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► To cite this version:

Gerardo Salinas, Malinee Niamlaem, Alexander Kuhn, Serena Arnaboldi. Recent Advances in Electrochemical Transduction of Chiral Information. *Current Opinion in Colloid & Interface Science*, 2022, 61, pp.101626. 10.1016/j.cocis.2022.101626 . hal-04032126

HAL Id: hal-04032126

<https://cnrs.hal.science/hal-04032126>

Submitted on 16 Mar 2023

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Recent Advances in Electrochemical Transduction of Chiral Information

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Abstract

Chirality governs many chemical and biological processes, since most active substances are chiral. Enantiomers are mirror images of the same molecule that can exhibit significant differences in terms of biochemical activity, toxicity and transport mechanisms in the human body. Thus, developing effective methods to achieve chiral recognition is of great significance and has been a hot topic in chemo/biological studies. In recent years, electrochemical methods have received considerable attention in this field since they can offer several advantages over chromatographic or spectroscopic methods. In this review, a comprehensive and critical description of the trends in electrochemical chiral recognition over the last five years is presented. In addition, some unconventional electrochemical methods for the transduction of chirality at different length scales are described and discussed.

Keywords: chirality, electroanalysis, bipolar electrochemistry, enantioselectivity, self-propelled swimmers

1. Introduction

Chirality is a geometric property strictly correlated to the symmetry of molecules. Chiral compounds exist as pairs of enantiomers (antipodes) at a chemical level, where both exhibit identical scalar properties, but differ in their pseudoscalar ones. Thus, chiral molecules have received considerable attention in recent years due to their potential applications in medicine, chemistry, biochemistry, pharmacology, nanotechnology, nanophotonics, and catalysis. , Different analytical methods have been developed to precisely achieve enantiodiscrimination including thin-layer chromatography (TLC), high performance liquid chromatography (HPLC), capillary electrophoresis (CE) and nuclear magnetic resonance (NMR). , , However, these methods require rather long sample pretreatment times, expensive instrumentation and complex manipulation. Electrochemical methods can be an interesting alternative for the transduction of chiral information, due to their low cost, simplicity, fast response, and high sensitivity. , , , , The rational design of selective electrochemical interfaces is crucial for the efficient separation and quantification of chiral probes. The present review aims to discuss the recent advances concerning different electrochemical approaches developed for the transduction of chiral information. In particular, we focus this contribution on the description of highly enantioselective electrode interfaces and their application in conventional and unconventional electrochemical systems.

2. Conventional electrochemical approaches

Conventional electrochemistry is based on a three- or two-electrode configuration, connected to a power source, where the applied potential can be fine-tuned. Theoretically the obtained potentiodynamic signals are related to the diastereomeric interactions between the enantioselective interface and the chiral probe. Such processes allow the recognition in terms of kinetic or thermodynamic differences between the antipodes. Among the various examples of enantioselective interfaces, electrodes modified with cyclodextrins, metallic-organic frameworks, molecularly imprinted electrodes, and inherently chiral oligomers, stand out due to their highly efficient enantioselectivity. In this section we discuss in detail the most recent advances involving the use of such chiral electrochemical transducers. It is important to emphasize that enantiorecognition can also be carried out with other alternative systems, such as electrodes modified with carbon nanotubes, gold spheres or nanodendrites, organic composite materials, conducting polymers, or magneto-electrodeposited metal structures. For a more detailed description of such systems, the reader might consult the original articles.

