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# Chiral Induced Spin Selectivity and Its Implications for Biological Functions

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chirality, electron transfer, spin, enantiorecognition, chiral induced spin selectivity

## Abstract

Chirality in life has been preserved throughout evolution. It has been assumed that the main function of chirality is its contribution to structural properties. In the past two decades, however, it has been established that chiral molecules possess unique electronic properties. Electrons that pass through chiral molecules, or even charge displacements within a chiral molecule, do so in a manner that depends on the electron's spin and the molecule's enantiomeric form. This effect, referred to as chiral induced spin selectivity (CISS), has several important implications for the properties of biosystems. Among these implications, CISS facilitates long-range electron transfer, enhances bio-affinities and enantioselectivity, and enables efficient and selective multi-electron redox processes. In this article, we review the CISS effect and some of its manifestations in biological systems. We argue that chirality is preserved so persistently in biology not only because of its structural effect, but also because of its important function in spin polarizing electrons.

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## Contents

INTRODUCTION .....	100
THE CHIRAL INDUCED SPIN SELECTIVITY EFFECT .....	101
SPIN SELECTIVE CONDUCTION THROUGH DNA, OLIGOPEPTIDES, AND PROTEINS: LONG-RANGE ELECTRON TRANSFER .....	103
ENANTIORECOGNITION .....	105
MULTI-ELECTRON PROCESSES .....	107
CONCLUSIONS .....	110

## INTRODUCTION

The chemical reactivity and biological function of biopolymers, like proteins and DNA, are often rationalized in terms of their structure, i.e., by the chemical identity of their monomers and co-factors, as well as their secondary and tertiary structures (22, 59). These considerations are often combined with the consideration of the electronic charge distribution of a molecule and its chemical reactivity, which is a fundamental paradigm in modern synthetic chemistry (19, 39). While the impact of charge transfer and charge reorganization on chemical reactivity has long been appreciated, the impact of spin transfer and spin reorganization in the electron density of molecules is often ignored. In this review, we describe recent studies that examine electron spin effects on biomolecular function that result from the coupling between the structure of biopolymers and the electron transfer through them and/or electron reorganization within them. To underscore the fundamental and broad implications of these phenomena, we describe how they manifest in a number of distinct biorelated processes, including long-range electron transfer, biorecognition, chemical selectivity, and the efficiency of redox processes. As described below, spin effects are linked to the chirality of biological structures and indicate that homochiral biostructures bring important benefits to biochemical processes.

Chiral biomolecules (i.e., molecules possessing nonsuperimposable mirror images like right and left hands; 10) are essential components of all organisms. In biology, however, chiral molecules appear mainly in one of their mirror image forms (enantiomers). Other than some interesting exceptions (2), biological systems are almost perfectly homochiral. The benefits that homochirality might offer for biological organisms and biochemical processes remain an open issue (see, for example, 29). More fundamentally, one might wonder why chirality, as such, is preserved so persistently through evolution. What makes chirality so important for the existence of an organism that it is maintained despite its significant entropic (or free energy) cost? Commonly, chirality is viewed as a structural property, and enantioselectivity in biochemical reactions is believed to result from a molecule's three-dimensional structural features (23). It has been assumed that no special interaction terms or electronic properties are associated with a molecule's chirality, other than its optical activity, which is used for detecting and characterizing it.

In 1999, it was first observed that chiral molecules do have special electronic properties (52), and recent work shows how these properties can affect reactivity. This early finding has been confirmed by a large number of experiments, some of them related to the role of chiral systems in biology (43). The findings in 1999 and those that followed are attributed to the chiral induced spin selectivity (CISS) effect (45, 48). The spin of an electron refers to its intrinsic angular momentum. In a simplified and classical model, it can be viewed as the rotation of the electron's charge density about its center (like the spinning of a top) and has two directions, clockwise and anticlockwise.

Indeed, the electron's spin can be either positive or negative, often referred to as spin UP and spin DOWN, and the spin direction is associated with the magnetic moment direction of the top—in keeping with the simplified model. Unlike in the classical model, however, the electron spin is quantized and can take on only one of two values,  $+h/(4\pi)$  or  $-h/(4\pi)$ , where  $h$  is Planck's constant. Moreover, two electrons in the same region of space (or orbital) must have opposite spins, as stated by the Pauli exclusion principle, a result that is well known in chemistry and underpins our understanding of the periodic table of the elements (30).

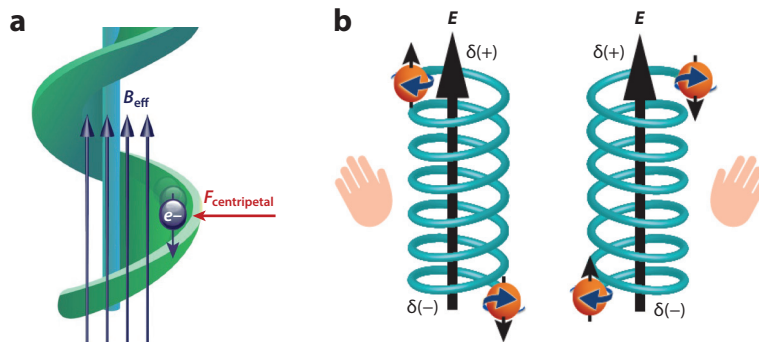
Despite the importance of spin for our understanding of the structure of matter, spins are commonly considered as affecting chemical processes only in the case of unpaired electrons, namely, when a system has a total spin different from zero. Even for the case in which a molecule has a nonzero net spin, the direction of the spin is not strongly coupled to the molecular frame, and therefore, the direction of the spins can be defined only when an external magnetic field is applied (11). Thus, the spin direction of a single electron is not considered as affecting the stereochemistry of a reaction. An important exception to this occurs in photochemistry, in which light is used to dissociate molecules. This exception (42) is, however, not discussed in this review. Instead, we discuss how the coupling between the electron's spin and a molecule's chiral structure endows the molecule with properties that lead to a new role for chirality in biology.

