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Asymmetric Reactions Induced by Electron Spin Polarization

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Abstract

Essential aspects of the chiral induced spin selectivity (CISS) effect and their implications for spin-controlled chemistry and asymmetric electrochemical reactions are described. The generation of oxygen through electrolysis is discussed as an example in which chirality-based spin-filtering and spin selection rules can be used to improve the reaction's efficiency and selectivity. Next the discussion shifts to illustrate how the spin selectivity of chiral molecules (CISS properties) allow one to use the electron spin as a chiral bias for inducing asymmetric reactions and promoting enantiospecific processes. Two enantioselective electrochemical reactions that have used polarized electron spins as a chiral reagent are described; enantioselective electroreduction to resolve an enantiomer from a racemic mixture and an oxidative electropolymerization to generate a chiral polymer from achiral monomers. A complementary approach that has used spin-polarized, but otherwise achiral, molecular films to enantiospecifically associate with one enantiomer from a racemic mixture is also discussed. Each of these reaction types use magnetized films to generate the spin polarized electrons and the enantiospecificity can be selected by choice of the magnetization direction, North pole versus South pole. Possible paths for future research in this area and its compatibility with existing methods based on chiral electrodes are discussed.

Introduction

Since Pasteur's early discoveries on chirality,[1] many of Nature's biomolecules have been found to be homochiral; for example, sugars exhibit dextrorotatory chirality and peptides levorotatory chirality. The adverse effects of diastereomers (and enantiomers) on human physiology have led to significant research in the synthesis of enantiopure products and the resolution of racemates into their enantiopure constituents.[2] Other than their unusual response to polarized light (optical activity), chemists do not commonly relate any special electronic properties to chiral molecules. For example, enantio-recognition is usually associated with the spatial structure of binding sites ('lock-and-key' mechanism),[3,4] and the chiral bias in asymmetric syntheses are explained through steric effects and the spatial orbital interactions of the reacting moieties.[5-8] Over the past two decades however, we and others have discovered that chiral molecules display significantly different interactions with an electron depending on the electron's spin direction and the molecule's handedness.[9] Here we introduce this phenomenon and discuss its implications for chemical reactivity; in particular, spin chemistry and asymmetric reactions.

The spin-dependent scattering of electrons from molecules was first studied in the latter part of the twentieth century. In the 1980's and 1990's, a number of theoretical and experimental physics groups began studying the scattering of spin-polarized electrons from randomly oriented chiral molecules in the gas phase.[10-15] These works found that the observed polarization (or dichroism) in the electron-chiral molecule scattering was very small; quantitatively the spin polarization P is defined as

$$P = \frac{I_+ - I_-}{I_+ + I_-}$$

where I_+ is the transmitted intensity of forward polarized (spin parallel to electron velocity) electrons and I_- is the transmitted intensity of backward polarized (spin antiparallel to electron velocity) electrons. For chiral organic molecules, P was found to be $< 10^{-4}$, but chiral organometallic complexes could have a polarization P as high as 10^{-3}. In 1999, Ray *et al.* examined the transmission of spin-polarized electrons through organized monolayer films of chiral molecules adsorbed on a metal surface and found P values of 0.1 – a thousand times higher than that found in the gas phase.[16] By removing the rotational averaging, which occurs in the gas phase experiment, and orienting the molecules in an ordered assembly (for example a 2D adsorbed ultrathin film of molecules adsorbed on a flat surface), they were able to reveal a strong spin-dependence of the electron scattering from chiral organic molecules.

In the years that followed, more experiments confirmed these initial observations,[17,18] and the phenomenon has become known as the Chiral Induced Spin Selectivity (CISS) effect.[19] In 2011, an important work reported the transmission of nonpolarized electrons through self-assembled monolayer films of double stranded DNA oligomers on Au(111) and showed that the electrons become spin-polarized, up to a ratio of 4-to-1 depending on the length of the oligomers.[20] A related work on oligopeptides used three different techniques (photoemission, electrochemical rates, and molecular conductance) to probe the spin-dependent filtering of electrons and reported similar spin polarization, *P,* for the solution phase and *in vacuo* measurements.[21] The CISS effect was observed in DNA in various studies[22,23] as well as in proteins.[24] These and other studies have revealed that chiral molecules, especially those with axial chirality, act as electron spin filters. The preference of one spin direction over the other (parallel or antiparallel to the electron velocity) changes with the handedness of the molecule, i.e., its enantiomeric form.

To date, CISS has been reported to manifest in a wide range of chiral molecules and materials and is being used in novel molecular spintronic devices. It has been reported for a single oligopeptide molecule, using the STM break-junction technique,[25] as well as for two-dimensional helical perovskite films.[26] In supramolecular stacks of chiral porphyrins, spin polarizations as large as 85%, a ratio of about 1:12 between the two spins, has been reported at room temperature.[27] Another exciting result is the demonstration of a molecular device concept in which a light-induced molecular configuration change was used to switch electron spin polarizations, realizing a light-triggered, molecular spin valve.[28] Very recently, a large CISS effect was reported also for chiral inorganic crystals.[29] While photoemission, electrochemical, and electrical measurements have been most often used in these studies, the CISS effect has been probed also using time-resolved spectroscopy,[30] electron paramagnetic resonance spectroscopy,[31] and the effect was used to explain cross-polarization studies in NMR.[32] Numerous reviews on CISS which discuss these various experiments and theoretical models are available.[9,33,34]

These findings raise an interesting question for the chemist. Is CISS an esoteric curiosity, or is CISS an important property of chiral molecules that affects their function and their reactivity? Spin selectivity in chemical reactions and molecular transformations, is mostly considered to be restricted to unimolecular processes in which the total spin of the system results from the correlation of two electron spin states. For example, is the molecule in a singlet or triplet state.[35,36] The reason why a single unpaired electron located on a molecule cannot be utilized for a spin selective process between two such molecules, is that the spin is typically weakly or not at all coupled to the molecule's principal axis.[37] Hence, the relative spin orientation of the two unpaired electrons is not defined unless one applies a large enough external magnetic field. The situation is different when one considers chiral molecules and the CISS effect. In this case the spin is defined relative to the molecular frame so that the relative spins directions and the collision geometry of two reacting molecules are coupled. In this perspective we describe several possible paths for spin-controlled chemistry in which the CISS effect may play an important role.

