a very thin chiral selector layer [41-51] or working with screen-printed cells with a thin layer of ionic liquid modified with a chiral additive (or itself chiral)[53-55,57]. Moreover, the modified surface could be recycled (at least in favourable cases with no filming/conditioning products) and in any case the experiment is non-destructive for the bulk probe. Furthermore, local cage/structuring/electromagnetic effects can enhance probe/selector interactions respect to bulk conditions.

Notably, the observed potential shifts (up to some hundreds mVs) are consistent with mild coordination, considering *e.g.* the well known Kolthoff and Lingane treatment for ligand effect on electrochemically reversible species [58], or the significant peak potential differences that are often observed for a given electroactive molecule upon changing the supporting electrolyte, on account of different tendency to ionic couple formation.

Remarkably, when considering the study cases provided in the above cited papers, the selectors can be considered “multipurpose”, because a given selector is effective with even very different probes, and a given probe can be discriminated by various selectors, although with different efficiency. This can be explained by the good number of elements available for probe/selector coordination (heteroatoms, (hetero)aromatic rings and π conjugated systems) in the reported examples.

However, besides such “molecular interaction” effect, an “electromagnetic” effect should be considered, too [59], related to the α - vs β - spin electrons in rototranslational motion across the chiral interphase being promoted or hampered by the latter’s chiral magnetic field, in turn modulated by the presence of a second chiral magnetic field corresponding to the chiral probe. Indeed, referring to **Scheme 1**, voltammetry case (I) must also include voltammetry case (IIb), and the concurrent presence of *two* chiral selectors should be considered, resulting in *two* contributions. It is worthwhile noticing that such considerations are possible on account of the electron flux being intrinsically unidirectional, *i.e.* perpendicular to the electrochemical interphase, while the parallel spectroscopic case (I), involving unpolarized light, implies infinite planes.

Of course a key issue is to evaluate the extent of such “electromagnetic” contribution.

The different interaction of α - vs β - spin electrons with a chiral magnetic field corresponding to a chiral molecular layer of (*R*)- or (*S*)- configuration, particularly modifying an electrode surface across which the chiral rototranslational motion of electrons takes place, is a fascinating subject that has been the object of extensive investigations (*e.g.* [59-85]), particularly by Naaman and colleagues [59-80], who termed it CISS (“chiral-induced spin selectivity”).

They observed that α - vs β - spin polarization induced by a molecular chiral electrode surface can be impressive, even surpassing common inorganic spin-filters [60], pointing to competitive applications such as molecular spin filters or giant magnetoresistive molecular spin valves [86-88] in spintronics, a field of great current applicative interest [89-92].