We describe how the electron's spin and molecular chirality are related through the CISS effect and how this contributes to enantioselectivity in chemical reactions and to enantiospecific intermolecular interactions between chiral molecules (49). Even for cases in which the molecules have all of their electrons paired, i.e., the total spin is zero, we find that CISS and spin selectivity can play an important role. We discuss several open questions in biology and how the CISS effect offers new perspectives on them. Among these questions are: (a) How is long range electron transfer in biology so efficient? (b) How is biorecognition, especially enantiospecific recognition, so efficient? (c) How does nature regulate redox reactions so that they are so specific and selective?

While CISS does not provide detailed and comprehensive answers to these questions, its principles manifest in these processes, and its appreciation may guide the search for answers to these questions.

## THE CHIRAL INDUCED SPIN SELECTIVITY EFFECT

The CISS effect refers to the preferential transmission (or transfer) of electrons with one spin orientation over those with the other through chiral molecules and materials (44, 47). While a full quantitative explanation for the effect and its implications is not yet available, the phenomenon can be rationalized by considering that the electron moves in a helical electrostatic potential. Every chiral system displays some amount of helicity in its electrostatic potential as a result of the nuclei and all of the electrons of the system. The motion of an electron in such a potential behaves as if a magnetic field is acting on it perpendicular to its velocity (see **Figure 1a**). Because of the electron's intrinsic magnetic moment, this effective magnetic field causes an energy splitting in the spin states: One is stabilized, and the other is destabilized. Namely, the spin of the electron and its velocity are coupled because of the chiral structure of the molecule. This property enhances the transport of one spin orientation over the other, which is determined by the handedness of the molecule and the direction of motion (**Figure 1b**). The coupling between the electron motion and its spin also suppresses backscattering of the electron (31) because flipping the velocity direction of the electron requires also flipping its spin direction. This effect also holds for classical spin, and it stabilizes a rotating football against scattering (26). Flipping



**Figure 1**

(a) A scheme of the proposed chiral induced spin selectivity (CISS) mechanism. As an electron moves in a chiral potential, represented as a helical slide, a centripetal force,  $F_{\text{centripetal}}$ , acts on it perpendicular to its velocity. In the rest frame of the electron, this force is like a magnetic field  $B_{\text{eff}}$ , parallel to the molecular axis, that acts on the electron charge keeping it within the molecular system. This effective magnetic field interacts with the magnetic moment of the electron's spin, stabilizing one spin direction and destabilizing the other. Thus, one spin has a lower barrier for being transmitted through the chiral potential than the other. (b) The spin-dependent charge reorganization (SDCR). When an electric field  $E$  (black arrows) acts on a chiral molecule, due to the molecule's interaction with other molecules or with surfaces, charge reorganization occurs in the molecule and is accompanied by spin polarization. One electron, or part of one (red spheres), with a specific spin (black arrows through the red spheres) moves to generate excess electron density on the negative pole, which is spin polarized, and the unpaired electron density left on the positive pole has the opposite spin polarization. Which spin is associated with which electric pole depends on the handedness of the molecule.

spin is a highly improbable process; therefore, the coupling between the spin and the velocity enhances the efficiency of electron transfer through chiral molecules.

The CISS effect can be quantified by defining a polarization for a measurable property and its dependence on the electron spin direction. Commonly, the polarization  $P$  is defined as

$$P = \frac{A_{\text{up}} - A_{\text{down}}}{A_{\text{up}} + A_{\text{down}}} \times 100\%,$$

where  $A_{\text{up}}$  and  $A_{\text{down}}$  are measurable properties of the system that depend on the spin direction (UP versus DOWN). Some properties for which polarizations have been measured include current, electron transfer rate, and yield of electrons. In some works, the polarization of a measurable property, such as the faradaic current through chiral oligopeptides in an electrochemical cell, has been shown to agree well with the direct measurement of spin polarization through the chiral oligopeptides by photoemission spectroscopy (21). A wide range of experimental efforts have examined and confirmed the CISS effect in many chiral molecules, chiral polymers, chiral organic–inorganic assemblies (28), chiral inorganic materials (5, 9, 50), and even biomolecules including nucleic acids (62) and proteins (46). Many CISS effect measurements reveal that chiral molecules can function as spin filters.

Several recent experiments show that the spin polarization correlates with the optical activity of a chiral molecule (9, 24, 38). These observations imply that the magnitude of the spin polarization depends on the interaction of the moving electron with the chiral molecule's electron cloud, which, in turn, is affected by the motion of the moving electron. This mechanistic description rationalizes another manifestation of the CISS effect, the spin-dependent charge reorganization (SDCR) (25). Consider a closed shell molecule (total spin zero). When a molecular system is exposed to an electric field, the charges in the molecule respond, and a charge polarization results.