Chirality and Spin Selection Rules

In the process of artificial water splitting, oxygen, which has a triplet ground state, is formed, making this important process an interesting candidate to probe the possible role of CISS in spin chemistry. Overall, the water electrolysis reaction involves six electrons and produces two hydrogen molecules for each oxygen molecule and the reaction efficiency is often limited by the high overpotential and side-reactions associated with the anodic oxygen evolution reaction (OER). Given that the ground electronic state of oxygen is a triplet and that of water (as well as hydroxide ions) are singlets, spin constraints on the reaction are expected. In fact, the overall reaction would even seem to be spin-forbidden, an issue that was discussed theoretically.[38,39] Surprisingly, most of the work on the OER reaction has neglected spin considerations. CISS based strategies might prove useful for improving the efficiency of the OER by better controlling the spin states of reactive intermediates.

Using chiral molecules on the surface of an OER anode, it is possible to spin-filter the electrons that are injected from the OH^- and thus to generate spin polarized radical intermediates on the electrode surface. Because the unpaired electron of the OH (as well as O and OOH) radicals, which are formed on the surface, are preferentially aligned parallel to each other, their association reaction can proceed along a triplet potential energy surface, making the formation of a triplet oxygen spin-allowed. This strategy has been demonstrated through a series of works, including coating the anode with self-assembled monolayers of chiral molecules,[40] chiral supramolecular structures,[41] chiral molecules coated nanoparticles,[42] and chiral polymers.[43] It is worth noting that a comparison of the current-voltage curves for electrolysis with the chiral molecule spin-filters are not dramatically better than those found for the achiral molecular analogues (typically a factor of 2 or less), but the reaction selectivity can be improved from 10 to 100 times. The achiral electrode materials produce large amounts of hydrogen peroxide (a singlet product) at more neutral pHs.

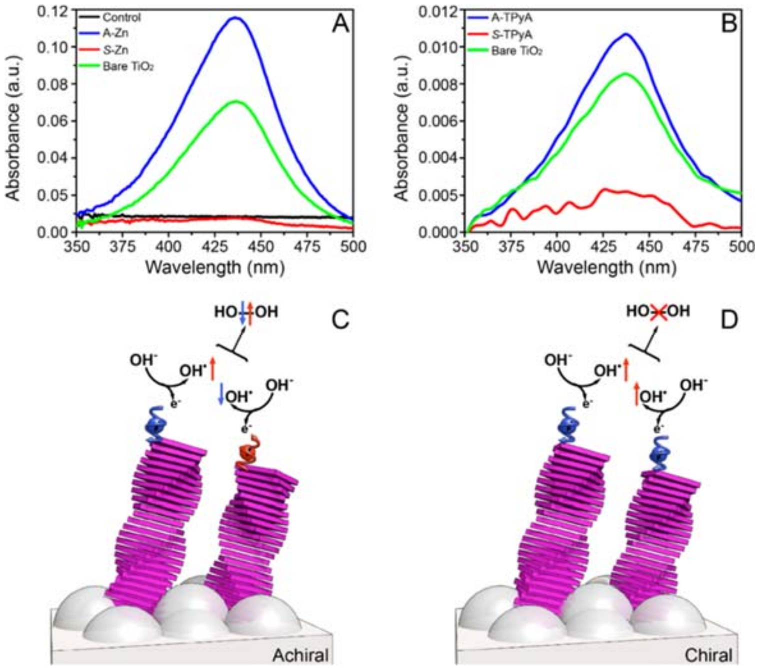

Figure 1: Control of the hydrogen peroxide production. UV−vis absorption spectra from the titration of the electrolysis solution (Na_2SO_4 base electrolyte, pH=6.56) with o-tolidine, bare TiO_2 and TiO_2 electrodes coated with (A) self-assembled Zn-porphyrins of either achiral or chiral molecules and (B) TPyA molecules. The control curve (black line panel A) refers to the titration of unused Na_2SO_4 with o-tolidine. (C) If the electron transfer to the anode is not spin specific, then the spins of the unpaired electrons on the two OH• are equally likely to be aligned antiparallel as parallel, which increases the probability for two OH• to recombine on a singlet surface and produce hydrogen peroxide (H_2O_2). (D) When the electron transfer to the anode is spin specific, the unpaired spins of the OH• are more likely aligned parallel and their recombination should proceed on a triplet surface, which forbids the formation of H_2O_2 and facilitates the production of triplet O_2. Reprinted from ref. 41 with permission from John Wiley and Sons.

Figure 1 shows data from a recent experiment that measured the hydrogen peroxide yield generated in water electrolysis for chiral porphyrin assemblies as compared to those for achiral porphyrin. Because the hydrogen peroxide's ground state is a singlet, its yield is considerable on the achiral surface, which creates a largely random ('up' versus 'down') distribution of spin orientations, and it is reduced on the chiral surface for which the spins are largely aligned. The studies cited above demonstrate that chiral molecules can be used to reduce the overpotential for water electrolysis and to improve significantly the selectivity, favoring O_2 generation over H_2O_2. A similar effect was observed using aggregates of triphenylamine-based dyes.[44]

While the works described demonstrate how the spin-filtering properties of CISS can be exploited in water electrolysis, their practical application requires much higher current densities than could be realized in the above experiments and will likely require robust inorganic electrocatalytic anodes. Ghosh et al[45] reported how to prepare chiral CuO films that were shown to act as spin filters and demonstrated their use for water electrolysis. Similar to the work with organic molecule coatings, the chiral CuO films showed improvements in the overpotential and in the selectivity for O_2 versus H_2O_2. These films show 10 to 100 times improvement in current density over the earlier chiral molecule coated anodes. The importance of spin control on the efficiency of practical devices was reported recently by Garcés-Pineda et al.[46] That work used magnetic anodes, with current densities of tens to hundreds of mA/cm^2 in the electrolysis, and analyzed the spin dependence by comparing magnetized electrodes to demagnetized electrodes. Magnetization of the ferromagnetic anode converts it into a spin filter for the injected electrons by splitting the spin sub-bands of the material's conduction electrons; thus, creating a preference for accepting one spin alignment over the other. Their findings show a significant increase in current density for magnetized versus demagnetized anodes, about a factor of two. Even though the current densities are very different in these experiments, similar relative improvements in the efficiency seem to be realized, suggesting that the benefit of spin polarizing the intermediates arises from changes in the reaction pathways that they follow. While more work is required to make the spin control process commercially viable, the ability to make chiral metal-oxides, and magnetic chiral metal-oxides, offers promise for making chiral electrocatalysts technologically relevant for the oxygen evolution reaction.