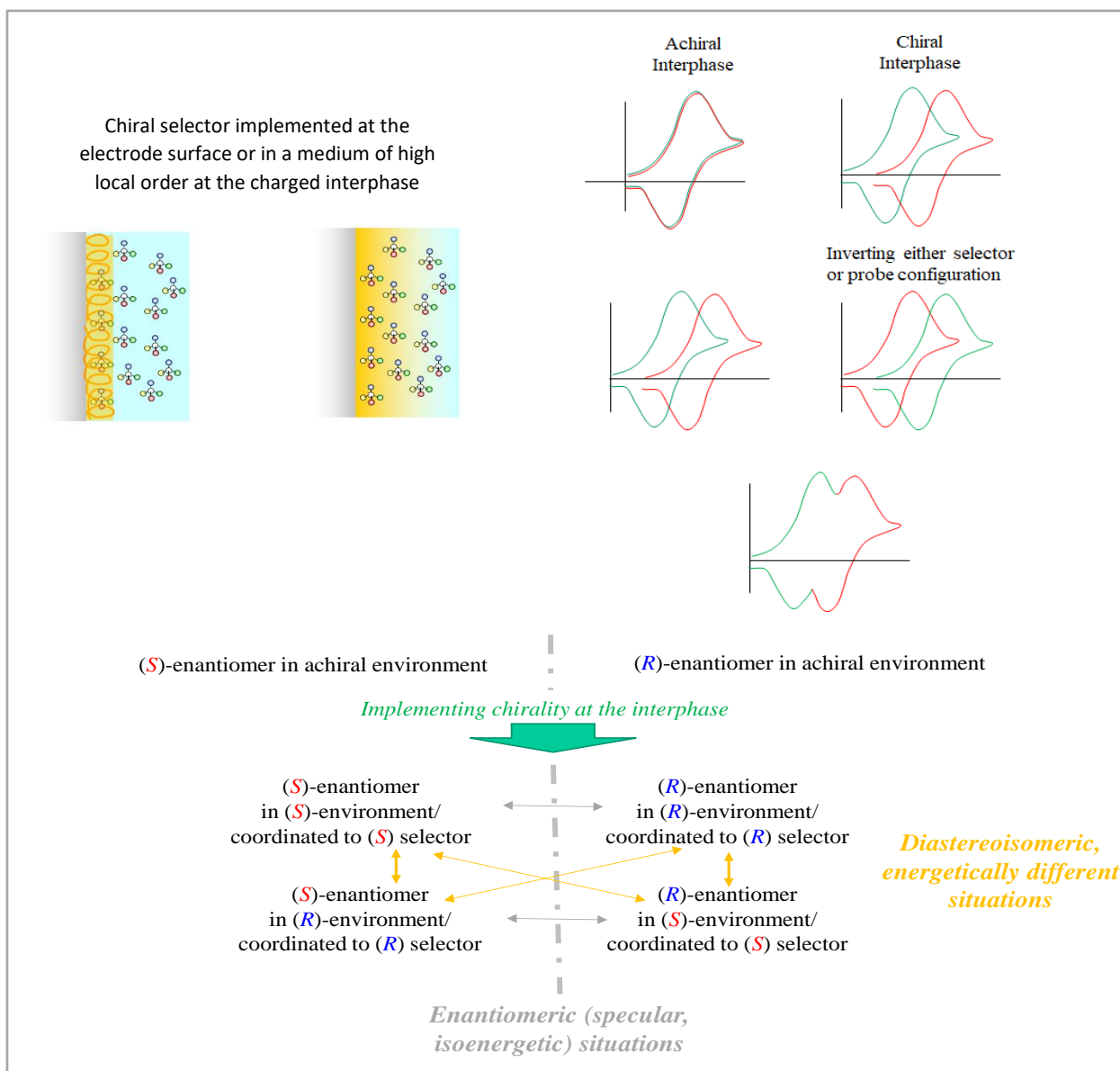


Figure 1. Chiral voltammetry basic features.

They also pointed out that to justify such high spin polarizations an unusually high spin-orbit coupling should be considered, of several orders of magnitude greater than normal cases of organic molecules [60]. To justify it, spin transport has been modelled in the electromagnetic field of an *helical* molecular structure [60,63,71,81,82] resulting in estimated energy splittings of even several hundreds of meV [60] between the two spin states. Also the tunneling probability for the favoured spin has been estimated to be enhanced with respect to normal cases by even 1-2 orders of magnitude [63]. The importance of electron correlation has also been pointed out [84], with the estimated spin polarization increasing in molecular chains with the number of ionic sites and laps.

To study the CISS effect, spin-specific/enriched currents were typically generated using a magnetic electrode under magnetic field [61,62] (which actually adds a further actor, although a

“false”, *i.e.* non time-invariant [93-95], chirality one), then evaluating their variations upon crossing the chiral layer under study [62]. More recently, however, a protocol based on a working electrode modified with a circuit implementing Hall effect has been proposed to avoid the presence of the magnetic field. [59] Actually spin-specific currents can also be produced by the CISS effect itself, at an electrode modified with a chiral molecular layer [93]. Very recently, spin-dependent charge transfer at chiral electrodes has been probed by magnetic resonance [69]. Moreover, Kelvin-probe experiments resulted in potential differences up to nearly one hundred mV. [76] The CISS effect has been shown to be applicable to enhance water splitting [66,78], to achieve asymmetric reactions [75] enantiomer separation [70] and enantiomer bio-recognition [63], and to propagate along achiral low-resistance molecular wires [72].

Fascinatingly, the CISS effect has also been related to the intriguing subject of biological homochirality [96].