2.1 Cyclodextrins modified electrodes

Cyclodextrins (CDs) are oligosaccharides mainly composed of six, seven or eight glucose units, called α -, β - and γ -CDs, respectively. Each unit contains five chiral carbons leading to a good host-guest interaction between the CD and the chiral probe.¹² In the majority of the examples the enantiorecognition is based on a difference of current amplitude, which limits the use of such modified electrodes for the possible analysis of enantiomeric mixtures. For example, the enantioselective discrimination of Tyrosine (Tyr) by using macroporous carbon electrodes modified with sulfato- β -CD was reported. In this work a relative low difference of current amplitude (1.12 μ A) between the antipodes was obtained (Figure 1a). Recently, enantiorecognition in terms of thermodynamic changes in oxidation potentials has been achieved, either by enhancing the conductivity of the support material or by increasing the number of chiral active sites on the surface of the electrode. In this context, graphene- β -cyclodextrin-nanocomposite (G- β -CD-CPE) has been used for the analysis of moxifloxacin hydrochloride (MOX) enantiomers, leading to a peak-to-peak separation for the different enantiomers of 120 mV. Upadhyay et al., observed a similar effect by using carbon paste electrodes modified with graphene-platinum nanoparticle- β -cyclodextrin (GNS-PNP- β -CD-CPE) for the enantiodiscrimination of R- and S-clopidogrel (R- and S-CLP). Although, cyclodextrin modified electrodes are widely used for chiral electroanalysis, these systems continue to exhibit relatively small kinetic or thermodynamic differences with respect to the presence of the two antipodes of a chiral molecule.

2.2 Modified electrodes with metal-organic frameworks

Metal-organic frameworks (MOFs) are a relatively new class of porous materials with a 3D structure mainly composed of metal ions and organic ligands. These systems have gained considerable attention due to their large surface area, strong host-guest interactions and highly ordered internal structure.¹³ Such remarkable physicochemical properties, allow to obtain well-defined electrochemical signals, with outstanding enantiorecognition in terms of kinetic changes. For example Niu et al., reported the combination of Ketjen Black (KB) and zeolitic imidazolate frameworks (ZIF) with chiral MOFs for the selective recognition of L-, D-Tyr enantiomers, with differences in current intensity of one order of magnitude (Figure 1b). Furthermore, a considerable effort has been made to achieve enantioselectivity based on thermodynamic changes in oxidation potentials. For example, Liu et al., used chiral carbon quantum dots (chiral C-dots) inserted into a MOF structure grown on a Cu foil (C-dots@MOF/CuF), in order to increase the number of enantioselective sites, for the discrimination of D-, L-Penicillamine (D-, L-PA). In this work the MOF works as a compatible porous support, whereas the chiral C-dots improve the electron transfer

during the oxidation of PA enantiomers. With a similar philosophy, urchin-like chiral MOF/reduced graphene oxide (urchin-CMOF/rGO) nanocomposites and MOF-based helical nanomaterials (h-HDGA@ZIF-67), were used for the efficient enantiodiscrimination of D-, L- Tryptophan (Try) and D-, L-PA enantiomers, respectively.