These different studies on water electrolysis, more specifically the anodic OER, make clear that chiral molecules (and chiral materials) are useful for guiding the spin pathways in chemical reactions. The experiments with chiral anodes and magnetized anodes above demonstrate that spin control significantly benefits the current efficiency (factor of two) and dramatically improves the selectivity (suppressing H_2O_2 production). While the selectivity is less severe a problem at high pH, because the H_2O_2 degrades quickly to generate O_2, it can severely affect the reaction outcome at more moderate pH to neutral pH. The experiments with magnetized electrodes underscore the importance that ferromagnetic surfaces might play, and therefore before proceeding further in discussing CISS and chemical reactions, it is useful to consider the interaction between chiral molecules and ferromagnetic surfaces.

Electric Field Induced Spin Polarization

In addition to spin-filtering via the CISS effect, recent studies show that charge polarization of a chiral molecule is accompanied by spin polarization. That is, a rearrangement of the electron distribution within a chiral molecule can generate both an electrostatic moment (transient electric dipole) and a spin moment (transient magnetic moment). Kumar *et al.* showed this phenomenon by measuring the spin polarization created in a monolayer film of chiral molecules as a function of a bias voltage applied on the monolayer.[47] Using a Hall bar device, as the working electrode in an electrochemical cell, they adsorbed a monolayer film of oligopeptides on the electrode surface and measured the magnetization that is generated as the double layer of the electrode is charged and discharged. Importantly, they showed that the sense of the magnetization, the sign of excess spin associated with each electric pole of the molecules in the layer, depends on the enantiomeric form of the chiral molecule. This effect can play an important role in collisions between chiral molecules or between chiral molecules and ferromagnetic surfaces. It is important to appreciate, that this spin polarization is a transient effect; however the collision times between molecules are typically much shorter than the spin depolarization time (sub-nanoseconds versus microseconds)[48,49] so that the spin polarization during the collision can be defined according to the handedness of the molecule through many collisions.

Consider a chiral molecule in a singlet state; the application of an electric field on the molecule or the molecule's interaction (or collision) with other molecules, causes an electronic rearrangement (induced electron polarization), and this charge reorganization is accompanied by transient partial spin polarization (See Fig. 2A). The spin polarization is such that one excess spin density is associated with one pole of the induced electric dipole and the opposite excess spin density is associated with the opposite pole of the induced electric dipole. Which spin is associated with which electric pole depends on the handedness of the molecule,[47] and the total spin of the system is still zero. The anisotropic spin density can affect the interaction energy between chiral molecules, and it is enantiospecific.

The schematic diagram in Fig. 2A (ii) illustrates an enantiospecific mechanism for the instantaneous dipole - induced dipole force (dispersion force) acting between two, closed shell, chiral molecules. The blue shaded region indicates the electron cloud of the molecule and the helix shows the molecular chirality (either left-handed or right-handed). For homochiral molecules interacting head-to-tail, their electron clouds in the overlap region (represented by the dashed circle) have opposite spin orientations (indicated by the red circles with arrows); Fig. 2A (iii). This interaction can be viewed as having singlet character so that Pauli exclusion (electrons in the same spatial orbital must be spin paired) is satisfied. Conversely, Fig. 2A (iv) shows a heterochiral interaction between two chiral molecules. In this case, the excess spin densities for the two molecules have the opposite sense (shown in the diagram by outward and inward red arrows, respectively), so that the spin orientations are aligned (display a triplet character) as the molecules collide. Because the singlet surface is less repulsive than the triplet one, an enantiospecific interaction is created. This spin interaction is a relatively short-range effect (resulting from the exchange interaction for electrons in orbitals) and only becomes important for molecules in intimate "contact", overlapping electron clouds. This schematic example makes it clear that a difference in energy exists between homochiral versus heterochiral interactions, even without inclusion of steric effects. Moreover, in chiral structures, much of the total energy difference can result from the Pauli exclusion. Namely, the difference in energy is mostly determined by the spin-exchange energy, and it can easily exceed the available thermal energy (kT) at room temperature.