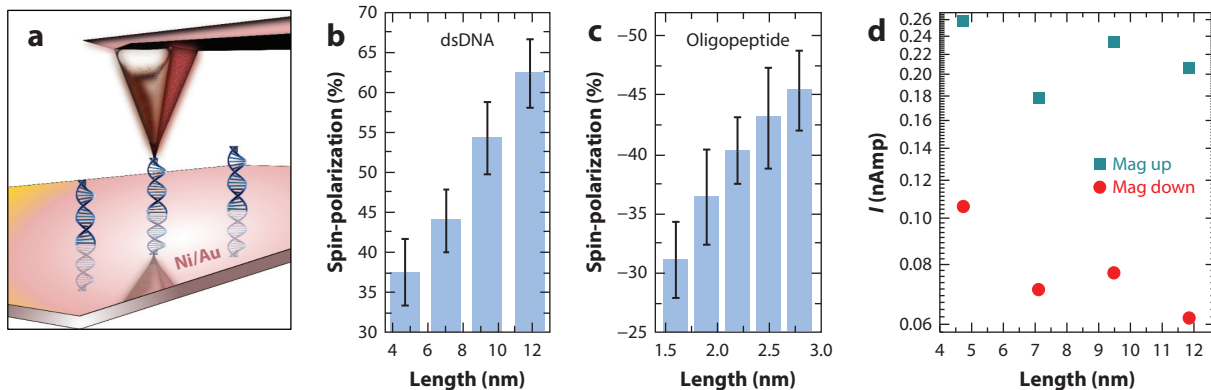
The charge polarization of the molecule generates a dipole moment by creating excess charge density in one region of the molecule and a depletion of charge density in the opposite region, i.e., the positive and negative poles of the dipole. In chiral molecules, the electron displacement current generates a spin dipole. Which spin is associated with which electrical pole depends on the handedness of the molecule (see **Figure 1b**). While the total spin of the molecule remains zero, the SDCR arises from spin polarization with opposite signs at the two electric poles. It is important to appreciate that any interaction of the chiral molecule with other molecules involves an effective electric field that causes charge displacement, for example, the ubiquitous van der Waals forces that result from induced dipoles between molecules and molecular assemblies (27). The SDCR affects the reactivity of chiral molecules and may contribute to enantioselectivity in the interaction between chiral molecules. The SDCR also affects the interaction of chiral molecules with ferromagnetic surfaces (15, 31), and it has been used to separate enantiomers.

## SPIN SELECTIVE CONDUCTION THROUGH DNA, OLIGOPEPTIDES, AND PROTEINS: LONG-RANGE ELECTRON TRANSFER

Electron flow dictates all biological energy conversion strategies (6, 18). In the case of respiration, cells harvest energy by controlling electron flow from electron donors to terminal electron acceptors through a chain of reduction–oxidation (redox) cofactors. Some microorganisms (including metal-reducing bacteria) can also extend this electron transport chain to terminal acceptors outside of the cells, allowing anaerobic respiration of solid minerals in the absence of soluble oxidants (e.g., O<sub>2</sub>) that enter the cells (54). Another process that utilizes long-range efficient electron transfer is photosynthesis. Even for DNA, long-range electronic interactions have been implicated in the damage control systems operating in cells (55). While much has been learned over the past 40 years about charge flow in biopolymers and the role played by electronic coupling pathways in directing the flow (20), the contributions of chirality and electron spin in these processes are largely unexplored. Yet electron transfer through chiral biopolymers (peptides, nucleic acids, and proteins) is strongly spin dependent (43).

Several researchers have shown that electron transmission and electron transport through DNA are spin dependent (see, e.g., 7); their studies range from photoemission spectroscopy (16) to fluorescence studies (1) and single-molecule conductance measurements (62). Recent work by Barton and coworkers (65) demonstrated that the spin-filtering of electron transfer through DNA arises directly from the handedness of the double helix. Other work describes spin-dependent charge polarization and charge transport through double-stranded DNA (dsDNA) of various lengths and even through dsDNA containing oxidative damage (37). Scanning tunneling microscope break junction measurements of transport through G-block DNA (and peptide nucleic acid) show long-range delocalization (approximately 5 nm) indicating long-range coherence in nucleic acids (58).

**Figure 2** presents some magnetic contact conducting probe atomic force microscopy results for self-assembled monolayers of mixed-sequence DNA duplexes and oligopeptides, SHCH<sub>2</sub>CH<sub>2</sub>CO-[Ala-Aib]<sub>n</sub>-COOH with  $n = 4, 5, 6, 7$  (where Ala indicates L-alanine and Aib indicates aminoisobutyric acid amino acid residues). The measurements reveal the length-dependent and spin-dependent conductance (35). In this case, the substrate, upon which the molecules are adsorbed, is a thin Ni film on top of which an 8-nm-thick Au film layer was deposited. The voltage was applied between the tip and the magnetic substrate. The polarization,  $P$ , is defined by  $P = (I_U - I_D)/(I_U + I_D)$ , where  $I_U$  and  $I_D$  are the currents measured when the magnetic north pole points up or down, respectively. **Figure 2d** shows a plot of the currents  $I$  versus the length  $l$  that was measured for different mixed-sequence DNA duplexes. The data show that



**Figure 2**

Spin transport measurements through DNA and oligopeptides. (a) The mcAFM setup. The chiral molecules are adsorbed as self-assembled monolayers on a gold-coated Ni surface that can be magnetized with the magnetic field pointing UP or DOWN relative to the surface. The voltage is applied between the substrate and the conducting tip of the AFM. (b) The polarization measured at 1V for DNA oligomers of different lengths. (c) Polarizations measured for different oligopeptides,  $\text{SHCH}_2\text{CH}_2\text{CO}-\{\text{Ala-Aib}\}_n-\text{COOH}$  with  $n = 4, 5, 6, 7$  (where Ala indicates L-alanine and Aib indicates aminoisobutyric acid amino acid residues). Note the negative value of the polarizations for the oligopeptides. (d) The currents measured at 1V through the DNA oligomers are plotted for each direction of the magnetic field separately. For the magnet pointing up (spins aligned antiparallel to the velocity), the current decreases as a function of length less than it does for the opposite spin. The ratio between the damping factors is 1:3. Figure adapted with permission from Reference 35, copyright ACS 2020. Abbreviations: AFM, atomic force microscopy; dsDNA, double-stranded DNA; mcAFM, magnetic contact AFM.

the current measured with the north pole oriented up ( $I_U$ ) is two to three times larger than that measured for the north pole oriented down,  $I_D$ . Notably, while the current  $I_U$  decreases by only approximately 15% over the 7 nm distance, the current  $I_D$  decreases by 50%. That is, the electrons with their spin oriented in the preferred orientation move more efficiently over distance in the chiral system than do those with their spin oriented in the disfavored orientation.