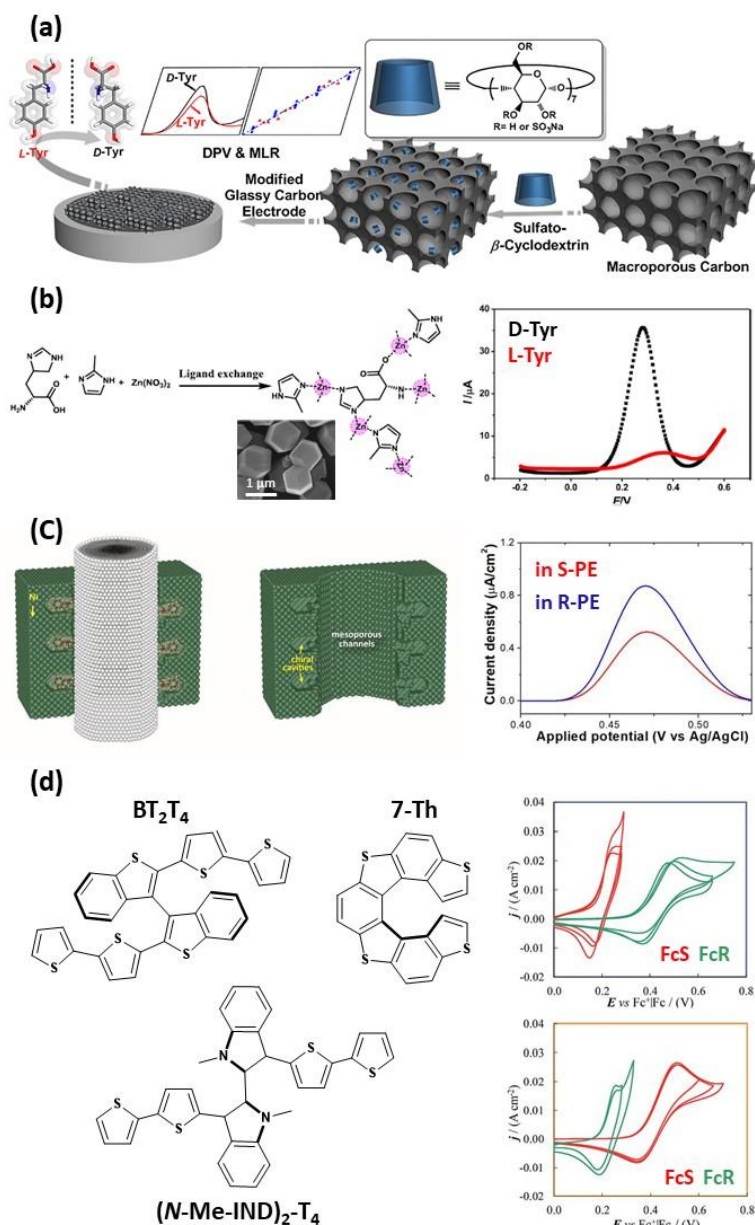


Figure 1. (a) Schematic illustration of the design of macroporous carbon electrodes modified with sulfato-β-CD with a representation of the obtained electrochemical response. Adapted from reference 33. (b) Representation of the associated reactions involved in the synthesis of KB/D-His-ZIF-8 (left) and the voltamperometric response for the enantirecognition of D- and L-Tyr (right). Adapted from reference 37. (c) Schematic illustration of Ni deposition and the obtained chiral imprinted mesoporous Ni after the dissolution of the corresponding templates (left) and voltamperometric response for the enantirecognition of R- and S-PE enantiomers (right). Adapted from reference 47. (d) Chemical structures of different inherently chiral oligomers (left) and the potentiodynamic responses of enantiopure (P)- and (M)-7-TH (top and bottom, respectively) for the recognition of S- and R-Fc (right). Adapted from references 51,52,53,54.

2.3 Molecular imprinted electrodes

Molecular imprinted materials, especially those based on polymeric matrices, have been extensively used for different applications ranging from pharmaceuticals to catalysis. However, metals can also be employed for imprinting. This concept is complementary with respect to various other approaches that have been developed for the synthesis of metal structures endowed with chiral features such as binding or grafting of chiral ligands, adsorption of chiral molecules or distortion of the symmetric metal structures. , Imprinting of metals with chiral molecules as templates has been demonstrated to be a straightforward strategy to encode metallic structures with chiral information. , Furthermore, the design of chiral imprinted metals in combination with mesoporous features improves the kinetic response of the electrode due to a considerable increase in electroactive area. , Recently a chiral imprinted mesoporous nickel (Ni) film was obtained by electrodeposition of Ni acetate in the presence of a lyotropic liquid crystal phase, Brij C10 as a non-ionic surfactant. Such electrodes were used for the enantioselective electrooxidation of phenylethanol enantiomers (R- and S-PE) (Figure 1c). Furthermore, these electrodes were successfully employed also for the enantioselective electroreduction of acetophenone as a prochiral starting compound. High enantioselectivity, up to 80% ee, was obtained for the electrocatalytic reduction of acetophenone. This is due to the high internal surface area of the imprinted mesoporous Ni electrode and an easy diffusion of fresh prochiral precursor into the mesoporous structure. Although monometallic matrices show enantioselectivity, they suffer from rather low stability. An interesting approach to overcome such problems is the design of chiral imprinted mesoporous alloys. For example, Butcha et al., synthesized Pt-Ir alloy nanostructures by co-electrodeposition from H_2PtCl_6 and H_2IrCl_6 mixtures in the presence of a chiral compound as asymmetric template and a lyotropic liquid crystal as mesoporegen. Such alloys exhibit high performance during the asymmetric electrosynthesis of phenylethanol (PE) with close to 100 % ee for first electrosynthetic cycle and up to 90 % ee after several cycles. The presence of Ir increases the hardness of the bulk structure, avoiding surface reconstruction at the atomic level and improving the tolerance to drastic electrochemical conditions. Recently such outstanding chiral imprinted mesoporous alloys were supported on high surface area Ni foam. This modified matrix showed high performance during the asymmetric electrosynthesis, achieving an enantiomeric excess up to 85%. Finally, the chiral electrocatalytic performance of such materials can be enhanced by the presence of a self-assembled monolayer at the outer electrode surface. Chiral imprinted mesoporous Pt electrodes were modified via the self-assembly of thiol ligands or by microcontact printing. An improvement of enantiomeric excess up to 90% was obtained by suppressing undesired side reactions at the outermost surface of the electrode.