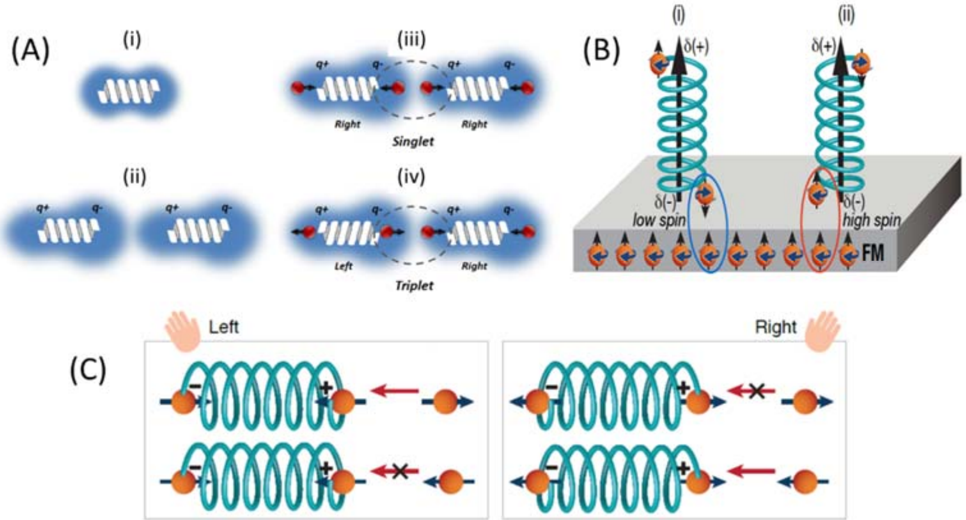

Figure 2: Schematics for the manifestations of the chiral induced spin dependent charge polarization effect in different systems. **(A)** The diagram shows the electron distribution (blue cloud) in a closed-shell, chiral molecule which does not have a dipole moment before (i) and after (ii) it interacts with another such molecule. The interaction creates an asymmetry in the electrons' charge distribution, resulting in an "induced dipole" in each molecule. (iii) This diagram illustrates the induced dipole interaction of two such molecules with the same handedness. As charge q transfers from one side of the molecule to the other, it generates a spin polarization (represented by a red ball and black arrow) of the same spin in the two molecules. Because the induced-dipoles of the two molecules are oriented head-to-tail the spin polarization at the interface of the two molecules is opposite, antiparallel, indicated by the dotted circle region. This is characterized as a singlet interaction. For two interacting molecules of opposite chirality (iv), the interaction between the molecules is characterized by two spins parallel to each other (dotted circle region) and is assigned as a triplet interaction. (Reproduced from reference 47 with permission from the National Academy of Sciences) **(B)** The scheme illustrates the process occurring when a right-handed (i) or left-handed (ii) chiral molecule approaches a ferromagnetic substrate. The spin alignment at the group pointing towards the surface and the magnetization direction of the surface determine the interaction (Reproduced from reference 50 with permission from American Association for the Advancement of Science) **(C)** This scheme illustrates the spin polarization induced enantioselective reaction mechanism. When an electron approaches a chiral molecule, charge rearrangement occurs and the molecule becomes charge polarized with the electron attracted to the positive pole of the molecule. Depending upon the molecule's handedness (i left-handed and ii right-handed) and the spin orientation of the electron, the interaction is more favored or less favored.

Interaction of Chiral Molecules with Ferromagnetic Surfaces

The CISS effect implies that chiral molecules will interact enantiospecifically with a ferromagnetic surface, and the scheme in Figure 2B illustrates a mechanism for it. As a chiral molecule approaches an electrode surface, it becomes charge-polarized and spin-polarized, which affects the nascent bond formation. If the electrode is magnetized perpendicular to the surface (along the surface normal), then it will have a spin-dependent interaction with the spin-polarized chiral molecules. That is, the excess of electron spins oriented along the surface normal will bind preferentially to chiral molecules whose spin polarization is opposite to that of the surface (singlet-like) than to the aligned case (triplet-like). As before, for fermions the exchange interaction is governed by the Pauli exclusion principle, which requires that two electrons have opposite spins in order to occupy the same spatial orbital. The phenomenon is very much like the case of the two interacting chiral molecules (Fig 2A), except now one of the chiral molecules is replaced by an electrode surface whose spin orientation is controlled by its magnetization direction; and the orbitals are forming a bond, chemisorption. From these considerations, it follows that molecules of one enantiomer have a propensity to bind more readily than the other with a magnetized (spin-polarized) ferromagnetic electrode, because their spin polarization is already favorable. Banerjee-Ghosh, *et al*[50] showed that the adsorption rate of chiral molecules onto a structurally achiral, but magnetized, substrate was enantiospecific. They showed that changing the magnetization direction of the ferromagnetic surface from Up to Down changed whether the left- or right-handed enantiomer adsorption was preferred, and that the selectivity required a direct interaction with the magnetized surface. In 2019, Tassinari *et al*[51] extended these ideas to the enantiospecific crystallization of amino acids with magnets, generating enantiopure (>80%) crystals. See recent review articles on CISS and enantio-separations.[52] It is important to appreciate that this effect is not a magnetic field effect, but rather it depends on the molecule's electron cloud overlapping with the electron density in the magnet (an exchange energy effect). The spin polarization that accompanies charge polarization and the enantiospecificity that arises from it, has important implications for chiral separations and for chemical reactions of chiral molecules.

These features of chiral molecule/ferromagnetic surface interactions were confirmed recently in three different reports. Ghosh *et al* [53] used Kelvin probe measurements to show that the electron penetration (tunneling) from a ferromagnetic electrode into adsorbed chiral molecules depends on the ferromagnet's magnetization direction, the magnetization strength, and the handedness and length of the chiral molecules. They observed contact potential differences as large as 100 mV for the two different enantiomeric forms on magnetized Co film electrodes. The interaction depends sensitively on whether the magnetization of the Co films was oriented along the surface normal, or not. In a separate study, Ziv *et al.* probed the enantiospecificity by measuring the interaction force between a chiral oligopeptide and a ferromagnetic surface using atomic force microscopy. In their study, they found a difference in the interaction energy, on the order of 100 meV (about 10 kJ/mol), for a ferromagnetic substrate magnetized in opposite directions.[54] This value is consistent with former calculations[50] and is much larger than thermal energy fluctuations at room temperature, therefore it should dominate the interaction of chiral molecules in the short range. Weiss and co-workers showed that the photoinduced ionization of chiral molecules,[55] which are adsorbed on ferromagnetic surfaces, display a binding energy shift that changes with the enantiomeric form of the molecule and the direction of magnetization. Together, these studies make a compelling case that magnetized electrodes, which are structurally achiral, can interact enantiospecifically with chiral molecules.

Common Approaches to Stereoselective Catalysis and Electrochemistry

Conventional methods for inducing enantiospecificity and enantioselectivity in chemical reactions, rely on a chiral bias, such as a chiral reactant, chiral catalyst, or a chiral solvent.[56,57] For example, chromatographic techniques for the separation of enantiomers from a racemic solution use a chiral stationary phase, in which a difference in energy between the homo and heterochiral interactions controls the residence time of each enantiomer in the column and hence its elution time.[58] Until now the same philosophy has been used for enantioselective synthesis and for enantioselective sensing of analytes in electrochemistry,[59,60] often by coating electrodes with chiral films. The chiral bias used to guide asymmetric electro-organic reactions is currently classified into three main categories: chiral electrodes, chiral medium, and chiral auxiliary effects.[61] Other methods, such as electrogenerated intermediates which are then converted using chiral catalysts or radical compounds,[62] also exist, however these methods fall outside of the scope of the electrode mediated effects discussed here.