Returning to the present issue, in principle the spin electron polarization upon interaction with the chiral probe could be sufficient as a selector for enantiomer discrimination, even without a molecular one, and would represent the electrochemical parallel of the ECD experiment. However unlike the spectroscopic case, (a) the approach based on two molecular actors has so far been very successful (it would be however interesting to evaluate how much is the spin polarization contribution) and (b) at least so far, evaluation of α - vs β - spin ratio is still critical/not trivial respect to evaluation of L-CPL to R-CPL ratio in spectroscopy. Were it to become easily accessible, an “electrochemical spin dichroism” could be developed for electrochemical enantiomer discrimination in the absence of molecular selectors!

2.c Substituting a “truly” chiral actor with a “falsely” chiral one: application of an external magnetic field

Achiral polarizable substrates can also give circular dichroism response under magnetic field application, proportionally to magnetic field intensity and presenting mirror image spectra upon inverting magnetic field orientation. Such “magnetic circular dichroism” (MCD) has been explained in terms of perturbation of electronic energy levels by an external static magnetic field and can be the sum of three contributions [97-99]: a first one, temperature-independent, of sigmoidal shape, related to loss of degeneration in excited states; a generally weak second one, also temperature-independent, bell-shaped, related to mixing of close excited states; and a third one, also bell-shaped and more intense, related to loss of degeneration in ground state, dominant especially at low temperatures, being linked to population distribution in α - vs β - ground sublevels. MCD is a well-established technique, exploited for molecular property elucidation (for example it has been widely applied to property elucidation of porphyrin and phthalocyanins properties since the ‘70s [100]) *e.g.* to resolve degenerate levels.

In a certain way, one might consider the combination achiral molecule+magnetic field as a [false] chirality probe substituting the [true] chirality molecular one. It must however be remarked that, as it was clearly pointed out by Barron [94,95], an external applied magnetic field can only result in “false”, *i.e.* non time-invariant, chirality, unlike the “true”, *i.e.* time-invariant, chirality of a chiral molecular magnetic field.

Symmetrically, mirror image spectra can be also obtained when working on chiral molecules with unpolarized light, by application of a magnetic field (“magneto-chiral dichroism” [101,102]). In this case the polarized light chiral actor is substituted by the combination of normal light+magnetic field.

Do similar considerations also apply to chiral voltammetry?

Magnetochemistry phenomena have been studied in the last two centuries since the first Faraday experiments (who incidentally in such context discovered the polarized light rotation under magnetic field, “Faraday effect”), encompassing magnetic field effects on electron transport (*e.g.* Lorentz force as well as Hall and spin Hall [90] effects) and on electrode processes, (involving interphase capacitance and electron transfer as well reactant diffusion/diffusion issues [103-107]). For example, chiral surfaces have been successfully prepared by electrodeposition exploiting magnetodynamic effects [105], and autonomous Janus swimmers driven by Lorentz force have been recently presented [108].

In the present context, performing voltammetry of an *achiral* molecule *under magnetic field*, a Zeeman effect must take place, resulting in loss of degeneration of α - vs β - spin levels and α - vs β - electron unbalance; and, of course, upon inverting the magnetic field orientation the opposite situation must be obtained. However, the two situations are enantiomeric, *i.e.* energetically coincident and undistinguishable from the voltammetry “scalar” point of view.

Symmetrically, performing voltammetry of the *achiral* probe *on a chiral electrode*, a Zeeman effect must take place (as already above discussed); in this case the effect is a true chirality one, originating from a magnetic field of chiral molecular origin, and therefore time-invariant. Again, however, the situations obtained with (*R*)- vs (*S*)- layers are enantiomeric and undistinguishable from the voltammetry point of view.

A “scalar” energy difference can be obtained by applying both magnetic fields, *e.g.* the molecular and the external one. In fact this implies a double splitting effect, modifying the couple of enantiomeric and therefore energetically equivalent combinations into two couples of diastereomeric and therefore energetically different ones). (**Figure 2** bottom)

Actually, very successful “pseudochiral voltammetry” experiments were recently obtained with achiral Fe(II)|Fe(III) redox couples (ferrocyanide|ferricyanide or ferrocene|ferricinium) working on chiral electrodes under magnetic field [93,46-48]. Potential differences were observed of hundreds of mVs, symmetrically upon inverting either magnetic field orientation or chiral surface configuration. A further analogy with MCD [97] is the dependence on the applied magnetic field strength (the observed potential differences regularly decrease with increasing magnet distance) and maybe also the temperature effect [93]. Importantly, while a similar phenomenon was observed with different chiral oligomer layers, it was entirely absent when the electrode was modified with an oligomer film of similar molecular properties but achiral.[93]