2.4 Electrodes modified with inherently chiral oligomers

Inherently chiral oligomers are very powerful ingredient for electrochemical recognition of chiral probes. In such materials, discrimination of the antipodes is caused by the different diastereomeric interactions between the chiral surface and the molecular target in solution, which leads to thermodynamic differences in oxidation potential.¹⁷ In recent years, different types of inherently chiral oligomers have been reported including 2-[5-(2,5'-bithienyl)]thianaphthene (BT2T4), , 3,3'-bis(2,2'-bithiophen-5-yl)-1,1'-dimethyl-1H,1'H-2,2'-biindole ((N-Me-Ind)2T4) and tetrathiahelicene-based oligomers (Figure 1d). The majority of these oligomeric structures present outstanding enantiodiscrimination features with respect to different chiral probes. For example, tetrathiahelicene-based inherently chiral films (7-TH) showed remarkable performance for the enantioselective recognition of (S)-(-)- and (R)-(+)-N,N-dimethyl-1-ferrocenylethylamine (S- and R-Fc) (Figure 1d), methyl L- and D-DOPA and L- and D-Tyr. Malacrida et al. recently reported three new inherently chiral N,N'-dipropyl-3,3'-diheteroaryl-2,2'-biindole monomers (Ind2T4, Ind2T6 and

Ind2Ph2T4) for the enantioselective recognition of R- and S-Fc enantiomers. Finally, these materials have shown spin-related effects in the presence of a constant magnetic field. In this work (R)- and (S)-BT2T4 films act as a spin injector that shifts the potential of oxidation of reversible iron couples by around 500 mV as a function of the orientation of the magnetic field. A similar phenomenon was observed when using tetrathiahelicene-based inherently chiral films in the presence of an external magnetic field. Such outstanding spin-related redox potential modulation provides strong evidence for the spin selectivity of the inherently chiral oligomeric films.

3. Wireless electrochemical approaches

Bipolar electrochemistry (BE) is an interesting alternative to produce, in a wireless manner, an asymmetric polarization of conducting objects. , , , A polarization potential difference (ΔV) is generated at the extremities of the object, due to the presence of an external electric field (ϵ). When ΔV exceeds the thermodynamic threshold potential (ΔV_{min}), redox reactions are triggered at both extremities of the device, which under this condition behaves as a bipolar electrode (BPE). This concept, although known for quite some time, has regained momentum during the last decade due to its numerous and unconventional applications, ranging from electroanalysis and materials science to the generation of motion. Furthermore, in recent years, this approach has gained considerable attention due to the possibility to transduce chiral information via different optical readout schemes, such as actuation and light emission. This can have tremendous advantages and we summarize recent findings in the following.