For chiral electrodes, the electrode itself has been made intrinsically chiral by cleaving single crystals along high-index symmetry planes,[63-65] by templating a material with the use of chiral molecules during the electrode preparation,[66] or by coating an electrode's surface with chiral molecules.[59,67-69] For enantioselective reactions with racemic solutions, the origin of asymmetry is associated with the difference in binding geometries and diastereomeric interaction energy between the molecule and the substrate's chiral sites. Experiments show that it is possible to generate large redox potential shifts, 0.35 V, and that the magnitude of the effect is both molecule and substrate dependent.[61]

Chiral media, such as solvents[70,71] and electrolytes,[72] can also be used to induce asymmetry in electrochemical reactions. Recent studies by Rizzo *et al.* demonstrated large redox potential shifts of chiral ferrocene and DOPA molecules in chiral ionic liquids; the potential difference was influenced by both the chirality and mole fraction of the ionic liquid's chiral component.[73]

Auxiliary effects, in which a chiral pendant molecule is attached to the reactant to guide the product stereocenter, have also been explored for asymmetric electro-organic reactions. This strategy was first demonstrated for the electroreduction of carbonyl groups on phenylglyoxamides,[74] and it has since been extended to many other reaction types.[61]

While the use of a chiral bias successfully introduces enantioselectivity into electro-organic reactions, amplification toward higher enantiopurity is required to increase the viability of this approach. Auto-catalytic reactions[75] and enantiospecific surface explosions[76] can accomplish this feat, however they may prove to not be sufficiently robust for many applications. It is more likely that the field will rely upon cooperative effects utilizing multiple strategies simultaneously to increase product asymmetry. Below we discuss a new type of chiral bias that is provided by the spin polarized electrons from a magnetized electrode. This approach could be exploited in tandem with a more traditional chiral bias, as suggested in a recent study by Benincori *et al.* that reports large potential shifts (~0.45 V) for an achiral ferrocene at magnetized chiral electrodes.[77] Combining the spin alignment effects with the diastereomeric interaction energy differences found for chiral molecules could create a much larger enantiopurity.

Enantioselectivity on Magnetized Electrodes

An important chemical manifestation of the CISS effect is illustrated schematically by Figure 2C; a process that can be described as a spin-polarization induced enantioselective reaction. As an electron approaches a molecule, charge rearrangement occurs within the molecule to accommodate the presence of the negatively charged electron. For chiral molecules, this charge polarization generates a spin polarization that depends on the enantiomeric form of the molecule. If the electron that is approaching the chiral molecule is spin polarized, *e.g.* coming from a magnetized ferromagnetic substrate, it interacts selectively with the excess spin density on the positive pole of the chiral molecule; if the spins are aligned antiparallel it is singlet-like and if they are parallel it is triplet-like. Because the excess spin density on the chiral molecule's positive pole depends on its enantiomeric form, the interaction is again enantiospecific. This proposed mechanism implies that the electron's helicity (spin direction along the electron velocity vector) provides the 'chiral bias'.

Metzger *et al*[78] reported three examples of enantioselective reactions at magnetized electrodes: the kinetic resolution of a racemate via electroreduction, the enantioselective adsorption onto an achiral, spin-polarized host site, and the electropolymerization of chiral films from achiral monomer units.

*Kinetic-resolution by electroreduction***:** This study used an achiral, magnetized working electrode (Fig. 3) to selectivity decompose one enantiomer of camphorsulphonic acid over the other.[78] A diagram illustrating the electrochemical cell design used in these studies is shown in Figure 3A, and Figure 3B shows the overall electrochemical reaction in which a racemic solution of camphorsulfonic acid (CSA) was enantioselectively reduced to produce isoborneol. Figures 3C and 3D show cyclic voltammograms taken for pure enantiomers of CSA under different (Up (red) and Down (blue)) magnetizations. Figure 3C reveals a larger faradaic current for the S-enantiomer when the magnetization is polarized Up as compared to that when it is polarized Down. In contrast, Figure 3D shows that the faradaic current for the R-enantiomer is lower when the magnetization is Up than when it is Down. From these data, it is clear that the current, *i.e.* reaction efficiency, for each enantiomer depends on the magnetization state of the electrode. Experiments in which the substrate was coated with a 1-hexanethiol self-assembled monolayer gave similar results and imply that the enantioselectivity is associated with the helicity of the electron, rather than an enantiospecific surface-confined interaction between the molecule and the ferromagnetic electrode.

The unreacted CSA in the solution was quantified using mass spectrometry, NMR, and circular dichroism spectroscopy. The changes in the CD spectrum at 292 nm (Fig. 3F), which corresponds to a change in the *enantiomeric excess* of the solution were found to depend on the orientation of the applied external magnetization during the electroreduction. When the electrode is magnetized Up (red), the CD signal is negative; and when the electrode is magnetized Down (blue), the CD signal is positive. Fig. 3G shows the change in the intensity of the CD peak at 292 nm as a function of time, for the two different