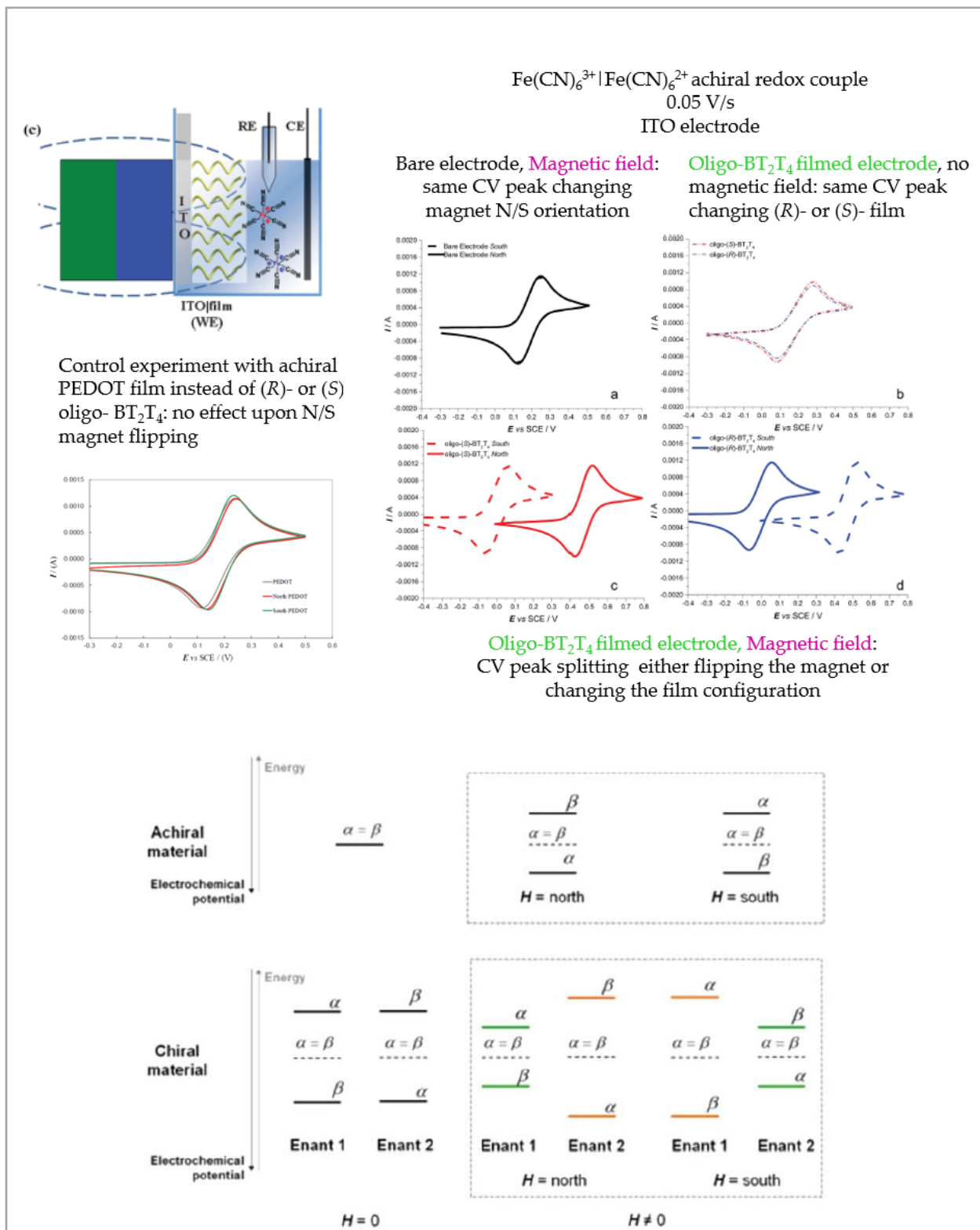


Figure 2. A “pseudochiral voltammetry” experiment obtained working on a chiral electrode with achiral probe under magnetic field. [93] Figure elements reproduced from Ref. 93 with permission from the Royal Society of Chemistry.