Interestingly, the spin-dependent transport is enhanced through oxidatively damaged DNA (46). This phenomenon can be rationalized by assuming either that the damaged DNA is characterized by a higher barrier for conduction or that charge transfer through the DNA is conducted through at least two channels, one involving the nucleobases that is highly conductive but less spin selective and another involving the ribophosphate backbone that is more insulating but is highly spin selective.

Spin filtering has also been demonstrated in large proteins. While the studies described above for dsDNA show that the preferred spin is aligned antiparallel to the electron velocity, similar studies on oligopeptides indicate that the spin is aligned parallel to the electrons' velocity. This change in spin direction is consistent with variation in the optical activity, as described above (9, 24, 38). While the oligopeptides made from natural amino acids are L, the DNA is D. The spin selectivity per unit length is approximately four times larger for the oligopeptides than for the dsDNA (35). Electron transfer in several proteins and protein assemblies, including cytochrome *c*, bacteriorhodopsin (34), bacterial cell surface multiheme electron conduits (36), and azurin (53), has been shown to be spin selective. In the case of azurin, it was found that the spin selectivity is reduced as the temperature is reduced from 298 K to 150 K, whereas the electron transfer efficiency itself is temperature independent below 273 K. This latter finding is interesting because it implies that the spin selectivity is significant at biologically relevant temperatures.

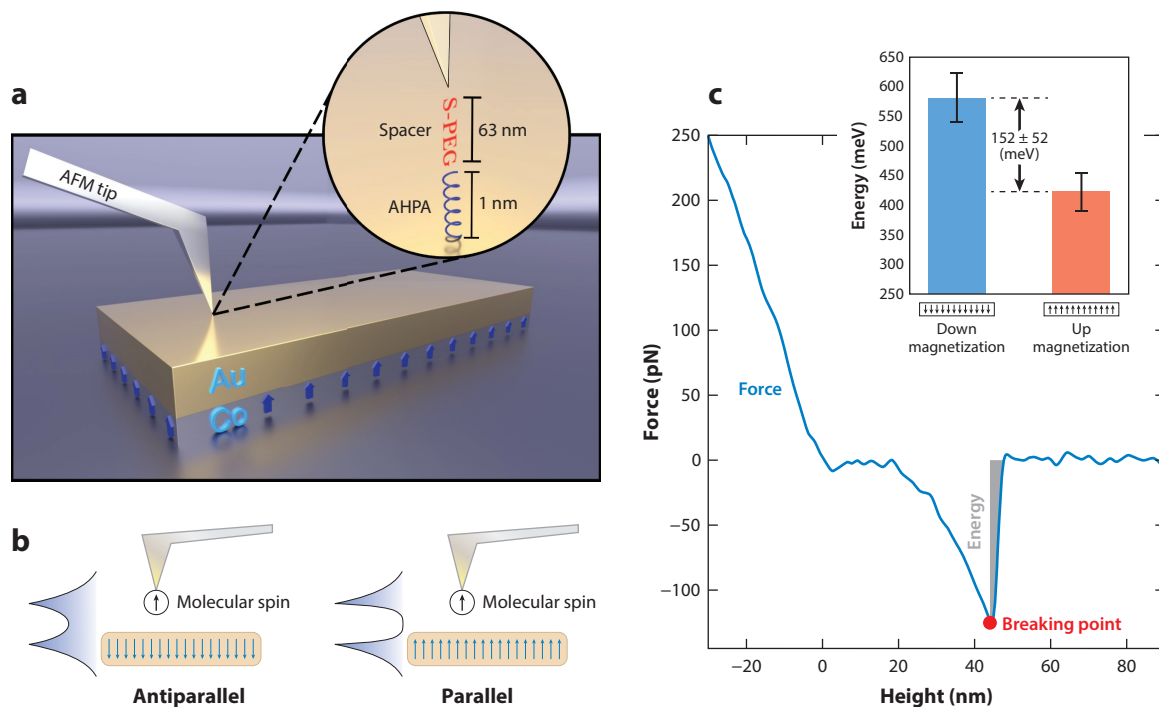
The results observed on numerous systems and with various techniques on the same systems indicate that charge motion through proteins and DNA is spin dependent. What is the benefit of spin-filtering? Long-range charge displacement in biomolecules often proceeds through redox cofactors embedded in proteins, and these cofactors drive chemical reactions. Because the reaction rates are limited by substrate concentration or turnover frequencies, the average number density of electrons moving through proteins per second (the current) can be modest, or low, in magnitude. Thus, high conductance is not an important factor. In contrast, it is important that any electron that starts to move get to its target, without side reactions, which can lead to chemical degradation and/or decreased efficiency. Chiral transport pathways provide a mechanism for locking the electron's spin direction with its velocity, and this reduces the probability of electron backscattering, as backscattering also requires a spin flip and is a low-probability process. In this way, the chiral structure enhances the reliability of the charge transport and protects the electron from environmental stresses and fluctuations. Thus, it is plausible that life makes use of proteins for electron conduction because their chirality promotes reliable long-range electron transport.

## ENANTIORECOGNITION

The existence of the SDCR in chiral molecules implies that the interaction of electron clouds of biomolecules must include spin-dependent forces. Spin effects on intermolecular forces have largely been neglected in the treatment of biomolecules and biomolecular processes. One reason for neglecting spin effects is the assumption that if the total spin of a molecule is zero, i.e., all electrons are paired, spin should not play a role. Even in the case of unpaired spin(s), e.g., a biradical, the spin direction is not strongly coupled to the molecular frame, so that the interactions between spins on different molecules do not strongly affect the interaction between the molecules. The weak magnetic interactions between the magnetic dipoles are small compared to typical thermal energies (relevant to terrestrial biology anyway), and electrostatic interactions drive the attractive forces between molecules. This assumption, however, neglects the importance of repulsive forces and their origin in Pauli exclusion constraints, which depend strongly on the electronic wavefunction's symmetry and spin symmetry. These forces are short range but strong enough to control atomic orbital filling and therefore interatomic and intermolecular interactions.