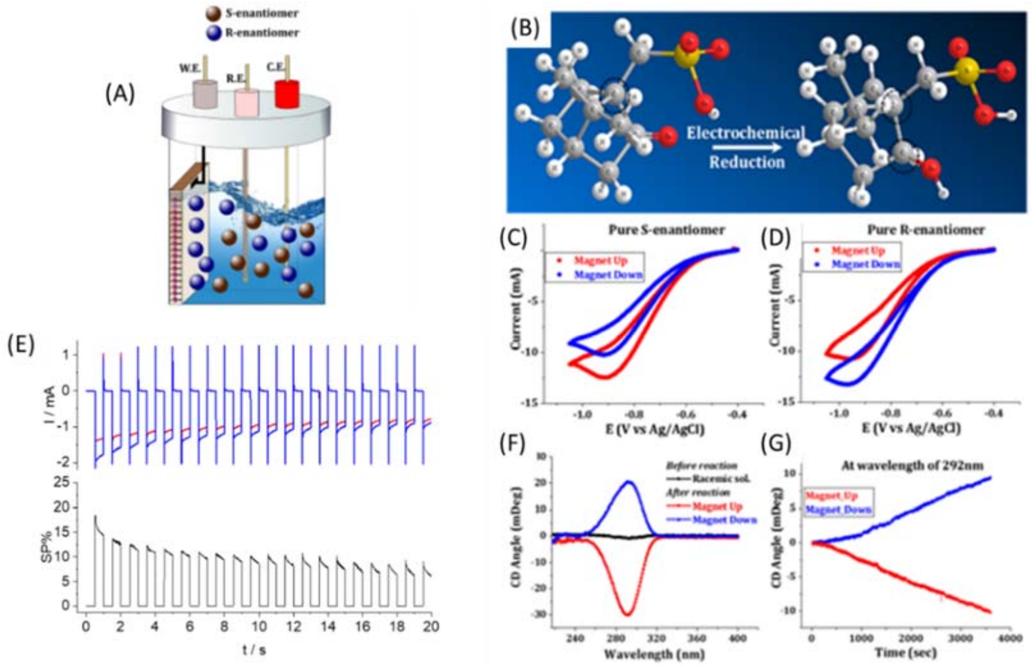

Figure 3: (A) The electrochemical reaction cell is illustrated, in which the magnetized ferromagnetic electrode has spins oriented normal to the electrode surface. The R- and S-enantiomer (blue and grey spheres) are in the solution. **(B)** The electroreduction reaction is the conversion of camphorsulfonic acid (CSA) to 10-mercaptoborneol on magnetized nickel electrodes. **(C&D)** Cyclic voltammograms are shown for (*S*)- and (*R*)- CSA with a Ni electrode magnetized in the Up (red) and Down (blue) orientation. **(E)** The measured current-time profile is shown for an S-CSA solution at -0.9 V with pulses of 0.5 s duration when the magnet is pointing up (red) or down (blue). In the bottom plot the difference in the polarization as a percentage (SP%) is plotted. **(F)** Circular dichroism (CD) spectra of the solution following electroreduction is shown for the magnetic electrode pointing Up (red) or Down (blue); the black spectrum shows the CD of the racemate mixture before the reaction. **(G)** The change in the CD peak at 292 nm as a function of reaction time for the magnet oriented Up (red) and Down (blue) is shown. (Reproduced from reference 81 with permission from John Wiley and Sons).

magnetization directions. An *enantiomeric excess* of 10-15% was achieved following 6 hours of electroreduction.

Figure 3E shows the current resulting by the application of a pulsed-potential waveform which was used for the reduction of a 20 mM S-CSA solution. In contrast to the data in the other panels, the data in panel 3E have not been previously published. The potential was stepped between -0.9 V and 0.0 V vs Ag|AgCl every 0.5 sec, with an external magnetic field oriented Up (red) or Down (blue) parallel to the electrode's surface normal. A difference in the current was observed for the two magnet orientations. For the S enantiomer, the current remains higher for the Down magnetization of the electrode (magnetization vector pointing towards the solution) than for the Up direction, but the difference in the currents decreases as the reaction proceeds. In fact, the enantioselectivity, as measured by the polarization (SP% = $\frac{I_{down}-I_{up}}{I_{down}+I_{up}}$x 100 is the spin polarization percentage) decreases with time, when I_{down} and I_{up} are the currents measured with the magnetic pole pointing Up or Down respectively. Thus, both the overall reaction yield (total current) and the enantioselectivity (SP%) decrease with time. XPS analysis of the electrode, following the reaction, indicates that the sulfonate on some of the CSAs are reduced to thiols which can bind to the electrode's surface and cause a decrease in the reaction yield and the enantioselectivity.

As shown by the data in Fig. 3E, electrode fouling and degradation of the spin selectivity over time will be an important consideration for practical applications. For the CSA system, the decrease in spin selectivity arises from the electrode being coated with thiols that reduce the spin polarization of the electrons ejected from the magnetic substrate. One expects that an important limitation on the enantioselectivity of the electrochemical process will be the extent of spin polarization of the electrons ejected from the electrode in the reduction process, or the spin polarization of the electrons injected into the electrode for an oxidation process.

Enantioselective Adsorption with Achiral Host Sites: Another approach towards asymmetric synthesis is to use a ferromagnetic substrate to control enantioselective association of chiral molecules with an achiral self-assembled monolayer film that is spin-polarized. In one example, the achiral self-assembled monolayer (SAMs of carboxyalkanethiols) were spin polarized by a magnetized ferromagnetic substrate (Ni(50 nm)/Au(10 nm)) because of the proximity effect.[79] In reference 78, the enantiospecific adsorption of 1-amino-2-propanol was used to collect an enantiomeric excess of about 20% by applying up and down magnetizations of the substrate. The same effect was observed for achiral naphthylthiol SAMs adsorbed on Au/Ni ferromagnetic substrates and exposed to solutions of 1-phenylethanol in ethanol, indicating that the enantiospecificity manifests for π-π interactions. Figure 4 presents the IR transmission spectrum and the association rate (insert) for Up and Down magnetization of the substrate. The spectrum is taken at the O-H stretching mode, 3340 cm^{-1}. The data show that the association rate depends on the magnetization direction; the Down magnetization displays significantly more association.

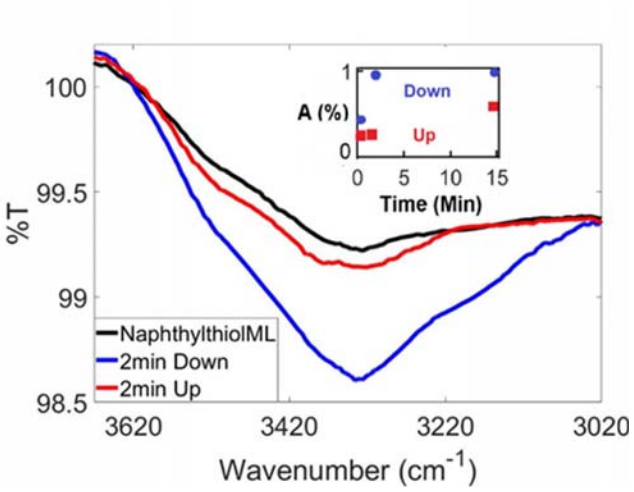

Figure 4: The π-π bonding association rate of R-1-phenylethanol to naphthylthiol monolayer, for Up and Down magnetization of the Ni/Au substrate. Using FTIR, monitoring the O-H stretching mode at 3340 cm^{-1}, the association process can be followed. After 2 minutes, for down magnetization (blue) a full layer was created, while for Up magnetization (red) small changes were measured as compared to the SAM only (black). The inset shows the rate for Up (red) and Down (blue) at different times.