In the frame of **Scheme 1**, this striking experiment, which implies spin-resolved electron energy levels (or, from the electrochemical perspective, spin-resolved electrochemical potentials), could correspond to either situations (IIIb) (considering the achiral probe+magnetic field combination to replace the chiral probe) or (IV) (regarding the chiral surface as probe, and the combination of α - / β - electron + magnetic field to replace the chiral selector).

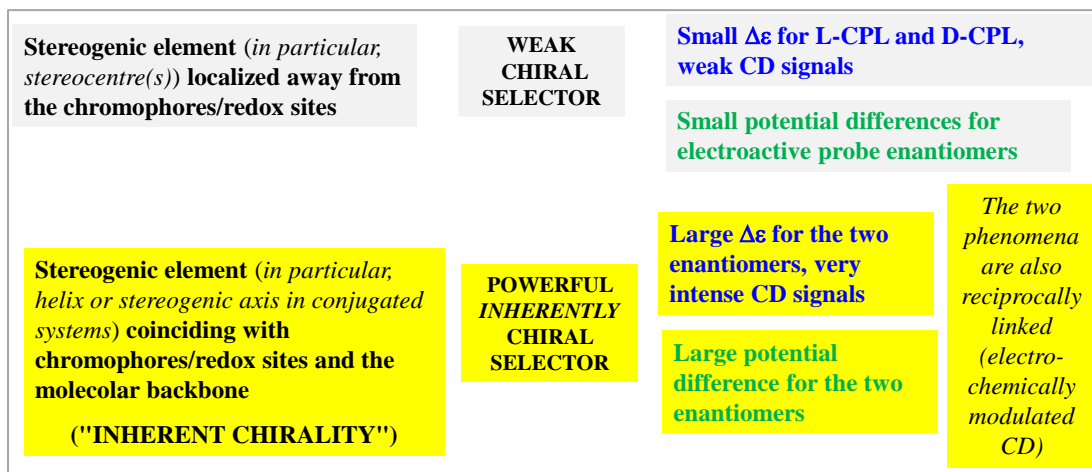
From a further different perspective, application of the external magnetic field can enable to highlight the molecular spin filter properties of the chiral film on the electrode surface, and to discriminate its configuration; moreover, modulating the magnetic field can enable to modulate spin polarization and energy difference. In this light, it has been proposed that such setup could be looked at as a solution-based equivalent of magnetoresistance determination in all-solid devices (except for the distinction between electron transfer and electron transport) [93]

2.d Focusing on the molecular chiral actors involved: structure-activity relationship analogies

Beautiful analogies also concern the relationship between the structural features of the involved molecular actors and the observed chiroptical / chiral voltammetry effects.

i) Both techniques share the same ideal selector features: inherently chiral molecules

As mentioned above, the stereogenicity element should be as strictly related as possible to the optically/redox active site(s). In this light, chiral spectroscopy and chiral voltammetry share the same ideal chiral actor features. In particular, huge chirality manifestations are observed both in chiroptical spectroscopy ([12,15], following the old concept of “Inherently Dissymmetric Chromophores and Circular Dichroism” [110]) and in chiral voltammetry [41-51,53-55,57] with “inherently chiral” molecules, in which the source of both chirality and key functional properties coincides, while generally less effective discrimination is obtained when the stereogenic element is a localized, often peripheral, stereocentre (*e.g.* [111,112] vs [53-55,57] concerning chiral vs inherently chiral ionic liquid based media).



SCHEME 2

For example, very effective are inherently chiral selectors having as molecular backbone a conjugated electroactive (hetero)aromatic system featuring an helical or axial (atropisomeric) stereogenic element, their molecular design being also tailored to promote propagation/amplification of stereogenicity from monomer to oligomer and supramolecular structures. Such systems can give both intense, well defined ECD signals (as well as neat circularly polarized luminescence and VCD), and large potential differences (up to some hundreds of mVs) when employed as one of the chiral molecular actors in voltammetry [41,47,112,113].

Remarkably, a given selector appears highly effective with very different chiral probes; this can be justified by the presence of many heteroatoms and aromatic systems available for coordination, consistently with recent chiral voltammetry tests in systematic sequences of molecular probes or selectors (*e.g.*[45,49,51,56]); however, the helical or foldamer structure of the inherently chiral actor should also powerfully enhance the electron orbital-spin coupling and therefore the “electromagnetic” contribution to the enantiomer discrimination. Actually with such selectors the above impressive magnetoelectrochemistry effect can also be observed [46-48,93].