In a tour de force experiment, Paltiel and coworkers (64) directly measured the spin exchange forces for a molecule forming a chemisorption bond with a metal spin orbital and showed that the energy and force depend on whether the spins are aligned antiparallel (singlet) or parallel (triplet). **Figure 3** presents the direct measurement method of the energies that define the interaction between a ferromagnetic substrate and chiral molecules. In this model study, the magnetic substrate replaces one of the chiral molecules; however, the measurements are performed at room temperature and occur on a similar energy scale as biorecognition events. In this experiment, a chiral helical polypeptide,  $\alpha$ -polyalanine, is adsorbed on the gold cantilever of an atomic force microscope, which is then used to measure the force between the molecule and a ferromagnetic substrate (**Figure 3a**). As the cantilever (and molecule) approaches the substrate, the spin dependence for the chiral molecule–surface interaction manifests in a different force acting on the atomic force microscope cantilever (**Figure 3b**). Integrating the force over the tip displacement provides an energy for the interaction, and the difference in energy for the two magnetization directions (UP versus DOWN) of the ferromagnetic substrate demonstrates the difference in the interaction energy of the chiral molecule and the magnetized sample. These experiments reveal an energy difference of approximately 150 meV at short range, which is approximately 6  $k_B T$  (or almost 3.5 kcal/mol) and significantly larger than the expected Zeeman splitting and therefore very





**Figure 3**

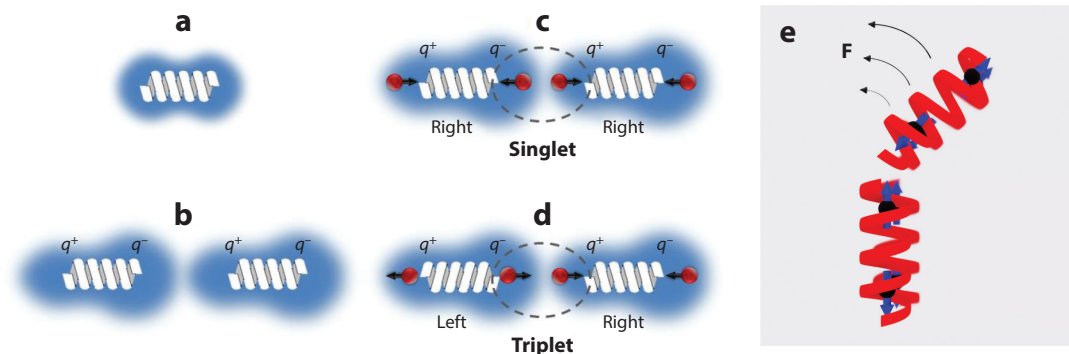
Determination of spin exchange energy in chiral systems. (a) A helical (and chiral) polypeptide,  $\alpha$ -polyalanine (AHPA), is adsorbed on a gold atomic force microscope (AFM) cantilever. When the tip is close to the sample, reorganization of the electric charges in the molecule results in spin polarization because of the chiral induced spin selectivity (CISS) effect. (b) Exchange interaction between the molecular wavefunction and the wavefunction of the magnetized substrate is sensed by the deflection of the AFM cantilever. (c) Typical force dependence on the tip–surface distance, the pulling point of the molecule, and the integrated area together represent the pulling energy of the molecule. (Inset) The mean pulling energy for the UP and DOWN directions of perpendicular sample magnetization, showing a difference of 150 meV. Figure adapted with permission from Reference 64, copyright Wiley.

relevant to biological interactions (**Figure 3c**). This energy is similar to the energy shifts measured by Kelvin probe microscopy for oligopeptides adsorbed on ferromagnetic substrates (15).

The SDCR observed in chiral molecules implies that the interaction between a chiral molecule and a magnetized surface is enantiospecific; that is, the spin orbitals of the metal interact differently with a chiral molecule depending on whether the molecule's orbitals have a preferred spin direction with respect to the metal. This effect has been exploited to promote enantioseparations by crystallization (57).

**Figure 4a–d** illustrates how SDCR leads to a transient spin polarization as two chiral molecules approach each other. The interaction term is the spin-exchange interaction, the same term that causes the splitting between singlet and triplet states in molecules and atoms, and it is relatively short range, typically a few angstroms. The spins are strongly coupled to the molecular frame because the charge displacement currents in the molecules generate the effective magnetic field and spin alignments. Because this interaction is directional, its magnitude depends on the relative angle between the spins that interact. **Figure 4e** illustrates how the force could guide the molecules to a narrow angle of interaction because the spins are coupled to the molecular frame. This interaction could enhance the rate for a recognition event because it constrains the configurations that the molecules can explore before binding (32) (**Figure 4e**). This mechanism implies





**Figure 4**

The effect of the spin-dependent charge reorganization (SDCR) on the interaction between chiral molecules. (a) The electron distribution (blue cloud) in a molecule that does not have a dipole moment before it interacts with another molecule. In this case, the distribution is symmetric. (b) The electron density distribution where the interaction between two molecules generates a charge polarization, i.e., an induced dipole–induced dipole interaction. (c) The induced dipole interaction of two molecules with the same handedness. As charge  $q$  transfers from one side of the molecule to the other, it generates a spin polarization (red ball and black arrow) of the same spin in the two molecules. The electron density left behind has the opposite spin polarization; thus, the interaction between the molecules is characterized by two opposite spins, as illustrated by the dotted circle singlet region. (d) When the two interacting molecules are of opposite chirality, the interaction between the molecules is characterized by two spins parallel to each other (in the dotted circle triplet region). Panels *a–d* reproduced from Reference 25. (e) The spin-dependent force is directional and therefore enhances interaction between chiral molecules.