Enantioselective Electropolymerization from Achiral Monomers: Asymmetric electrochemical reactions with spin polarized electrons do not require that the reactant molecules possess chirality, because the electron's helicity can evoke chirality in the reaction products. Figure 5 shows data for the growth of chiral polymers from achiral monomers. In this case, a Ni/Au ferromagnetic electrode is used to electropolymerize achiral monomers into a chiral polymer that is probed by circular dichroism spectroscopy of the polymer film. Panels A, B, and C, show absorbance spectra of electropolymerized pyrenecarboxylic acid, carbazole, and 3,4-ethylenedioxythiophene thin films respectively; and panels D, E, and F show their corresponding circular dichroism spectra. The handedness of the polymer thin film is determined by the orientation of the magnet (Up (red) or Down (blue)) that is used to magnetize the electrode. Note that the polypyrene data

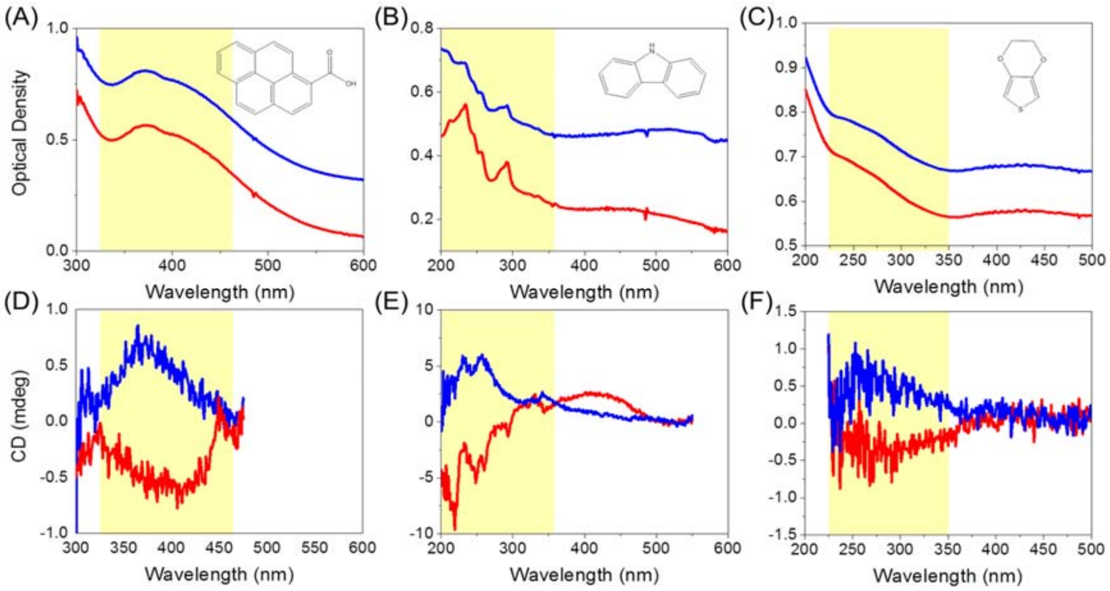

Figure 5: Absorbance (A, B, C) and circular dichroism (D, E, F) spectra of electropolymerized thin films using pyrenecarboxylic acid (left), carbazole (middle), and 3,4-ethylenedioxythiophene (right) monomers with a magnetic field applied Up (red) or Down (blue) during polymerization. The inset shows the molecular structure of the monomer and the absorbance spectra in the upper panels are offset from one another for clarity. The yellow highlighted region illustrates the electronic transitions in which chirality is present. (The data in panels A) and D) are reproduced from reference 78 with permission from John Wiley and Sons), whereas the other data are new (see text).

shown in panels A and D are taken from reference 78, and the data for polycarbazole and PEDOT are unpublished data; see the supplemental information for details on those experiments.

Although a mechanism for how chirality manifests in these electrochemical polymerization reactions has not yet been elucidated, it is possible to make a conjecture based on the CISS effect and spin-dependent charge polarization ideas. All three monomers have been reported to form a radical cation intermediate upon electro-oxidation.[80] Given that the monomers are not chiral, the polymerization at early time likely creates equal amounts of right- and left-handed dimers (and small *n*-mers) at the surface, but as the reaction proceeds the electron's helicity and the delocalization of the spin-polarized electrons from the substrate into the small *n*-mers could control the reactivity of the different enantiomers. Thus, the propagation of the polymerization reaction would depend on the orientation of the electron spin, which is controlled by the electrode's magnetic moment direction, and would favor the formation of one enantiomer over the other in a manner that depends on the electrode's magnetization. The chirality indicates regularity in the polymer's secondary structure and thus, can be viewed as an additional order parameter controlled by spin injection. The precise control over orientation can facilitate improved charge-carrier mobility which may be important in optoelectronic and electronic applications.[81]

The electropolymerization reactions have some additional constraints on the *ee* that will need to be considered. For example, the initial stage of generating the radical cation and its association with the substrate, or not, will strongly affect the efficiency and enantioselectivity of the process. While the presentation in Figure 5 is intended to show the generality of the approach, it is evident that the carbazole data display a much more significant circular dichroism signal than is found for the other two monomers. Moreover, the thickness of the film is likely to place an important constraint on the *ee* for these reactions. As the film thickness grows, the likelihood of electron scattering and spin depolarization increases; thus, one expects that the enantioselectivity will degrade as the electrons being extracted from the growing polymer randomize their spins more effectively.

These findings imply that the introduction of enantioselectivity into chemical reactions by the electron spin is general and point to the possibility of synthesizing complex chiral structures with multiple chiral centers on surfaces using several steps while controlling both the electric and magnetic fields of the surface. This can be achieved by multiple stages of association each done under different magnetic field and electric field orientations of the substrate.

Synopsis and Future Directions

The two chemical reaction classes described above, spin-selective chemistry on chiral electrodes and enantioselective (asymmetric) electro-organic reactions on magnetized electrodes, originate from the enantiospecificity that arises from the spin selective interaction of chiral molecules with electrons, the CISS effect.