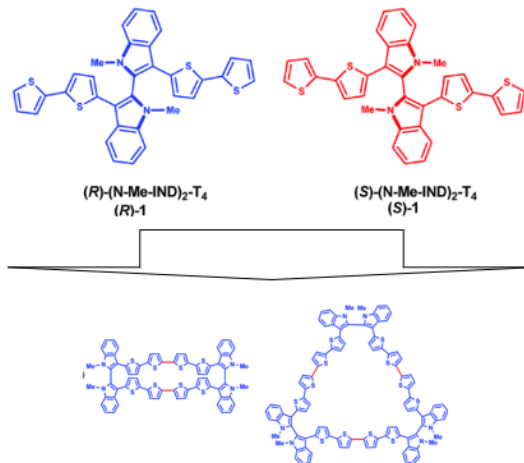
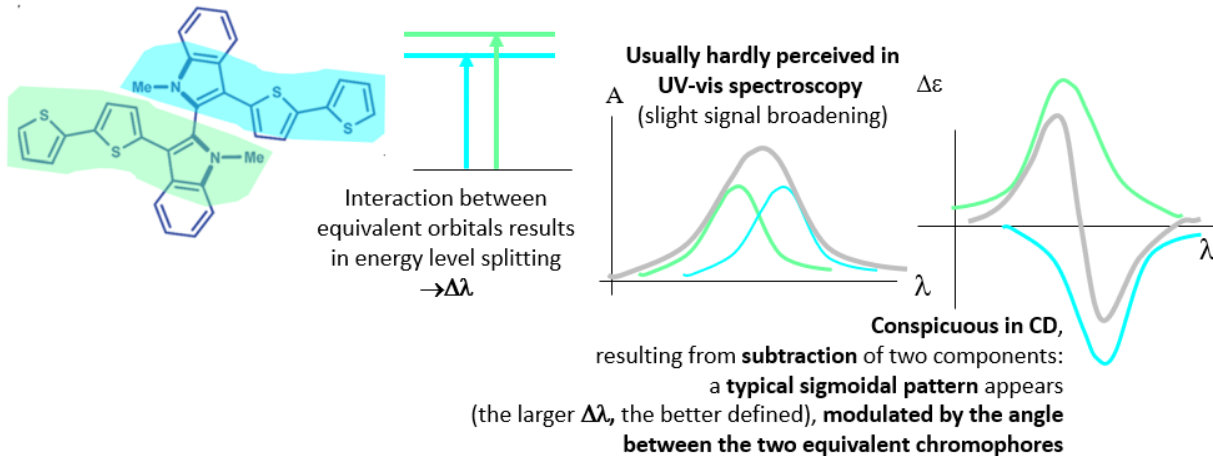
ii) Both techniques highlight coupling effects of interacting chromophores/redox sites

Inherently chiral selectors with axial stereogenicity consisting of two equivalent and reciprocally interacting redox centres/chromophores (the two symmetrical moieties), like the biindole-based monomer described in [47], also provide very nice model cases to highlight similar energy splitting effects in spectroscopy and in voltammetry. (**Figure 3**)

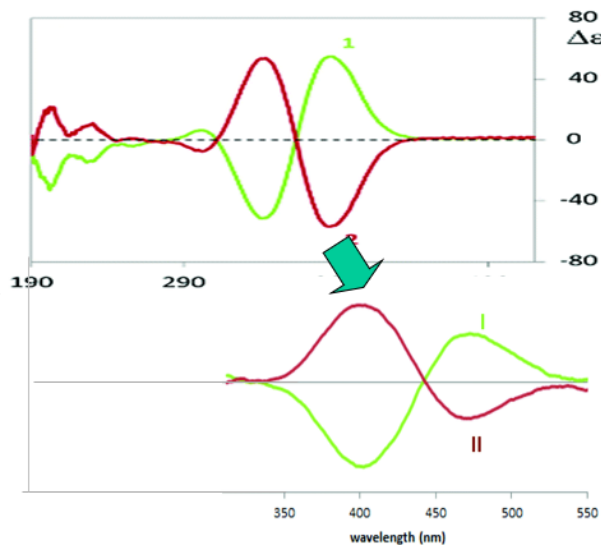
From the perspective of intramolecular electronic transitions, the interaction between the two equivalent chromophores results in an energy level degeneration removal and a wavelength splitting, which however is usually difficult to resolve in UV-vis spectroscopy, only corresponding to a slight signal broadening. Instead the same effect (“exciton coupling” resulting in “Davydov splitting”) becomes evident in CD, since in this case the two components have opposite sign: thus a typical sigmoidal pattern appears (the larger the $\Delta\lambda$, the better defined is such pattern) [12,15,26] (**Figure 3** top). The effect is modulated by the angle between the two equivalent chromophores, is affected by the chromophore environment and working conditions, and can provide important information about the molecule conformation [12,15] in case the magnetic dipole transition moment contribution can be well represented by two independent electric dipole transition moments dissymmetrically disposed [114].