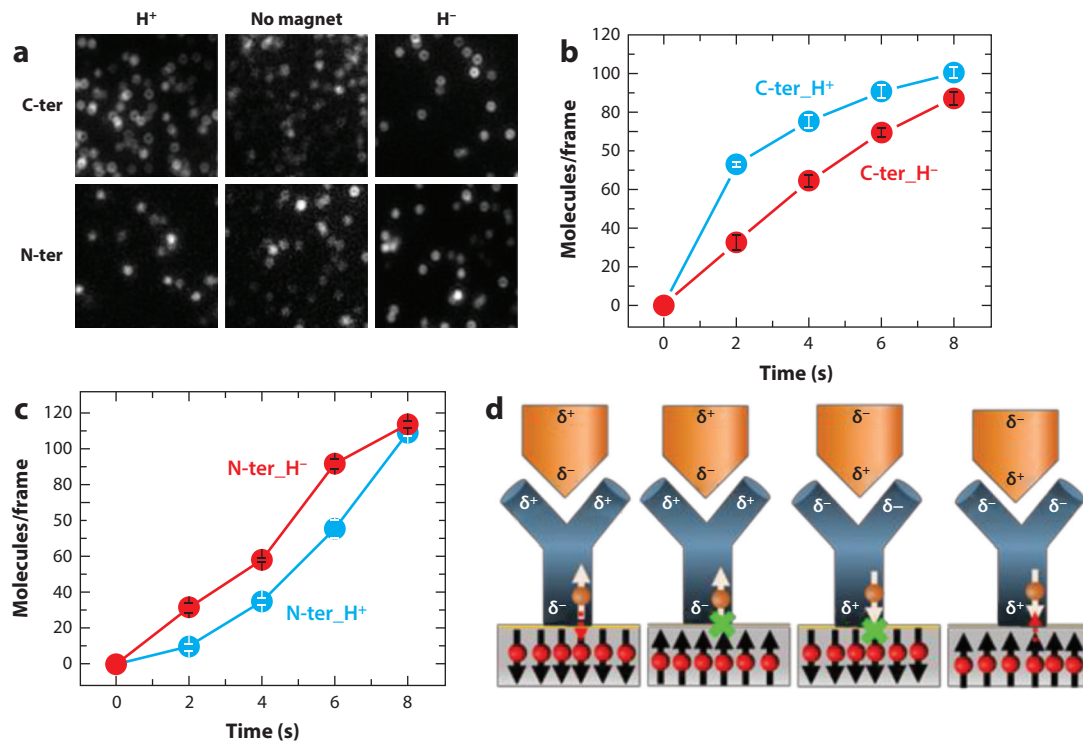
that enantioselectivity in the interaction between chiral molecules should depend on both a three-dimensional spatial or steric shape effect, the lock and key effect, and a spin-dependent electronic term. These metastable spin states could also stabilize a folded structure, keeping it closely packed.

Investigation of the SDCR and its impact on enantioselectivity has been extended to the study of protein–protein interactions by attaching an antibody to a ferromagnetic surface that serves as a source for spin-polarized electrons (4) (**Figure 5**). The antibody recognizes a polyhistidine tag (His-tag) attached to another protein, the antigen (ClpB from *Thermus thermophilus*). By switching the magnet direction (UP,  $H^+$ , or DOWN,  $H^-$ ), the charge flow between the antibody and the surface was modulated. It was found that the rate of association of the antigen (His-tagged ClpB) depends on the magnetic field direction; i.e., the spin that is injected at a site far away from the antibody's reaction site affects the association rate. Thus, the direction of the magnetization of the substrate serves as a valve, which operates under rules of CISS, that controls the charge flow between the adsorbed antibody and the substrate. This study shows unequivocally that the modulation of the association kinetics arises from charge reorganization within the protein and represents a novel allosteric mechanism. The valve in a biological structure could be the proximity of other chiral molecule(s) to the reactant.

The existence of SDCR and its manifestation over large distances through proteins imply that chirality plays more than just a structural role in biomolecules and biological structures. The findings described above imply that spin polarization through chiral molecules and that through helical structures generate significant energy differences and directional forces that act between molecules.

## MULTI-ELECTRON PROCESSES

Many redox processes in biology involve the transfer of multiple electrons, and this includes critically important reaction steps in respiration and photosynthesis. CISS and the chiral structure