3.1 Wireless electromechanical and optical readouts

The first efforts to use BE, involved the transduction of chiral information across different length scales, from the molecular to the macroscopic level. The idea is based on the electromechanical deformation of polypyrrole (Ppy), due to an asymmetric uptake or release of ions, coupled with the enantioselective oxidation of chiral molecules in solution.⁵⁹ For example, Assavapanumat et al. reported the first wireless enantioselective actuator, by using an imprinted hybrid Pt-Ppy bipolar electrode. The mechanical deformation of the Ppy strip is related to the difference in oxidation kinetics of the two enantiomers of mandelic acid on the imprinted mesoporous Pt. However, enantioselectivity based on a kinetic difference limits the use of such devices for the possible analysis of enantiomeric mixtures. An interesting alternative is the use of inherently chiral oligomers, since, as mentioned before, the discrimination of the enantiomers of chiral analytes is based on thermodynamic differences in oxidation potential. For example, a hybrid Ppy film modified with the inherently chiral oligomer (oligo-BT2T4) was used as BPE for the absolute enantiomeric discrimination of L- or D-DOPA. In this work, the induced redox reactions lead to well-pronounced wireless actuation only in the presence of DOPA with the appropriate chirality. Furthermore, the enantiomeric excess of unbalanced mixtures of chiral antipodes can be determined by using simultaneously both hybrid Ppy films, modified respectively with the (S)- and (R)-oligo-BT2T4, as BPEs (Figure 2a). In this work a correlation between the degree of actuation and the concentration of the corresponding analyte in solution was obtained (Figure 2b). Recently, the propagation of structural chiral information along different scales has also been achieved. In this case a freestanding lamellar BPE, composed of Ppy and both (S)- and (R)-oligo-BT2T4, was exposed to either L- or D-DOPA in solution. The presence of an external electric field induces an electrochemical deformation of the objects, which produces the corresponding macroscopic enantiomorphs, thus transducing the chiral information from the molecular scale to a macroscopy event. Finally, the synergy between the enantioselective oxidation of a chiral probe and the emission of light produced by a light emitting diode (LED) has been reported. A static hybrid bipolar electrode was designed by connecting a strip of the corresponding oligo-BT2T4-Ppy film and a non-modified Ppy strip to the anode and the

cathode of a miniaturized red LED, respectively. The enantio-recognition of such an oligo-BT2T4-LED-Ppy bipolar device is based on the coupling of the selective oxidation of a chiral probe on the surface of an inherently chiral oligomer and the reduction of an oxidized Ppy strip that generates a selective electron flow. Thus the wireless induced electrochemical reactions trigger the switching-on of the devices only when the correct chiral probe is present in solution. By extending this approach, it is possible to evaluate the enantiomeric excess of unbalanced mixtures of enantiomers by using simultaneously two hybrid light emitting devices modified respectively with the (S)- and (R)-oligo-BT2T4 oligomer (Figure 2c). Such a double light emitting device was used to simultaneously measure the ratio between L- and D-Try, both present in solution (Figure 2d). Following this concept, the double light-emitting bipolar device was used as analytical tool for the quantitative analysis of ascorbic acid in a commercial juice sample. In this work, the measured concentration of L-ascorbic acid correlates well with the value reported on the sample specifications.