Figure 3. (*following page*) A comparative study case of equivalent, reciprocally interacting chromophores/redox sites in ECD and in CV. Figure elements reproduced from Ref. 47 with permission from the Royal Society of Chemistry.

In spectroscopy: "Exciton coupling" → "Davidov splitting" → Typical bisignate CD pattern



The effect is maintained upon electrooligomerization (*open and cyclic oligomers of various dimensions, but all of them retaining the monomer configuration*)

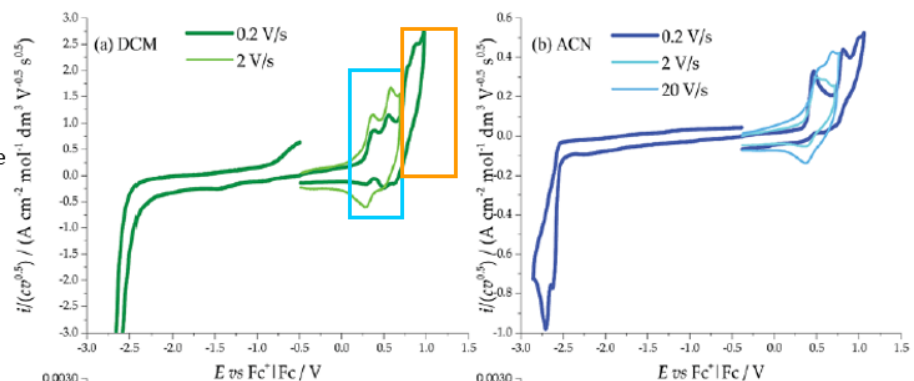


Similar CD signals, although shifted at higher wavelength on account of the improved intra- and intermolecular conjugation.

In voltammetry: twin peak system corresponding to equivalent interacting redox sites

- Electron richer core: oxidations mainly localized on the core, reductions on the terminals
- **First system of twin reversible oxidation peaks** (equivalent interacting redox centres, mainly localized on the two core moieties), better evidenced in the less polar solvent.
- **Oligomerization requires to cycle the potential around the subsequent oxidation system**

Peak splitting, increasing with efficiency of redox site interaction, decreasing with increasing solvent polarity



The voltammetry pattern of the same molecule features a typical first oxidation twin peak system which is related to the presence of two equivalent, reciprocally interacting redox sites, mainly localized in the two moieties of the atropisomeric biindole core, which is the electron richest part of the molecule. (This is confirmed by the observation that oligomerization, requiring radical cation formation on the thiophene terminals, does not occur when limiting the potential in the range of the twin peak system, and can only be obtained at potentials corresponding to the subsequent oxidation peak system).

Also in this case the effect provides interesting information on the molecular properties (in particular, the peak splitting increases with the extent of reciprocal interaction/electronic communication [115]) and is affected from the redox site environment (for example the peak splitting decreases upon increasing the solvent polarity [47,115]).

iii) Exploiting the intrinsic reciprocal connection of the three outstanding properties in inherently chiral molecules

Finally, an attractive property of the above inherently chiral molecules is that since chirality, optical activity and electrochemical activity all originate from the main backbone, they are reciprocally strictly linked. For example, chiroptical activity can be regularly and reversibly modulated by electrochemistry, as nicely demonstrated in CD spectroelectrochemistry experiments. [41,112]

1. Conclusions and perspectives

Absorption spectroscopy and voltammetry, having well known analogies and connections, share even more fascinating similarities and connections at a superior complexity level, when “upgrading” them with the ability to discriminate between enantiomer probes, which requires implementation of a chiral selector.