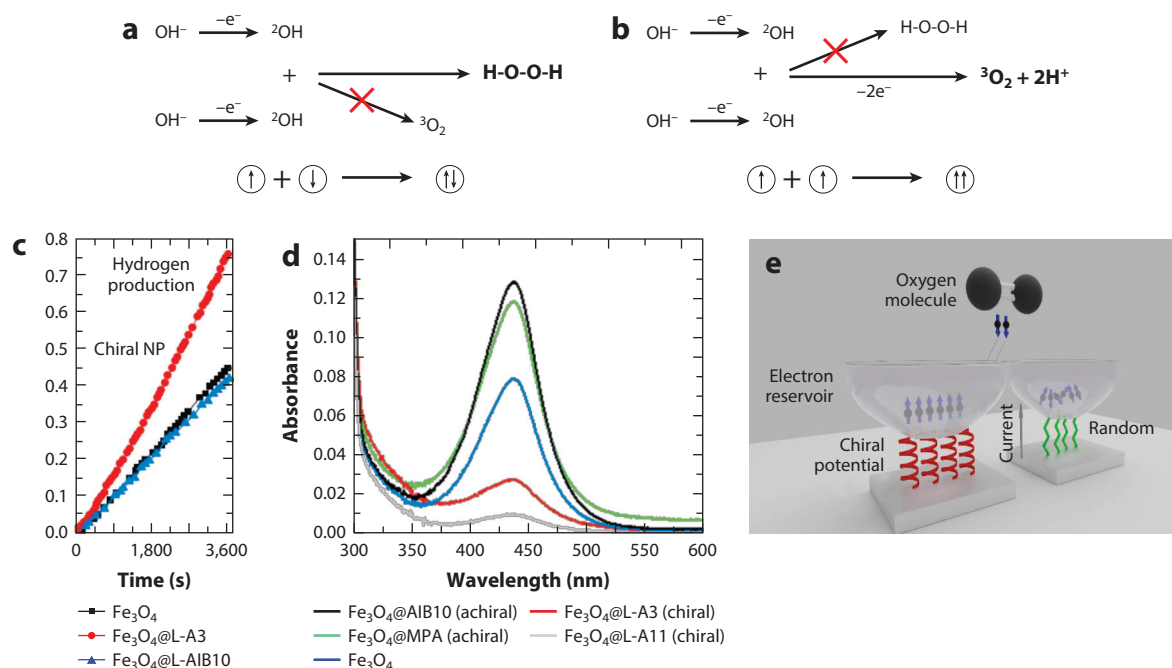


**Figure 5**

Effect of surface magnetization on the kinetics of antigen–antibody binding. (a) Fluorescence microscope images of individual complexes formed between adsorbed anti-His antibodies and ClpB molecules His-tagged either at the C terminus (C-ter) or at the N terminus (N-ter). The interaction time is 2 s, with the North magnetic pole of the magnetized substrate pointing either UP (H<sup>+</sup>) or DOWN (H<sup>-</sup>) and also without the magnet as a control. For the C-terminal His-tag, the number of adsorbed antigen molecules is larger for H<sup>+</sup>, while for the N-terminal His-tag, the number is larger for H<sup>-</sup>. (b) Reaction kinetics of the antibody with C-terminal His-tagged ClpB under the two magnetic orientations. (c) Reaction kinetics of the antibody with N-terminal His-tagged ClpB under the two magnetic orientations. (d) Schematic representation of the mechanism of the effect of spin on the antigen–antibody interaction. When the spin on the ferromagnet is pointing opposite to the momentary spin of the charge at the interface of the antibody and the ferromagnet, charge flows more efficiently between the antibody and the surface. The charge flow facilitates charge redistribution in the antibody, which in turn increases the antigen–antibody binding rate. Figure adapted with permission from Reference 4, copyright ACS 2021.

of biopolymers may play an important role in these processes, as one can envision a mechanism in which a protein or enzyme's chiral structure causes electron spins to be delivered in a manner that ensures the efficient and selective formation of desired products. Although CISS has not yet been directly implicated in biochemical cycles, work on the oxygen evolution reaction (OER) in electrochemical cells has demonstrated how CISS can affect a reaction's selectivity (46).

The OER at the anode of an electrochemical cell involves the generation of diatomic oxygen, which exists in a triplet ground state, from reactants that exist in a singlet ground state. In principle, reactions that involve a transition between singlets and triplets are forbidden; i.e., they cannot occur without a specific perturbation such as spin-orbit coupling, which often requires that high-atomic-number (heavy) atoms be involved. Catalysts for the OER present binding motifs that stabilize doublet intermediates (e.g., OH, O, and OOH radicals) as part of a multistep reaction mechanism. This complex reaction involves multiple electrons and protons and represents a significant challenge for the widespread deployment of water electrolysis. Moreover, side reactions,



**Figure 6**

The oxidation of water and the formation of oxygen and hydrogen. (a) The formation of oxygen from water involves four electrons, two of which are transferred from two  $\text{OH}^-$  ions to the anode. If the two transferred electrons have opposite spins, then they leave behind two OH radicals with opposite spins, which must recombine on a singlet surface to form hydrogen peroxide. (b) If the two transferred electrons have the same spins, then the OH radicals are spin aligned and recombine on a triplet surface to form  $\text{O}_2$ ;  $\text{H}_2$  is formed on the cathode. (c) When the anode, in this case composed of  $\text{Fe}_3\text{O}_4$  nanoparticles, is coated with chiral oligopeptides, the electrons transferred to the cathode have the same spin, and as a result, the hydrogen production (red curve) is enhanced compared to that of electrodes coated with achiral molecules or a bare electrode (blue and black curves, respectively). (d) Control of the hydrogen peroxide production, including UV-visible absorption spectra from the titration of the used electrolyte with o-tolidine of bare  $\text{Fe}_3\text{O}_4$  electrodes (blue curve), an electrode coated with two different achiral molecules (green and black lines), and an electrode coated with a chiral six-amino-acid-long oligopeptide (red line) or 22-amino-acid-long oligopeptide (gray line). The area of the peaks is proportional to the hydrogen peroxide production. (e) In the case of oxygen reduction, two electrons are transferred initially, and if they have the same spin orientation, which is opposite to the spins on the oxygen, then they can induce the dissociation of the oxygen more efficiently than they otherwise could. Abbreviation: NP, nanoparticle.

such as the generation of hydrogen peroxide, can be significant. Recent work shows that both the efficiency and the selectivity of the OER are improved by inclusion of homochiral electrocatalysts and chiral molecules. Based on the CISS effect, it was suggested that the difference between the artificial system and the natural one is the chirality of the molecules, which affects the electrons' spin (40).

As shown in **Figure 6a,b**, the formation of oxygen from water involves the transfer of two electrons from the  $\text{OH}^-$  ions to the electrode. If the electron acceptor (the electrode) is chiral, then the two electrons that are transferred have the same spin polarization, and this leaves behind two OH radicals that have their electron spins aligned. In the electrochemical case, these radicals are adsorbed on the electrode surface, and this helps to maintain their spin alignment. Because of their spin alignment, the OH radicals interact on a triplet surface, and triplet oxygen can be formed through a spin-allowed process. If the electron acceptor is not chiral, then it is probable that the OH radicals will be formed with opposite spins, and thus they interact on a singlet surface. Thus,

a spin flip must occur to form triplet oxygen; alternatively, the OH radicals can form hydrogen peroxide, which is a singlet species, or an excited singlet oxygen diatom.