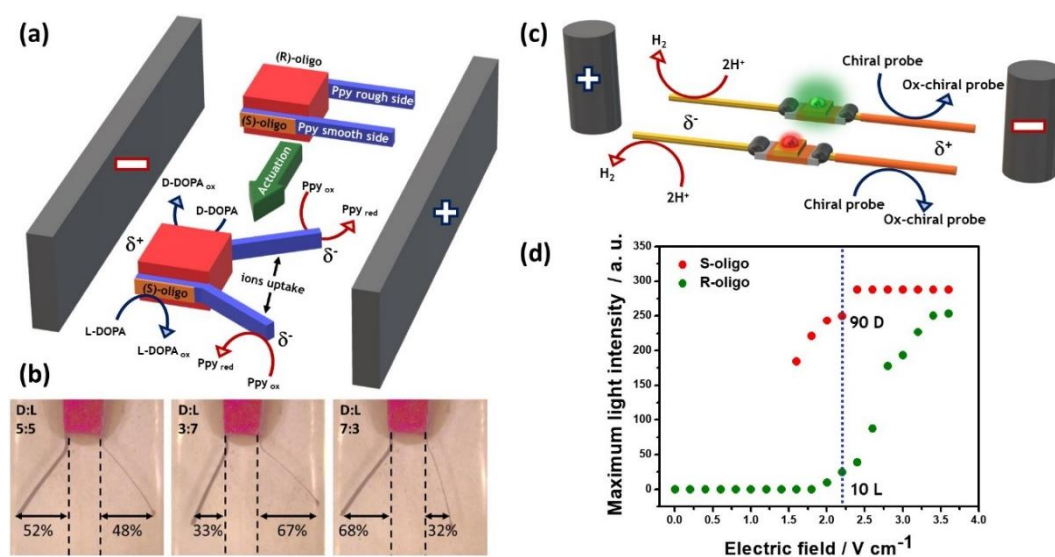


Figure 2. (a) Schematic illustration of the bipolar electrochemical setup used for wireless enantiomeric excess quantification before and after applying the electric field, with a representation of the associated chemical reactions. (b) Bipolar electrochemical experiments for the enantiomeric excess determination of solutions with different molar ratios between D- and L-DOPA probes (indicated in the figure). Adapted from reference 64. (c) Schematic illustration of the bipolar set-up used for the wireless quantification of chiral probes based on the double light emission with a representation of the associated chemical reactions. (d) Maximum light intensity as a function of the applied electric field for a red and green light emitting system in solution containing a 90:10 ratio of D:L Tryptophan. The orange part stands for the oligo-BT2T4 oligomer, whereas blue symbolizes the Ppy film. Adapted from reference 67.

4. Dynamic enantioselective systems

Self-propelled swimmers are devices that can transform different kinds of energy into motion. , , These systems have gained considerable attention due to their interesting applications in the frame of chemical analysis, cargo delivery, environmental remediation and to mimic collective behavior. , , , In particular, their mobility in the 2D and 3D space, in synergy with specific functionalities, allow the use of these devices to perform “chemistry-on-the-fly” experiments. , , This concept is based on the use of self-propelled swimmers as mobile binding surfaces and reaction platforms or as reagent dispersion systems. Furthermore, the associated physico-chemical interactions allow the transduction of chemical information into variations of speed or trajectories. In recent years, self-propelled swimmers for “chemistry-on-the-fly” have been introduced for the possible analysis and

recognition of chiral information in solution. In this section, we summarize the recent findings in this context and discuss some examples of self-propelled swimmers used for the transduction of chiral information in solution.

4.1 Dynamic enantioselective systems

The first example of a self-propelled swimmer designed for “on-the-fly” bio-detection of D- and L-amino acids, takes advantage of the dispersion of the enzymes D- or L-amino acid oxidase. Self-propulsion of these devices is based on the Marangoni effect, where the asymmetric release of surfactant induces fluid convection, whereas the enantiorecognition is carried out by the corresponding enzymatic reaction. In another example, Muñoz et al. designed a self-propelled Ni@Pt micro-rocket, functionalized with fluorescent CdS quantum dots carrying a chiral host biomolecule, β -cyclodextrin (β -CD). In this device the enantiorecognition is carried out by the β -CD moieties, thanks to their capability to form stable host-guest complexes with a wide range of small enantiomers. Thus, such micro-rockets work as enantioselective supramolecular cargo platforms in aqueous solution. In addition, motion is produced either by a bubble propulsion mechanism, due to the electrocatalytic decomposition of H_2O_2 , or by the presence of an external magnetic field. However, for the previously mentioned cases, an ex-situ transduction mechanism (optical or electrochemical) is required in order to perform a quantitative analysis of chiral information in solution. Direct in-situ dynamic enantiorecognition of chiral information in solution has also been achieved by taking advantage of the synergy between the selective oxidation of a chiral probe on the surface of an inherent chiral oligomer and the spontaneous enzymatic reduction of oxygen driven by bilirubin oxidase (BOD) (Figure 3a). These coupled reactions produce a proton-flux, from the anode to the cathode of the devices, generating a corresponding motion in the opposite direction. Furthermore, due to the presence of both enantiopure oligothiophenes on the anodic extremity of the swimmer, a site-specific proton flux is formed, producing enantioselective clockwise or anticlockwise motion as a function of the enantiomer present in solution (Figure 3b). In addition, such enantioselective trajectories allow using the curvatures, produced during the motion, as an optical readout of the degree of enantiomeric excess in solution. Finally, the concept of “chemistry-on-the-fly” bubble-propelled Janus swimmers could be extended to enantioselective synthesis. These devices are based on the synergy between the spontaneous oxidation of Zn and the enantiospecific reduction of prochiral molecules on the surface of inherently chiral oligothiophenes (Figure 3c). The asymmetric reduction, mediated by the inherently chiral material, allows the selective formation of only one enantiomer. In addition, motion is induced via a bubble propulsion mechanism, triggered by the spontaneous reduction of protons on the swimmer surface. In this work, an ensemble of self-propelled Zn/Oligo-BT2T4 microswimmers, moving autonomously in solution, have been shown to transform the prochiral starting compound, acetophenone, into the specific R- or S-PE with an enantiomeric excess close to 100 % (Figure 3d).

