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## PAPER

## Chiral-induced spin selectivity in the formation and recombination of radical pairs: cryptochrome magnetoreception and EPR detection

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E-mail: [peter.hore@chem.ox.ac.uk](mailto:peter.hore@chem.ox.ac.uk)**Keywords:** radical pair mechanism, chiral-induced spin selectivity, magnetic compass, animal navigation, spin polarization, EPR spectroscopy, cryptochromeSupplementary material for this article is available [online](#)

## Abstract

That the rates and yields of reactions of organic radicals can be spin dependent is well known in the context of the radical pair mechanism (RPM). Less well known, but still well established, is the chiral-induced spin selectivity (CISS) effect in which chiral molecules act as spin filters that preferentially transmit electrons with spins polarized parallel or antiparallel to their direction of motion. Starting from the assumption that CISS can arise in electron transfer reactions of radical pairs, we propose a simple way to include CISS in conventional models of radical pair spin dynamics. We show that CISS can (a) increase the sensitivity of radical pairs to the direction of a weak external magnetic field, (b) change the dependence of the magnetic field effect on the reaction rate constants, and (c) destroy the field-inversion symmetry characteristic of the RPM. We argue that CISS polarization effects could be observable by EPR (electron paramagnetic resonance) of oriented samples either as differences in continuous wave, time-resolved spectra recorded with the spectrometer field parallel or perpendicular to the CISS quantization axis or as signals in the in-phase channel of an out-of-phase ESEEM (electron spin echo envelope modulation) experiment. Finally we assess whether CISS might be relevant to the hypothesis that the magnetic compass of migratory songbirds relies on photochemically-formed radical pairs in cryptochrome flavoproteins. Although CISS effects offer the possibility of evolving a more sensitive or precise compass, the associated lack of field-inversion symmetry has not hitherto been observed in behavioural experiments. In addition, it may no longer be safe to assume that the observation of a polar magnetic compass response in an animal can be used as evidence against a radical pair sensory mechanism.

## 1. Introduction

Reactions of organic radicals generally conserve electron spin angular momentum: pairs of radicals in electronic singlet (triplet) states are formed from and recombine to molecular singlet (triplet) states. This spin-selectivity leads to reaction rates and yields being sensitive to applied magnetic fields and to electron and nuclear spin polarization [1]. Studies of these phenomena have included radical pairs formed by photo-induced electron transfer reactions in proteins, in particular photosynthetic reaction centres [2] and the cryptochrome (Cry) flavoproteins thought to be responsible for the magnetic compass sense of migratory songbirds [3]. Dating back to the first experimental observations in the late 1960s and the development of the radical pair mechanism (RPM) [4–13], these and related effects constitute the field of spin chemistry [14].

Discovered some 30 years later [15], chiral-induced spin selectivity (CISS), is a distinctly different source of electron spin polarization. It has become clear from the work of Naaman, Waldeck and colleagues that chiral molecules can act as spin filters that preferentially transmit electrons that have spins polarized either parallel or antiparallel to their direction of motion [16–29]. Although the mechanism is not completely understood, most theoretical treatments seem to agree that CISS has its origin in the spin–orbit interaction of the spin with the linear momentum of electrons moving in the helical electrostatic potential of a chiral medium [17, 25, 30–37]. In a typical experiment, electrons are injected into a layer of chiral material—DNA for example—and emerge spin-polarized.

There have been speculations on its importance in biology [21, 26, 38–40], but it is not yet clear whether CISS should be expected to arise in electron transfer reactions of the type  $DA \rightleftharpoons D^{\bullet+}A^{\bullet-}$  occurring, for example, in the chiral interior of a protein. The only theoretical discussion of CISS in this context is a very recent report which suggests that the chirality should give rise to spin coherence rather than spin polarization [41]. To the best of our knowledge, there is only one report of CISS arising from an electron transfer reaction that creates a radical pair. Carmeli *et al* [39] have reported electron spin polarization in experiments on the photosynthetic reaction centre, photosystem I (PSI), a protein in which spin-correlated radical pairs are formed by light-induced charge separation between bound cofactors [42–46]. Using a spintronic detection device, with a monolayer of oriented PSI attached, Carmeli *et al* found strong spin selectivity throughout the photo-induced electron transfer pathway and established that the electrons were transferred with their spins aligned parallel to their momenta [39]. The only other overlap between CISS and the RPM of which we are aware is in the recombination of pairs of  $OH^{\bullet}$  radicals but in that case the spin-correlation arises separately in two  $OH^{\bullet}$  radicals created by conduction of electrons from  $OH^-$  ions to an electrode through an adsorbed layer of chiral molecules [47–51].

Although there have been many hundreds of studies of radical pairs using electron paramagnetic resonance (EPR) spectroscopy [2, 44, 45, 52, 53], a technique ideally suited for observing spin polarization, spin correlation and spin coherence, there seems to be no strong evidence for spin-selection effects that cannot be explained by the RPM. However, absence of evidence cannot be interpreted as evidence of absence.

In the following paragraphs, inspired by Carmeli *et al* [39], we start from the assumption that CISS *can* arise in radical pair reactions alongside the conventional RPM spin selectivity and attempt to answer the following questions. (1) How can CISS effects be included in the conventional modelling of radical pair spin dynamics? (2) How could CISS be detected by EPR and distinguished from RPM effects? (3) Could CISS be relevant to the cryptochrome hypothesis of the mechanism of the magnetic compass of migratory songbirds?

## 2. Theory

### 2.1. Radical pair spin selectivity

We start by briefly reviewing the conventional description of the spin dynamics and spin-selective reactivity of radical pairs before outlining the changes required to incorporate CISS effects. Consider the formation of a radical pair by the transfer of an electron from a closed shell donor to a photoexcited singlet acceptor:



For organic molecules, in which the spin–orbit coupling is small, such reactions generally conserve spin angular momentum and produce the radical pair predominantly in an electronic singlet state:

$$|S\rangle = \frac{1}{\sqrt{2}} (|\alpha_D\beta_A\rangle - |\beta_D\alpha_A\rangle), \quad (2)$$