Spin-selective chemistry: In nature, many redox reactions occur via multiple electron processes. In these cases, the relative spin of the electrons involved may determine the reaction paths and/or the production of by-products. The water splitting reaction, discussed above, is one example. It can be expected that by controlling the spin of the electrons one will be able to increase the efficiency of multi-electron redox reactions and define better the product. Possible candidates for such studies are for example CO_2 reduction and hydrocarbon redox processes.

Spin constraints on chemical reactions has a long history, however it is rare that those studies include chiral molecules.[82-84]The importance of the electron spin in understanding radical pair formation and recombination is well appreciated, and Wasielewski has explored the importance of spin effects in a range of different model systems.[85] In photosynthesis, which contains chiral constituents, the radical pair formation in the photosynthetic reaction (PSI) generates a non-Boltzmann spin distribution (is spin polarized).[86] What role CISS might contribute to this phenomenon is not yet certain, but experiments show that spin polarization exists in the charge transfer of PSI assemblies on electrodes.[87] Many other biochemical and enzymatic reactions necessarily involve chiral molecules but their study from the viewpoint of CISS is largely unexplored.

Asymmetric reactions: The studies of enantioselective reactions with magnetized electrodes promise a wholly new approach for asymmetric synthesis in which the chiral bias in the reaction comes from the electron spin. This feature is shown most explicitly in the electropolymerization studies, in which none of the reactants possess structural chirality, but is also evident in the other two examples given above. Importantly, these studies demonstrate how chirality can emerge from an achiral system and may offer yet another alternative explanation for the origin of homochirality and its prevalence in biological systems. More generally, these studies show that magnetized ferromagnetic substrates can be used to break the symmetry of chemical reactions and create products with an enantiomeric excess.

At this time only a few cases of spin-induced asymmetric electrochemical processes have been demonstrated. While the CISS based mechanism described in Figure 2 implies that the phenomenon should be general, much needs to be explored and much needs to be learned before the breadth and implications of this approach will become wholly clear. Even in cases where the enantioselectivity is not very high, it may prove possible to enhance the enantiomeric enrichment, by amplification methods.[88,89] The approach of using spin polarized electrons from a magnetized electrode is general and its coupling with other ways of introducing chiral bias should be possible. Thus, this approach may improve the performance of existing chiral electrodes, by using a magnetic electrode material and providing the appropriate magnetic field to raise their enantioselectivity.

What is needed to realize the fields promise? Many basic issues about what parameters affect the enantioselectivity and how to quantify them remain to be elucidated. The question is complex because it involves several entangled processes: the electrochemical reaction (including the role of the double layer and the diffusion rate), the spin selectivity of the elementary electrochemical redox steps, and the possible secondary reactions of the products produced in the initial stages of the process. For example, consider the enantioselective reactions with racemic mixtures, like that shown in Figure 3. For such reaction processes, there is a growing increase in concentration of the "unfavored enantiomer" with time, as a result of depletion of the favored enantiomer by the enantiospecific electrochemical reaction. Hence, eventually the kinetics are expected to become nonspecific, and an inherent limit will be placed on the enantiomeric excess that can be achieved. The limit depends of course on the extent of spin specificity in the fundamental electrochemical steps, but for the system considered in Figure 3 it seems that an enantiomeric excess (*ee*) exceeding 20% is not realistic. The situation is wholly different for the case in which a chiral product can be generated from an achiral one, like the case of the polymerization described above. In this case the *ee* depends mainly on the spin selectivity of the redox process.

A better understanding of the intrinsic spin selectivity of the redox process and the CISS effect will prove to be key in advancing this area. Establishing structure-function relationships for the CISS effect will provide key guidance for making progress. While theoretical models for the CISS effect have made significant progress over the past decade and make important qualitative predictions, quantitative comparisons with measured spin-filtering responses of molecules reveal a significant gap in our theoretical description/understanding.[34] Theory and experiment have both shown that the CISS response increases with the length of helical molecules (over the range of a few nm), but other connections are lacking. For example, experiment shows a correlation between a molecule's chiro-optical response and its CISS response, but the theory has not yet been developed for this. Even 'simple' questions, such as how the CISS response scales with the number of chiral centers, or the importance of axial chirality, remain to be addressed by a comparison of theory and experiment. These various issues, and more, must be studied in detail in order to understand how to optimize the *ee* for electrochemical reactions.

In addition to a deeper theoretical understanding of CISS for molecules, it will prove important to have a deeper and predictive understanding of molecule/ferromagnetic surface interactions, the 'spinterface'.[90] A term more popular in the physics and spintronics communities, the spinterface refers to the spin-dependent orbital interactions of molecules and ferromagnetic surfaces that can give rise to spin-polarized electron transport, even with achiral molecules.[91] The interaction of chiral molecules with ferromagnetic surfaces promise to reveal additional complexities arising from the rich (complex), spinterface interactions in combination with the CISS response.

Beyond a better chemical understanding of the reaction mechanism and process variables, it will be important to create stronger and more chemically robust magnetic electrodes. In addition to creating magnetic films with strong magnetization (large energy differences in the spin sublevels), the magnetic electrodes must be chemically stable in the working electrochemical cell conditions and the spin polarization has to be out-of-plane. Such considerations limit the materials that can be used, and this will be a future challenge for this nascent research field.

The elements described above, including improved control over process variables, better magnetized film electrodes, structure-function relationships for CISS, and a deeper understanding of ferromagnetic-molecule orbital interactions, will provide the foundation for developing this new area. A promising feature of the CISS-based approach is its generality and compatibility with established strategies for introducing chiral bias in electrochemical reactions. Progress on these fronts will enable the improvement of electrosynthetic methods that increase *ee* and reveal whether it will be possible to introduce multiple chiral elements into electrosynthesis in a controlled way. Even if the ability to further develop molecular complexity is limited, spin-selective electrosynthesis promises to become an important tool in the synthetic chemist's toolbox for obtaining pure enantiomers. From a wider point of view, CISS considerations may prove to be important for expanding our understanding of biochemical processes and the effects of chiral molecular compounds in chemical biology.

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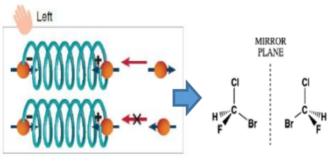

Spin polarized electrons can control asymmetric electrochemical reactions.