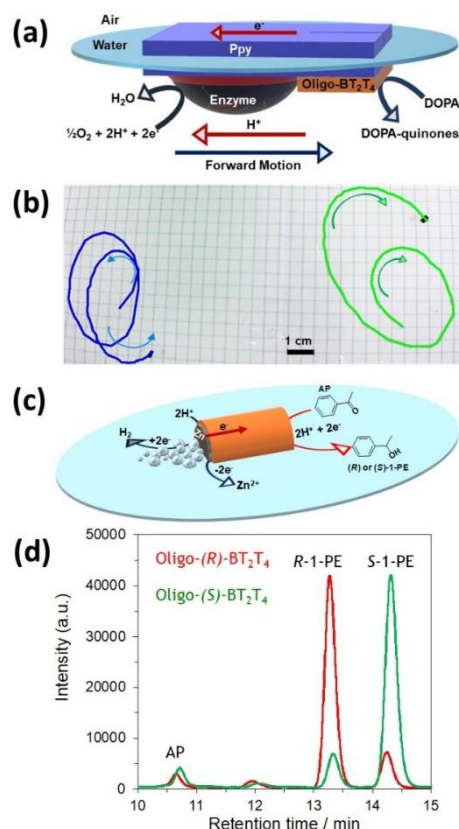


Figure 3. (a) Schematic illustration of an enantioselective hybrid swimmer in an upside-down configuration at the air/water interface together with a representation of the mechanism of selective motion induced by proton flux. (b) Macroscopic enantiospecific motion of two swimmers with opposite configuration, placed simultaneously at the air/water interface of a solution containing 5 mM of L-DOPA. Adapted from reference 81. (c) Schematic illustration of an autonomous chiral swimmer, placed at the air/water interface, together with the redox reactions involved in the enantiospecific conversion. (d) Chromatograms recorded with the product mixtures obtained from the asymmetric synthesis carried out by microswimmers functionalized with the oligo-(R)- (red line) and oligo-(S)-BT2T4 (green line). Adapted from reference 82.

5. Conclusions and perspectives

As discussed in this review, conventional and unconventional electrochemical approaches prove to be a powerful tool for the transduction of chiral information in solution. The versatility of the electrochemical approaches has been illustrated with recent literature examples, ranging from systems leading to classic thermodynamic or kinetic responses, to concepts based on wireless actuation and/or light emission, and eventually also ex-situ and in-situ dynamic readouts. In addition, all approaches show the characteristic advantages of electrochemical methods, such as low cost, simplicity, fast response, and high sensitivity. The synergy between the chiral materials, deposited on the electrode surface, and the different physico-chemical readouts, open up new opportunities in the field of chiral electroanalysis in order to improve the sensitivity and selectivity. Nonetheless there are still many challenges on this field, involving for example the biocompatibility of these systems, their straightforward visualization at the micro- and nano scale, their biodegradability, and the life-time of the functional electrode interfaces.

6. Acknowledgements

The work has been funded by the European Research Council (ERC) under the European Union's Horizon 2020 research and innovation program (grant agreement n° 741251, ERC Advanced grant ELECTRA) and under the HORIZON-ERC-2021 work program (grant agreement no 101040798, ERC Starting grant CHEIR).

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•Paper of special interest.

••Paper of outstanding interest.

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Graphical abstract