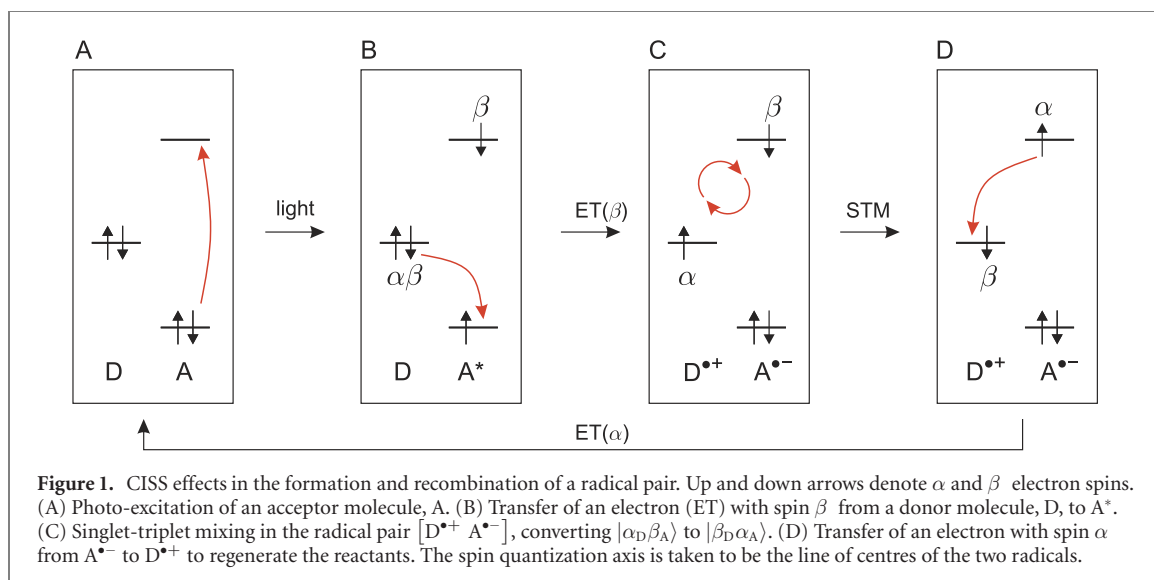
in which  $|\alpha\rangle$  and  $|\beta\rangle$  are the  $m = \pm\frac{1}{2}$  electron spin states. Various subsequent reactions are possible, including spin-selective back electron transfer to regenerate D and A in their (singlet) ground states,



and/or formation of the triplet state of one of the reactants, e.g.



Reactions (3) and (4) are both spin-conserving. Additionally there may be reactions that involve just one of the radicals (e.g. a change in protonation state), are therefore not subject to spin-selection rules and occur



at equal rates for singlet and triplet pairs, e.g.



In equations (3)–(5),  $k_S$ ,  $k_T$ , and  $k_F$  are first order rate constants.

In almost all treatments of radical pair spin dynamics over the last 40 years, such reactions have generally (and very successfully) been modelled by means of ‘Haberkorn’ operators [54] in a master equation of the form,

$$\frac{d\hat{\rho}(t)}{dt} = -i[\hat{H}, \hat{\rho}(t)]_- - \frac{1}{2}k_S[\hat{P}^S, \hat{\rho}(t)]_+ - \frac{1}{2}k_T[\hat{P}^T, \hat{\rho}(t)]_+ - k_F\hat{\rho}(t), \quad (6)$$

where  $\hat{\rho}(t)$  and  $\hat{H}$  are the spin density operator and spin Hamiltonian of the radical pair comprised of the two unpaired electrons and all hyperfine-coupled nuclei.  $[B, C]_{\pm} = BC \pm CB$ , and  $\hat{P}^S$  and  $\hat{P}^T$  are projection operators onto the singlet and triplet electronic subspaces. For a radical pair formed in a singlet state with no nuclear spin polarization,  $\hat{\rho}(0) = \hat{P}^S/N$ , where  $N$  is the total number of nuclear spin states. At least one of  $k_S$  and  $k_T$  must be non-zero for the yields of the reaction products to be affected by a weak applied magnetic field. The anti-commutator terms in equation (6), originally proposed phenomenologically [54–56], have recently been derived explicitly for electron transfer reactions [57, 58].

As usual in simulations of the anisotropic effects of weak magnetic fields on radical pairs [59–62],  $\hat{H}$  has the general form:

$$\hat{H} = \omega \cdot (\hat{\mathbf{S}}_D + \hat{\mathbf{S}}_A) + \sum_{i \in \{D, A\}} \sum_k \hat{\mathbf{S}}_i \cdot \mathbf{A}_{ik} \cdot \hat{\mathbf{I}}_{ik} + \hat{\mathbf{S}}_D \cdot \mathbf{D} \cdot \hat{\mathbf{S}}_A - J \left( 2\hat{\mathbf{S}}_D \cdot \hat{\mathbf{S}}_A + \frac{1}{2} \right). \quad (7)$$

$\hat{\mathbf{S}}_D$  and  $\hat{\mathbf{S}}_A$  are the electron spin operators of the two radicals and  $\hat{\mathbf{I}}_{ik}$  is the spin operator of nucleus  $k$  in radical  $i$ .  $\omega = -\gamma_e B (\sin \theta \cos \phi, \sin \theta \sin \phi, \cos \theta)$  is the external magnetic field vector (in angular frequency units) with magnitude  $|\gamma_e| B$  and direction specified by angles  $\theta$  and  $\phi$ .  $\mathbf{A}_{ik}$  is the hyperfine tensor that couples electron  $i$  with nucleus  $k$ .  $\mathbf{D}$  and  $J$  are, respectively, the dipolar coupling tensor and the exchange interaction of the two electron spins.  $\mathbf{D}$  has eigenvalues  $4D/3, -2D/3, -2D/3$ , where  $D$  varies as the inverse cube of the separation of the radicals.

## 2.2. Chiral-induced spin selectivity

How should equation (6) be modified to account for CISS-type spin polarization effects when the radical pair is formed by electron transfer in a chiral medium such as a protein? We start with the limiting case of 100% CISS polarization such that only an electron with spin  $\beta$  can move from D to  $^1A^*$  in reaction (1), leaving behind an electron with spin  $\alpha$  in  $D^{\bullet+}$  [26, 51]. The result is a radical pair initially in the state  $|\alpha_D\beta_A\rangle$  with the electron spins quantized along the direction of the electron transfer, i.e. the vector connecting the centres of D and A (figure 1). The following can easily be adapted for the initial state  $|\beta_D\alpha_A\rangle$ , as would be the case for the opposite chirality of the intervening medium.

In the general case, where the polarization is less than 100%, we propose that the initial state of the radical pair can be written  $\hat{P}^I = |\psi_I\rangle \langle \psi_I|$  where

$$\begin{aligned} |\psi_I\rangle &= \cos\left(\frac{1}{2}\chi\right) |S\rangle + \sin\left(\frac{1}{2}\chi\right) |T_0\rangle \\ &= \frac{1}{\sqrt{2}} \left[ \sin\left(\frac{1}{2}\chi\right) + \cos\left(\frac{1}{2}\chi\right) \right] |\alpha_D\beta_A\rangle + \frac{1}{\sqrt{2}} \left[ \sin\left(\frac{1}{2}\chi\right) - \cos\left(\frac{1}{2}\chi\right) \right] |\beta_D\alpha_A\rangle, \end{aligned} \quad (8)$$

with  $|T_0\rangle$  the  $m = 0$  triplet state,

$$|T_0\rangle = \frac{1}{\sqrt{2}} (|\alpha_D\beta_A\rangle + |\beta_D\alpha_A\rangle). \quad (9)$$

Hence

$$\begin{aligned} \hat{P}^I &= \frac{1}{2} (1 + \sin(\chi)) |\alpha_D\beta_A\rangle \langle \alpha_D\beta_A| + \frac{1}{2} (1 - \sin(\chi)) |\beta_D\alpha_A\rangle \langle \beta_D\alpha_A| \\ &\quad - \frac{1}{2} \cos(\chi) (|\alpha_D\beta_A\rangle \langle \beta_D\alpha_A| + |\beta_D\alpha_A\rangle \langle \alpha_D\beta_A|) \\ &= \frac{1}{4} \hat{E} - \hat{S}_{DZ} \hat{S}_{AZ} - (\hat{S}_{DX} \hat{S}_{AX} + \hat{S}_{DY} \hat{S}_{AY}) \cos(\chi) + \frac{1}{2} (\hat{S}_{DZ} - \hat{S}_{AZ}) \sin(\chi), \end{aligned} \quad (10)$$

in which  $\hat{S}_{DQ}$  and  $\hat{S}_{AQ}$  ( $Q \in X, Y, Z$ ) are components of the electron spin angular momentum operators of the two radicals. The  $Z$ -axis here is the CISS quantization axis. In equations (8) and (10), the angle  $\chi$  determines the extent of the CISS polarization of the initial state, the limiting cases being  $\chi = 0$ ,  $\hat{P}^I = |S\rangle \langle S|$  (pure singlet, no CISS) and  $\chi = \pi/2$ ,  $\hat{P}^I = |\alpha_D\beta_A\rangle \langle \alpha_D\beta_A|$  (100% CISS, no RPM). The four operator terms in the final line of equation (10) are as follows: the identity operator, two-spin order, zero quantum coherence (ZQC), and single-spin polarizations, all defined with respect to the CISS  $Z$ -axis. It is clear that a CISS contribution to the initial state modifies the amplitude of the ZQC and introduces equal and opposite spin polarization in the two radicals. It also causes the initial state to be anisotropic.

The CISS effect couples the linear momentum of an electron to its spin angular momentum such that electron transport is more efficient when they are either parallel or antiparallel, depending on the chirality of the medium [17]. This correlation implies that if only an electron with spin  $\alpha$  can move from D to  $^1A^*$  then only an electron with spin  $\beta$  can move in the opposite direction when the electron returns from  $A^{\bullet-}$  to  $D^{\bullet+}$  (figure 1). We therefore propose that the corresponding projection operator for back electron transfer should be  $\hat{P}^R = |\psi_R\rangle \langle \psi_R|$  where

$$\begin{aligned} |\psi_R\rangle &= \cos\left(\frac{1}{2}\chi\right) |S\rangle - \sin\left(\frac{1}{2}\chi\right) |T_0\rangle \\ &= -\frac{1}{\sqrt{2}} \left[ \sin\left(\frac{1}{2}\chi\right) - \cos\left(\frac{1}{2}\chi\right) \right] |\alpha_D\beta_A\rangle - \frac{1}{\sqrt{2}} \left[ \sin\left(\frac{1}{2}\chi\right) + \cos\left(\frac{1}{2}\chi\right) \right] |\beta_D\alpha_A\rangle \end{aligned} \quad (11)$$

and

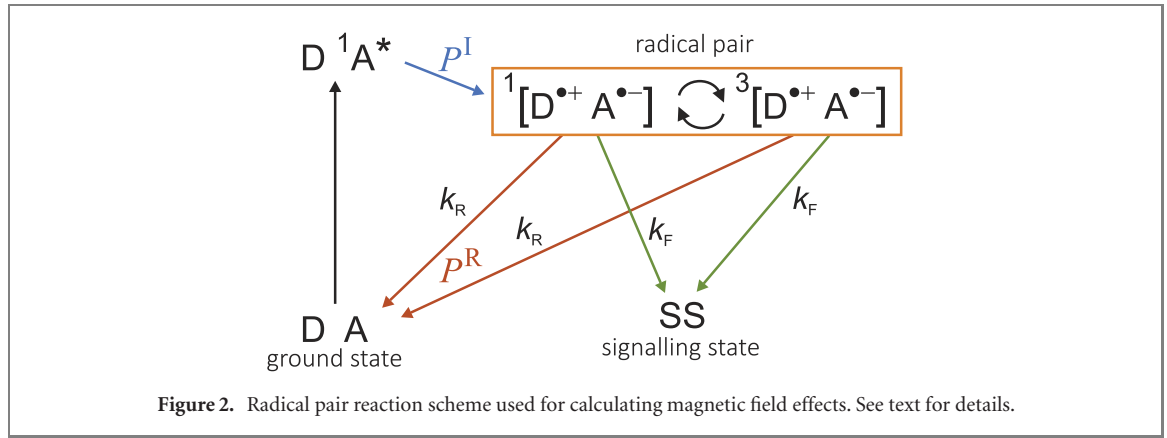
$$\hat{P}^R = \frac{1}{4} \hat{E} - \hat{S}_{DZ} \hat{S}_{AZ} - (\hat{S}_{DX} \hat{S}_{AX} + \hat{S}_{DY} \hat{S}_{AY}) \cos(\chi) - \frac{1}{2} (\hat{S}_{DZ} - \hat{S}_{AZ}) \sin(\chi). \quad (12)$$

The only difference between  $\hat{P}^I$  and  $\hat{P}^R$  is the sign of the spin-polarization term,  $(\hat{S}_{DZ} - \hat{S}_{AZ})$ .  $\chi$  plays the same role here as in equations (8) and (10), with limiting cases  $\chi = 0$ ,  $\hat{P}^R = |S\rangle \langle S|$  (pure singlet, no CISS) and  $\chi = \pi/2$ ,  $\hat{P}^R = |\beta_D\alpha_A\rangle \langle \beta_D\alpha_A|$  (100% CISS, no RPM). If  $|\beta_D\alpha_A\rangle$  is favoured over  $|\alpha_D\beta_A\rangle$  in the forward electron transfer, and vice-versa in the recombination step,  $\chi$  will be in the range  $[0, -\pi/2]$ .

Assuming the rate of the triplet reaction in equation (4) is negligible (as is the case in cryptochromes [3, 63]), the master equation for the density operator with CISS effects included becomes

$$\frac{d\hat{\rho}(t)}{dt} = -i[\hat{H}, \hat{\rho}(t)]_- - \frac{1}{2} k_R [\hat{P}^R, \hat{\rho}(t)]_+ - k_F \hat{\rho}(t), \quad (13)$$

where  $k_R$  is the rate constant for back electron transfer,  $[D^{\bullet+} A^{\bullet-}] \rightarrow D + A$ , and the initial condition is  $\hat{\rho}(0) = \hat{P}^I/N$ . We propose equations (10) and (12) here in the same spirit as the Haberkorn approach [54] in an attempt to merge Carmeli's observations of electron spin polarization in photosynthetic reaction centres (outlined above) [39] with the conventional RPM. Other formulations are possible. For example, the singlet and triplet parts of  $|\psi_I\rangle$  and  $|\psi_R\rangle$  could have different phases, and  $\hat{P}^I$  and  $\hat{P}^R$  could be mixed states instead of pure states [41]. An advantage of the forms we have chosen is that they involve the minimum number of parameters.



The new equation of motion, equation (13), and the associated initial condition differ from the conventional forms (equation (6) and  $\hat{\rho}(0) = \hat{P}^S/N$ ) in that they break time-reversal symmetry. This can be seen to be a consequence of the antisymmetry of angular momentum operators under the time-reversal operator,  $\hat{T}$ , for example  $\hat{T} \hat{S}_{Dz} \hat{T}^{-1} = -\hat{S}_{Dz}$  [64, 65]. The term for the Zeeman interaction in the spin Hamiltonian, equation (7),  $\omega \cdot (\hat{S}_D + \hat{S}_A)$ , is therefore antisymmetric. All other terms in  $\hat{H}$  (hyperfine, dipolar, and exchange interactions) and the projection operators  $\hat{P}^S$  and  $\hat{P}^T$  in equation (6) contain only bi-linear products of spin operators and are therefore symmetric under time-reversal. For example:

$$\hat{T} \hat{P}^S \hat{T}^{-1} = \hat{T} \left[ \frac{1}{4} \hat{E} - \sum_{j=x,y,z} \hat{S}_{Dj} \hat{S}_{Aj} \right] \hat{T}^{-1} = \frac{1}{4} \hat{E} - \sum_{j=x,y,z} (\hat{T} \hat{S}_{Dj} \hat{T}^{-1}) (\hat{T} \hat{S}_{Aj} \hat{T}^{-1}) = \hat{P}^S. \quad (14)$$

These properties result in the reaction yields being even functions of the magnetic field,  $\omega$ . By contrast, neither of the CISS spin projection operators,  $\hat{P}^I$  and  $\hat{P}^R$  in equations (10) and (12), has time-reversal symmetry because of the  $(\hat{S}_{Dz} - \hat{S}_{Az})$  terms, and are in fact interconverted by  $\hat{T}$ :

$$\hat{T} \hat{P}^I \hat{T}^{-1} = \hat{P}^R \quad \text{and} \quad \hat{T} \hat{P}^R \hat{T}^{-1} = \hat{P}^I. \quad (15)$$

In passing, we note an apparent parallel between the CISS effects discussed here and the ALTADENA experiment [66–68] (see [appendix](#)).

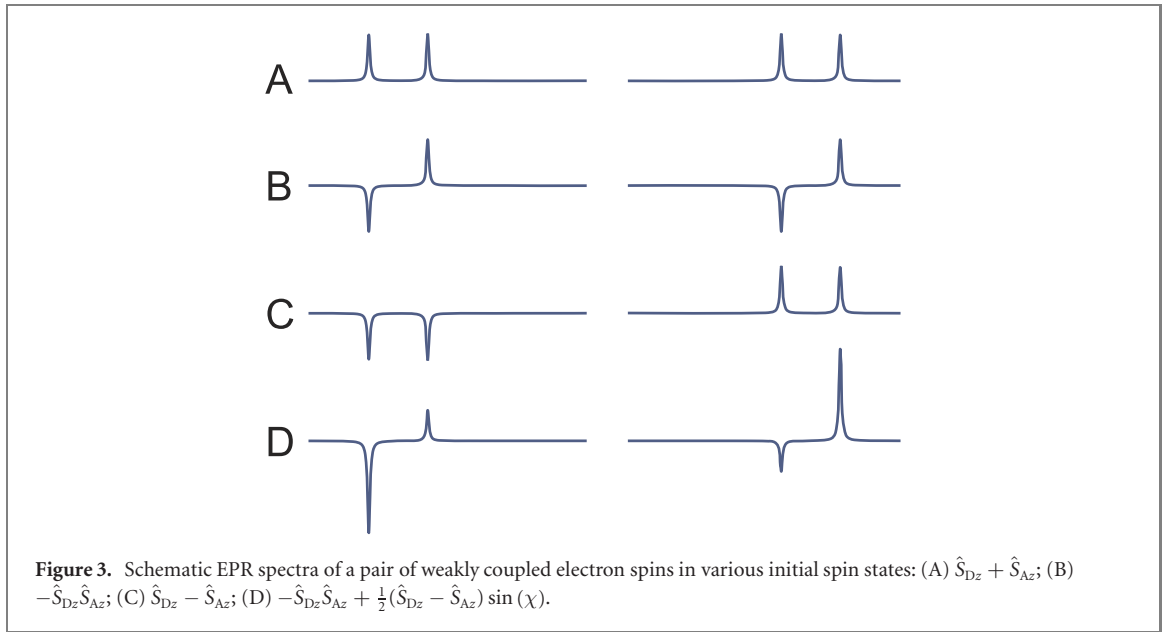
### 2.3. Magnetic field effects

We use the reaction scheme in figure 2 to assess the effects of including CISS in the radical pair model of magnetoreception in migratory birds. In cryptochrome, the donor and acceptor radicals are  $\text{TrpH}^{\bullet+}$  and  $\text{FAD}^{\bullet-}$ , respectively, formed by intra-protein electron transfer from a tryptophan residue (TrpH) to the photo-excited singlet state of the non-covalently bound chromophore, flavin adenine dinucleotide (FAD) [63]. This reaction is spin-selective ( $\hat{\rho}(0) = \hat{P}^I/N$ ) and is assumed to be much faster than subsequent processes. The radical pair undergoes coherent spin dynamics as a result of the Zeeman, hyperfine, dipolar and exchange interactions and either reverts to the ground state with rate constant  $k_R$  and spin-selectivity given by  $\hat{P}^R$ , or reacts non-spin-selectively with rate constant  $k_F$  to give a signalling state of the protein. The latter is thought to occur via deprotonation and subsequent reduction of the  $\text{TrpH}^{\bullet+}$  radical, and protonation of the  $\text{FAD}^{\bullet-}$  radical, to give a state of the cryptochrome with altered binding affinity to a signalling partner [69]. The ultimate yield of the signalling state once all radical pairs have reacted is

$$\Phi_F = k_F \int_0^\infty \text{Tr} [\hat{\rho}(t)] dt, \quad (16)$$

in which  $\hat{\rho}(t)$  is obtained from equation (13) and  $\text{Tr}$  is the trace over the electron and nuclear spin spaces.  $\Phi_F$  depends on the direction of the external magnetic field through the anisotropy of the hyperfine and dipolar interactions (and CISS when  $\chi \neq 0$ ) and is the source of the directional information from which the bird is assumed to derive a compass bearing. In what follows, we present this information as  $\Phi_R = 1 - \Phi_F$ , the yield of the recombination reaction.  $\Phi_R$  was calculated for a range of magnetic field directions ( $\theta, \phi$ ) (equation (7)) to obtain the following measure of the anisotropy of the reaction yield:

$$\Delta\Phi_R = \Delta\Phi_F = \max_{\theta, \phi}(\Phi_R) - \min_{\theta, \phi}(\Phi_R). \quad (17)$$



### 3. Results

#### 3.1. EPR detection of the CISS effect

Before presenting calculations of magnetic field effects, we discuss how CISS could manifest in the EPR spectra of radical pairs. We consider the simple case of a weakly coupled pair of electrons, with different  $g$ -values, an isotropic exchange interaction, and no dipolar or hyperfine interactions. At thermal equilibrium, its EPR spectrum would comprise four equally intense lines arranged as two well-separated doublets (figure 3(A)). If the same radical pair were created by electron transfer, with the magnetic field of the EPR spectrometer ( $z$ ) aligned parallel to the CISS quantization axis ( $Z$ ), the initial spin state,  $\hat{\rho}(0) = P^I/N$ , would be given by equation (10) with  $X, Y, Z$  replaced by  $x, y, z$ , respectively:

$$\hat{P}^I = \frac{1}{4}\hat{E} - \hat{S}_{Dz}\hat{S}_{Az} - \left(\hat{S}_{Dx}\hat{S}_{Ax} + \hat{S}_{Dy}\hat{S}_{Ay}\right) \cos(\chi) + \frac{1}{2}\left(\hat{S}_{Dz} - \hat{S}_{Az}\right) \sin(\chi). \quad (18)$$

When there is no CISS contribution ( $\chi = 0$ ),  $\hat{\rho}(0)$  comprises correlated two-spin polarization,  $\hat{S}_{Dz}\hat{S}_{Az}$ , and ZQC,  $(\hat{S}_{Dx}\hat{S}_{Ax} + \hat{S}_{Dy}\hat{S}_{Ay})$  [70, 71]. In a continuous wave, time-resolved EPR experiment, in which the magnetic field is swept in the presence of a constant microwave field, the oscillatory ZQ term would average to zero, leaving only the two-spin order [72]. The latter gives rise to the antiphase doublets that are characteristic of spin-correlated radical pairs (figure 3(B)) [72–76]. In the same experiment, the final term in equation (18), which would most clearly reveal a CISS effect, corresponds to the spectrum in figure 3(C) in which the doublet signals of the two radicals are equally and oppositely polarized. In general, when  $0 < \chi < \pi/2$ , the EPR spectrum (figure 3(D)) would be a linear combination of figures 3(B) and (C) with the inner pair of lines in the four-line spectrum stronger or weaker than the outer pair.

Now contrast this with the situation in which the spectrometer field is parallel to the molecular  $X$ -axis. The initial state is now given by:

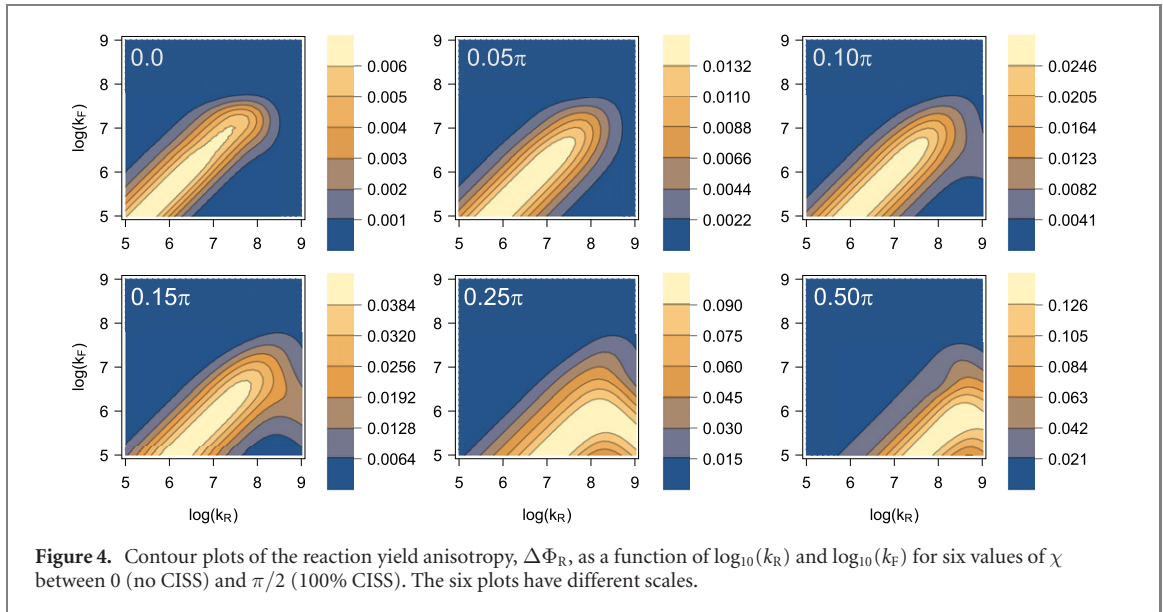
$$\hat{P}^I = \frac{1}{4}\hat{E} - \hat{S}_{Dx}\hat{S}_{Ax} - \left(\hat{S}_{Dy}\hat{S}_{Ay} + \hat{S}_{Dz}\hat{S}_{Az}\right) \cos(\chi) + \frac{1}{2}\left(\hat{S}_{Dx} - \hat{S}_{Ax}\right) \sin(\chi). \quad (19)$$

Again assuming that the coherences (i.e.  $x$  and  $y$  operator terms in equation (19)) would be averaged out in a continuous wave, time-resolved experiment, we are left with:

$$\hat{P}^I = \frac{1}{4}\hat{E} - \hat{S}_{Dz}\hat{S}_{Az} \cos(\chi), \quad (20)$$

so that the spectrum would resemble figure 3(B) rather than figure 3(D). Thus, one could expect a clear difference in the spectra when the magnetic field is parallel and perpendicular to the CISS axis.

The schematic spectra in figure 3 are for an ensemble of idealised, aligned radical pairs. In reality, one would need to consider also  $g$ -anisotropy, dipolar and hyperfine interactions [72, 73, 76]. Nevertheless, it might be possible to identify the contribution from the  $(\hat{S}_{Dz} - \hat{S}_{Az})$  term which would be diagnostic of a CISS component in the spin selectivity.



For a randomly oriented ensemble of radical pairs one would have to average over all directions of the magnetic field with respect to the CISS quantization axis. Rotating  $\hat{P}^I$  in equation (10) from the molecular frame ( $X, Y, Z$ ) to the laboratory frame ( $x, y, z$ ) gives:

$$\hat{\rho}(0) \propto \exp(-i\hat{S}_{DAy}\theta_C) \hat{P}^I \exp(i\hat{S}_{DAy}\theta_C) = \frac{1}{4}E - \hat{S}_{Dz}\hat{S}_{Az} [\cos^2(\theta_C) + \sin^2(\theta_C)\cos(\chi)] + \frac{1}{2}\cos(\theta_C)\sin(\chi)(\hat{S}_{Dz} - \hat{S}_{Az}) + \dots \quad (21)$$

where  $\theta_C$  is the angle between the magnetic field and the CISS axis,  $\hat{S}_{DAq} = \hat{S}_{Dq} + \hat{S}_{Aq}$ , and only the non-oscillating polarization terms, involving exclusively  $z$ -operators, have been retained. Spherical averaging causes the  $(\hat{S}_{Dz} - \hat{S}_{Az})$  term to vanish, leaving the average initial state:

$$\langle \hat{\rho}(0) \rangle \propto \frac{1}{4}E - \hat{S}_{Dz}\hat{S}_{Az} \left[ \frac{1}{3} + \frac{2}{3}\cos(\chi) \right]. \quad (22)$$

The spectrum would therefore comprise antiphase doublets (figure 3(B)), as expected in the absence of CISS. Any CISS effects would therefore be difficult to distinguish from the conventional RPM polarization.

Finally, we consider the electron spin echo envelope modulation (ESEEM) experiment which has been used extensively to determine the distance between radicals in radical pairs via the echo modulation arising from the electron dipolar coupling [71, 77–79]. Applying the pulse sequence  $(45^\circ)_x - \tau - (180^\circ)_x - \tau - \text{echo}$  [71, 80] to  $\hat{\rho}(0)$  in equation (21) gives the expected out-of-phase component from the  $\hat{S}_{Dz}\hat{S}_{Az}$  term,

$$-\frac{1}{4}\sin(2J\tau)(\hat{S}_{Dx} + \hat{S}_{Ax})[\cos^2(\theta_C) + \sin^2(\theta_C)\cos(\chi)], \quad (23)$$

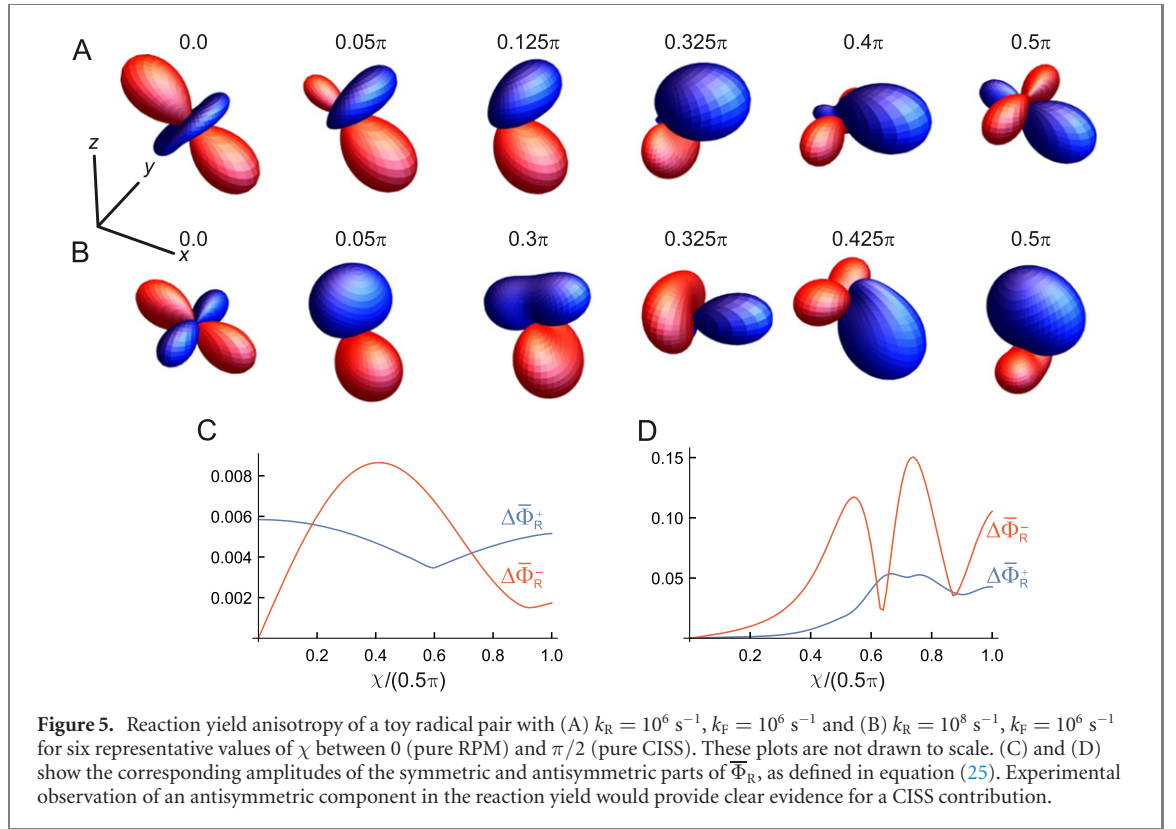
as well as a signal in the in-phase channel originating in the  $(\hat{S}_{Dz} - \hat{S}_{Az})$  term,

$$\frac{1}{2\sqrt{2}}\cos(2J\tau)(\hat{S}_{Dy} - \hat{S}_{Ay})\cos(\theta_C)\sin(\chi). \quad (24)$$

As before, the latter should be observable for an oriented sample but would average to zero for a randomly oriented collection of radical pairs.

### 3.2. Magnetic field effects—a toy radical pair

We have used the equations set out in section 2 to simulate the anisotropic reaction yields of radical pair reactions taking place in the geomagnetic field. The aim is to see how CISS might affect the signal that is thought to form the basis of magnetic compass sensing in migratory birds. We start with a basic ‘toy’ model and then proceed to a semi-realistic model of the  $[\text{FAD}^{\bullet-} \text{TrpH}^{\bullet+}]$  radical pair that gives rise to the magnetic field effects observed for purified cryptochromes [63, 81, 82] and which could be the magnetic sensor *in vivo* [3].



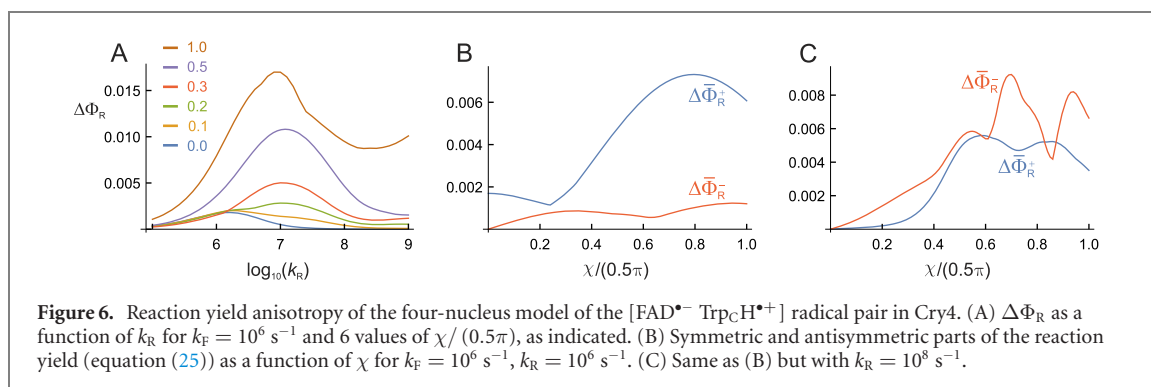
To get a clear initial impression of the changes that can be expected when CISS effects are included, we start with a radical pair with the simplest possible internal magnetic interactions. One radical contains a single spin-1/2 nucleus with an axial hyperfine interaction and principal components  $a_{xx} = a_{yy} = 0$ ,  $a_{zz} = 1.5 \text{ mT}$ . The other radical has no nuclear spins. The electron–electron dipolar interaction,  $D = -0.4 \text{ mT}$ , corresponds to the  $\sim 1.9 \text{ nm}$  separation of  $\text{FAD}^{\bullet-}$  and  $\text{Trp}_\text{C}\text{H}^{\bullet+}$  [83] where  $\text{Trp}_\text{C}\text{H}$  is the third of the four tryptophan residues that make up the electron transfer chain in avian Cry4 [84–88]. The CISS quantization axis is taken to be parallel to the dipolar axis (the line of centres of the two radicals) which makes an angle of  $45^\circ$  with the hyperfine  $z$ -axis. The exchange interaction of the two electrons in  $[\text{FAD}^{\bullet-} \text{Trp}_\text{C}\text{H}^{\bullet+}]$  is much smaller than  $D$  [86, 87]; we have taken it to be zero here. The external magnetic field strength is  $B = 50 \mu\text{T}$ , approximately the mean geomagnetic field. Spin relaxation was not included.

Figure 4 shows the reaction yield anisotropy ( $\Delta\Phi_R$ , equation (17)) plotted as a function of the rate constants,  $k_R$  and  $k_F$  for six values of the parameter  $\chi$ . Without CISS ( $\chi = 0$ ), the maximum anisotropy ( $\sim 0.007$ ) is small and occurs when  $k_R \approx k_F \leq 10^7 \text{ s}^{-1}$  [89]. As the contribution of CISS polarization in the formation and recombination steps is increased, the maximum value of  $\Delta\Phi_R$  increases (by a factor of  $\sim 20$  when  $\chi = \pi/2$ ) and now occurs when  $k_R \gg k_F$ .

Figures 5(A) and (B) show the shape of the anisotropy of the reaction yield,  $\Phi_R$ , for two sets of rate constants chosen to be close to the conditions that maximise  $\Delta\Phi_R$  when  $\chi = 0$  and  $\chi = \pi/2$ , respectively:  $(k_R, k_F) = (10^6, 10^6) \text{ s}^{-1}$  in figure 5(A) and  $(k_R, k_F) = (10^8, 10^6) \text{ s}^{-1}$  in figure 5(B). In this representation, the spherical average of the reaction yield,  $\langle\Phi_R\rangle$ , i.e. the part of  $\Phi_R$  that is independent of the magnetic field direction, has been subtracted to reveal the anisotropic component,  $\bar{\Phi}_R$ , which contains the directional information. Red/blue regions correspond to positive/negative  $\bar{\Phi}_R$ , i.e. reaction yields larger/smaller than  $\langle\Phi_R\rangle$ . It is clear from figures 5(A) and (B) that the shape of the anisotropy plots is strongly dependent on  $\chi$ , that exact inversion symmetry (see below) is only found for a pure RPM initial state (i.e. when  $\chi = 0$ ), and that there is a significant antisymmetric component even for small CISS contributions (e.g.  $\chi = 0.05\pi$ ). The latter can be seen more clearly in figures 5(C) and (D) where the symmetric ( $\Delta\bar{\Phi}_R^+$ ) and antisymmetric ( $\Delta\bar{\Phi}_R^-$ ) parts of  $\bar{\Phi}_R$ ,

$$\Delta\bar{\Phi}_R^\pm = \frac{1}{2} \left[ \max_{\theta, \phi} (\bar{\Phi}_R(\theta, \phi) \pm \bar{\Phi}_R(\theta + \pi, \phi)) - \min_{\theta, \phi} (\bar{\Phi}_R(\theta, \phi) \pm \bar{\Phi}_R(\theta + \pi, \phi)) \right], \quad (25)$$

are plotted as a function of  $\chi$ .



### 3.3. Magnetic field effects—a model of the FAD-TrpH radical pair

Although toy models have the potential to reveal some aspects of the spin dynamics of radical pairs, they can also be misleading. We have therefore performed similar calculations for a semi-realistic model of the  $[\text{FAD}^{\bullet-} \text{TrpC}^{\bullet+}]$  radical pair in Cry4. The two nuclei with the largest anisotropic hyperfine interactions in  $\text{FAD}^{\bullet-}$  (nitrogens N5 and N10) and in  $\text{TrpC}^{\bullet+}$  (N1 and its directly bonded proton H1) were included [60, 61]. The relative orientation of the isoalloxazine ring system of the FAD and the indole ring of  $\text{TrpC}^{\bullet+}$  was taken from the x-ray structure of pigeon Cry4 [83]. As in the case of the toy model, the electron–electron interactions were  $D = -0.4 \text{ mT}$  and  $J = 0$ , and the external magnetic field was again  $50 \mu\text{T}$ . The dipolar axis, again assumed parallel to the CISS quantization axis, was also taken from the pigeon Cry4 structure [83]. See the supplementary information (<https://stacks.iop.org/NJP/23/043032/mmedia>) for atom labelling schemes and hyperfine tensors.

Figure 6 shows some results of these simulations. In figure 6(A) we see that the reaction yield anisotropy grows as  $\chi$  is increased from 0 to  $\pi/2$ , and its maximum shifts from  $k_R \approx 10^6 \text{ s}^{-1}$  to  $k_R \approx 10^7 \text{ s}^{-1}$  when  $k_F \approx 10^6 \text{ s}^{-1}$ . The latter contrasts with the toy model for which the largest anisotropy was found when  $k_R \approx 10^8 \text{ s}^{-1}$  (for  $\chi = \pi/2$ ) (figure 4). We attribute this difference to the presence of hyperfine interactions in both radicals which facilitate the double spin-flip,  $\alpha_D\beta_A \leftrightarrow \beta_D\alpha_A$ , that must take place before recombination can occur (figure 1). Another difference between the two models is that  $\Delta\Phi_R$  is larger when one radical has no hyperfine interactions (see, e.g. references [60, 90–92]). Figures 6(B) and (C) show the symmetric and antisymmetric parts of  $\bar{\Phi}_R$  for  $k_R = 10^6 \text{ s}^{-1}$ ,  $k_F = 10^6 \text{ s}^{-1}$  and  $k_R = 10^8 \text{ s}^{-1}$ ,  $k_F = 10^6 \text{ s}^{-1}$ , respectively. In both cases there is a significant antisymmetric component even for small values of  $\chi$ .

## 4. Discussion

The results shown in figures 4–6 have three main consequences relevant to the radical pair hypothesis of avian magnetoreception.

- One of the many unresolved aspects of the cryptochrome hypothesis is whether radical pair reactions could be sensitive enough to the direction of the geomagnetic field to form the basis of a viable magnetic compass sensor [3, 60, 61, 93, 94]. Factors with the potential to boost the signal are therefore of interest. When radical pairs are formed in, and recombine from, the singlet state ( $\chi = 0$ ), the directional information encoded in the yield of the signalling state arises exclusively from the hyperfine and dipolar interactions. When CISS is present ( $\chi \neq 0$ ), spin-selective initial and reactive states both depend on the direction of the magnetic field in the molecular frame. As seen in figures 4, 5(C) and (D) and 6, this additional source of anisotropy results in increases in  $\Delta\Phi_R$  that could translate into a more precise compass bearing.
- When  $\chi = 0$ , the formation of a radical pair in a pure singlet state, equation (1), can be followed immediately by spin-allowed back electron transfer to the ground state, equation (3). By contrast, in the opposite extreme ( $\chi = \pi/2$ ), a radical pair formed in the  $\alpha_D\beta_A$  state would have to wait for spin-mixing to populate the  $\beta_D\alpha_A$  state before it could revert to the ground state (figure 1). The consequence (figures 4 and 6(A)) is that the largest values of  $\Delta\Phi_R$  are found when  $k_R \gg k_F$  instead of  $k_R \approx k_F$ . Effective competition between the recombination and forward reactions, requires a larger value of  $k_R$  to compensate for the time required to reach the reactive  $\beta_D\alpha_A$  state. The presence of CISS could, therefore, relax the normal criterion for optimal magnetic sensitivity ( $k_R \approx k_F$ ) [95] giving evolution greater scope for maximising the performance of the compass sensor.
- One of the arguments in favour of a radical pair magnetosensor over a mechanism based on magnetic nanoparticles (reviewed in [96–100]) is that migratory songbirds are indifferent to the polarity of the

magnetic field, instead using the angle between the field direction and the horizontal to distinguish equatorward and poleward directions [101, 102]. This axial compass is distinct from a hypothetical polarity compass based on single-domain crystals of e.g. magnetite,  $\text{Fe}_3\text{O}_4$ . The observation of polar magnetic responses [103] has been used as an argument against a radical pair sensory mechanism in those species.

The projection operators  $\hat{P}^I$  and  $\hat{P}^R$  used here to merge CISS spin selectivity with the conventional RPM lack time-reversal symmetry (see section 2.2) so that reaction yields are no longer expected to be even functions of the magnetic field,  $\omega$ . This is the reason why, as soon as  $\chi \neq 0$ , we see antisymmetric contributions to the reaction yield anisotropy in figures 5 and 6(B) and (C).

## 5. Conclusions

On the assumption that CISS effects can arise in the electron transfer reactions of organic radical pairs, we have proposed a formulation for merging CISS spin selectivity with that which arises in the conventional RPM.

The principal change in the initial state of a radical pair when CISS effects are included is the spin-polarization term  $\hat{S}_{Dz} - \hat{S}_{Az}$  which is absent when only the RPM is considered. Because the polarization is quantized along an axis in the molecular frame it should be detectable in measurements on oriented samples, either as differences in continuous wave, time-resolved EPR spectra recorded with the spectrometer field parallel or perpendicular to the CISS axis or as the in-phase signal in an ESEEM experiment. CISS contributions to the EPR spectra of randomly oriented samples are likely to be small. We hope this analysis may stimulate experimental searches for CISS effects in the EPR spectra of radical pairs and be of use to those who may have already embarked on such investigations.

In the context of avian magnetoreception, there are three principal ways in which CISS changes the response of a radical pair to the geomagnetic field. (a) The reaction yield signal that encodes the field direction is more strongly anisotropic and could therefore afford a more precise compass bearing or allow the compass to operate at lower light levels [93]. (b) The signal has a different dependence on the reaction rate constants, and so could give greater scope for evolutionary optimization. (c) In contrast to behavioural experiments showing that migratory songbirds have an axial compass [101, 102], the directional information from a radical pair sensor with a significant CISS component would no longer be invariant to reversal of the magnetic field. Although CISS effects, if they can occur in radical pair reactions, offer the possibility of evolving a more sensitive or precise compass, the associated lack of field-inversion symmetry has not hitherto been observed in behavioural experiments. Additionally, it may no longer be safe to argue that a polar magnetic response in an animal behaviour experiment is evidence against a radical pair mechanism.

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## Data availability statement

The data that support the findings of this study are available upon reasonable request from the authors.

## Appendix. Parallel between CISS and ALTADENA

The formation of a radical pair in a spin-polarized  $\alpha_D\beta_A$  or  $\beta_D\alpha_A$  state from singlet state precursors is reminiscent of the ALTADENA (Adiabatic Longitudinal Transport After Dissociation Engenders Net Alignment) effect in which molecules, formed by reaction with para-hydrogen ( $p\text{-H}_2$ , a nuclear singlet state,  $2^{-1/2}[\alpha_1\beta_2 - \beta_1\alpha_2]$ ) in a weak magnetic field, are transferred adiabatically into the strong magnetic field of an NMR spectrometer [66–68]. Transport from a situation in which the nuclear spin–spin interaction dominates the nuclear Zeeman interaction to one in which the Zeeman interactions are much larger than the spin–spin coupling results in the population of only one of the four high-field nuclear spin states,  $\alpha_1\beta_2$  or  $\beta_1\alpha_2$ . At least phenomenologically, it appears that the CISS effect can be thought of in the

same way. One starts with the electronic singlet state of the photo-excited precursor in which the electron exchange interaction is very large, and ends in a radical pair state that has very weak electron–electron coupling. The difference from ALTADENA, is that with CISS there is no obvious parallel to the strong NMR field. However, the origin of CISS is often described in terms of an effective magnetic field, arising from the motion of the electrons in a helical electrostatic potential, which leads via spin–orbit coupling to the spin polarization.

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