**Figure 6c,d** shows data for the reaction efficiency with different molecular adsorbates. **Figure 6c** presents the formation of hydrogen that accompanies the oxygen formation when chemically modified iron oxide ( $\text{Fe}_3\text{O}_4$ ) nanoparticles are used as a catalyst. These nanoparticles are coated with achiral molecules,  $\text{SH}-(\text{CH}_2)_2-\text{NH}-(\text{Aib})_{10}-\text{NH}_2$ , where Aib is 2-aminoisobutyric acid (Aib10), or  $\text{SH}-(\text{CH}_2)_2-\text{COOH}$  (MPA), or with chiral oligopeptides,  $\text{SH}-(\text{CH}_2)_2-\text{NH}-(\text{Ala}-\text{Aib})_3-\text{COOH}$  (L-A3) or  $\text{SH}-(\text{CH}_2)_2-\text{NH}-(\text{Ala}-\text{Aib})_{11}-\text{COOH}$  (L-A11). The data in **Figure 6d** show that the yield of the side product, hydrogen peroxide, is greatly reduced when the anode is coated with the chiral oligopeptides  $\text{SH}-(\text{CH}_2)_2-\text{NH}-(\text{Ala}-\text{Aib})_3-\text{COOH}$  (L-A3) and  $\text{SH}-(\text{CH}_2)_2-\text{NH}-(\text{Ala}-\text{Aib})_{11}-\text{NH}_2$  (L-A11). Together, these experiments show that the addition of chiral molecules increases the yield of  $\text{H}_2$  and improves the selectivity of the reaction. Indeed, a large number of experiments proved that, when using electrodes coated with chiral molecules (13, 17, 41), intrinsically chiral electrodes (5, 14), or magnetic electrodes that preferentially accept one spin (12, 14), the production of oxygen and hydrogen is enhanced, and the production of hydrogen peroxide is suppressed.

Biomolecular respiration faces similar challenges; however, because of the complexity of the process and the involvement of many enzymes, some of them containing metal cofactors, it is assumed that the spin-orbit coupling is large enough that spin constraints are relaxed. Because of an enzyme's chiral structure, however, it may be that CISS plays an important role by reducing the number of spin states for the electrons. In a chiral system of specific handedness, the electrons are more likely to have their spins aligned parallel to each other, and therefore, the probability of two electrons interacting with a triplet oxygen in a favorable spin configuration is higher than if the two electrons are equally likely to have any spin state combination (see **Figure 6e**). For multi-electron processes like respiration (3) or photosynthesis (8), which have a number of possible intermediates, the spin alignment may have an important impact on the most probable mechanism. While enhancing the efficiency of these processes benefits the organism by reducing the free energy cost, it also improves selectivity and may reduce the production of reactive oxygen species that create oxidative stress.

An analog of respiration in artificial systems is the oxygen reduction reaction (ORR). As described above for the OER, magnetic surfaces can enhance the efficiency of the ORR, and several studies show that magnetic electrodes can enhance oxygen reduction (51, 63). One has to be aware that the effect in this case is not a result of the magnetic field, but instead the result of the spin alignment of electrons injected from the ferromagnet or inserted into it (33). An important difference between biochemical and artificial processes involving oxygen is that chirality is present in the biological case. Control over the spin alignment by chirality improves the efficiency and the selectivity (in the OER,  $\text{H}_2\text{O}_2$  production is suppressed) of the biological processes.

## CONCLUSIONS

Despite the chiral symmetry of molecules being known since the time of Pasteur and Kelvin, chemists often consider it only a burden, as it increases the effort needed to produce compounds that can interact efficaciously with biological systems. Other than being a way to help control shape, no important functionalities have been attributed to chirality per se. The discovery of CISS requires a paradigm shift in our understanding of molecular chirality and in the development of new tools for predicting chiral-related forces.

Biopolymer chirality facilitates long-range electron transfer in molecules (**Figure 2d**). The transfer of the electron with the preferred spin is protected by the coupling between the spin

and the velocity. This protection is analogous to the angular momentum protection afforded by the rifle effect, which improves the accuracy and range of a bullet by causing it to spin about its velocity direction. This property is advantageous in biology, where the average flux of electrons transferred is typically low (low current), but it is important that electrons not scatter even as a molecule fluctuates.

Chirality enhances the selectivity of biorecognition through an interaction term that does not exist for achiral molecules. This interaction term enhances the binding, and its neglect in molecular modeling may account, in part, for the difference between experimentally measured binding energies and calculated ones (60, 61). Because of its directionality, the force resulting from this interaction is expected to direct molecules into a preferred range of approach angles and thereby enhance reaction rates. Extending these ideas to protein folding processes seems straightforward. The directional nature of the SDCR can act to limit the available structures that a protein explores before folding. In other words, the chirality reduces the entropy of the system before folding and facilitates the folding process.

Many redox reactions involve the transfer of multiple electrons, and control of electron spin can impact the efficiency and selectivity of these processes. Controlling the spin can reduce free energy barriers in redox reactions; i.e., by transferring one spin direction, the number of spin states associated with the reactants in an elementary reaction step is reduced, and thus, the initial entropy of the reactant is lower than in the case where spin is not controlled. Despite the recognized role of spin states in affecting the thermodynamics of reactions (56), the chiral-induced spin effect is often not taken into account in calculations, yet it may explain the enhanced rate of reactions occurring *in vivo* versus those that are measured *in vitro*.

While the issue of homochirality in biology remains open, the discovery of CISS and its implications for biochemical and biophysical processes offers a new perspective on chirality in biochemistry and biology. The fact that CISS leads to selective spin-dependent interactions for chiral molecules, which do not exist for achiral ones, provides a new rationale for understanding why chirality has been maintained so persistently through evolution. It seems that homochirality, which is a signature of life, may actually be one of life's driving forces.

## DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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