Both “molecular” selectors, having significantly different coordination ability for the probe enantiomers, and “electromagnetic” selectors (L- vs R- circularly polarized light components for spectroscopy, α - vs β - spin electrons in voltammetry) can be considered in both techniques.

In the more mature area of chiral spectroscopy, the technique of choice for enantiodiscrimination, electronic circular dichroism, is based on the second alternative, which requires no development/consumption of high-value reagents and is not probe-destructive, and is made possible by the commercial availability of instrumentation enabling to evaluate differential adsorption of the polarized light components. In the “younger” chiral voltammetry technique, very good results in terms of enantiomer potential differences have been so far obtained with molecular chiral selectors, which in voltammetry case is not critical concerning material quantity (for example, working with chirally modified electrodes requires very little selector quantities) and is not probe-destructive. However, recent evidence concerning the differential interactions of α - vs β - spin electrons with molecular chiral magnetic fields at the electrode surface (CISS effect) suggest that an additional contribution be present besides the molecular one, and could be even exploited alone, analogously to the dichroism technique, should it become reasonably feasible from a technical point of view.

Another analogy between spectroscopy and voltammetry is the possibility of applying an external magnetic field, which may be regarded as replacing a chiral actor (although with “false chirality”), as in the well established magnetic circular dichroism technique, and in intriguing recent magnetoelectrochemistry experiments.

Many analogies and connections also concern the molecular side of the enantiodiscrimination events. In both techniques – circular dichroism and voltammetric enantiomer discrimination – outstanding performances can be obtained with inherently chiral molecular actors. In this context, a helical or atropisomeric molecular structure, in which a conjugated molecular backbone with a tailored torsion is the source of both chirality and optical as well as electrochemical activity, offers a fascinating and useful reciprocal three-fold connection of functional properties. Such molecular design results *inter alia* in nice cases of equivalent and reciprocally interacting chromophores/redox sites, evidenced both by sigmoidal patterns in CD and by twin peak splitting in CV.

The powerful chirality manifestations of inherently chiral molecules can be justified by both molecular considerations (many heteroatoms and aromatic rings available for molecular interactions) and electromagnetic ones (powerful molecular chiral magnetic field, for which they can be regarded as excellent potential molecular spin filters). Discriminating between the two contributions in order to rationalize and exploit the impressive observed phenomena represents a very desirable target as well as a fascinating challenge.

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Itemized reply to Referee Issues

We are indeed delighted with the Referee's kind appreciation!

Concerning the points raised:

- *"Authors use the term "actors", it is not clear why authors do not use the proper word which is "system". This is a scientific paper going to be published in a scientific journal"*

Actually we really feel that "system" does not fit our intended meaning, nor have we found a more appropriate term than "actor", which is used here in a generic meaning of "taking part to an (inter)action", and can be found also as "molecular actor(s)" in recent scientific papers.

Thus we have now specified in the (newly added) supporting information, to justify our adoption of the "actor" term in the present context:

"As in various examples including recent scientific papers, the term has been employed in the present discussion in its original generic meaning (also accounted for in dictionaries, according to the Latin meaning "who does/acts"), i.e. to indicate an entity (molecular or electromagnetic in our cases) which is taking active part to the described interactions/recognition events."

- *Figure 1. Frankly speaking a reader of Current Opinion in Electrochemistry is supposed to know everything it is shown there. Figure 1 should be simply dropped. Making also the manuscript a bit more compact.*

We are not sure that an electrochemistry researcher not dealing with chirality issues can be undoubtedly assumed to be an expert of circular dichroism fundamentals. Thus we have followed the Referee advice to drop Figure 1 from the main paper to make it more compact, but have moved it (with a slight modification) to the supporting information in case it can be useful to the reader.

In the revised Manuscript we are submitting, we have also

- made a few small corrections in the paper (besides renumbering figures, of course)
- added in the supporting information some explanation about enantiomer descriptors used in the molecular case and in the spectroscopic one, since we realized that comparing R/S vs R/L could be somehow puzzling for the reader
- added a possible TOC image
- as already mentioned, added a small supporting information file with the above elements



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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: