Antisymmetric Couplings Enable Direct Observation of Chirality in Nuclear Magnetic Resonance Spectroscopy

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Abstract

Here we demonstrate that a term in the nuclear spin Hamiltonian, the antisymmetric $J$-coupling, is fundamentally connected to molecular chirality. We propose and simulate a nuclear magnetic resonance (NMR) experiment to observe this interaction and differentiate between enantiomers without adding any additional chiral agent to the sample. The antisymmetric $J$-coupling may be observed in the presence of molecular orientation by an external electric field. The opposite parity of the antisymmetric coupling tensor and the molecular electric dipole moment yields a sign change of the observed coupling between enantiomers. We show how this sign change influences the phase of the NMR spectrum and may be used to discriminate between enantiomers.
Molecular chirality is an extremely important yet often difficult to measure property. Chiral molecules form many of the basic building blocks of living organisms, such as L-amino acids and D-sugars. Because of this biochirality, the effect of chiral pharmaceuticals can differ greatly between enantiomers [1], leading to great interest in enantioselective synthesis and methods to analyze chiral products [2]. Molecular chirality is also of interest in the study of fundamental symmetries [3], where parity violation in molecules is predicted but has not yet been observed [4–6]. The search for spectroscopic techniques to probe chirality is a field of great interest where many proposals and experiments may be found in the recent literature [7–10]. Meanwhile, liquid-state NMR is the preeminent technique for chemical analysis owing to its generality and chemical specificity. The introduction of direct chiral detection to NMR, without the need to add derivatizing agents to the sample, would be a major step forward in the field of chiral analysis. Several proposals exist for direct observation of chirality via an electric-field-induced pseudoscalar term in the NMR Hamiltonian. These involve either the detection of an induced oscillating molecular electric dipole moment [11–14] or a magnetic dipole signal induced via application of an electric field [15–17].

In this Letter, we present a method for detection of chirality using liquid-state zero-field NMR, taking advantage of the antisymmetric spin-spin coupling. By analyzing the symmetry properties of this interaction we first demonstrate the connection between the antisymmetric J-coupling tensor and molecular chirality. We then propose and simulate a prototype experiment using established techniques and predict a signal amplitude comparable to previous zero-field NMR experiments. Although not yet observed, terms in the Hamiltonian arising from the antisymmetric J-coupling are predicted in a wide array of molecules from symmetry considerations [18, 19], perturbational calculations [20, 22] and from quantum chemical calculations [23, 24]. In addition to the connection to chirality made here, measurement of the antisymmetric J-coupling has been suggested as a means to observe molecular parity violation [3], which is predicted to cause a first-order energy shift to the antisymmetric J-coupling.

The J-coupling coupling Hamiltonian (in frequency units) for two spins may be written:

\[ H = I_1 \cdot J \cdot I_2. \] (1)

\( I_1 \) and \( I_2 \) are vector spin operators, and \( J \) contains the spatial coordinates. The total nuclear spin-spin coupling tensor may include terms from magnetic dipole-dipole coupling as well as
the $J$-coupling, but the antisymmetric terms we are interested in can only arise from the $J$-
 coupling. This is because the $J$-coupling involves indirect interactions through electron spins,
which need not have local inversion symmetry while the magnetic dipole-dipole coupling is
symmetric under inversions and is described by a rank-2 irreducible spherical tensor. The $J$
tensor describes the coupling between two angular momenta and may be decomposed into
irreducible spherical tensor components up to rank-2:

$$ J = J^{(0)} + J^{(1)} + J^{(2)}, $$

where the $J^{(1)}$ component is antisymmetric with respect to the spatial coordinates. Since
$J^{(1)}$ is traceless, its components average to zero for unoriented molecules, and thus cannot
be observed in isotropic liquids. Alignment techniques such as liquid crystals and stretched
gels can revive rank-2 terms, but to observe rank-1 interactions molecular orientation is
required (see Supplemental Material). Solid-state studies in principle could detect antisym-
metric couplings, but in practice have insufficient resolution [25]. Here we propose molecular
orientation by an applied electric field [26, 27].

$J^{(1)}$ has three independent quantities, $J^{(1)}_{\alpha\beta}$, where $\alpha, \beta = x, y, z$:

$$ J^{(1)} = \begin{pmatrix}
0 & J_{xy} & J_{xz} \\
-J_{xy} & 0 & J_{yz} \\
-J_{xz} & -J_{yz} & 0
\end{pmatrix}. $$

It has been shown that the number of independent components of the $J$ tensor depend on
the local symmetry of the spin pair, and that three independent components of $J^{(1)}$ exist
only if the two nuclear sites have local C$_1$ symmetry [18], which includes all chiral molecules
and meso compounds.

We now address the question: “Given $J^{(1)}$ in a molecule-fixed coordinate system for a
chiral molecule, how will it be different for the complementary enantiomer?” The transfor-
mation between enantiomers may be visualized as a reflection through a plane containing
the molecular electric dipole vector (which we will call the z-direction). The electric dipole
will remain unchanged, as required by the orienting field, while the xy-component of $J^{(1)}$ will
acquire a negative sign ($J_{xy} \rightarrow J_{x(-y)} = -J_{xy}$) (Fig. 1). This sign change is a manifestation
of the pseudovector nature of $J^{(1)}$. Since we are considering oriented liquids rapidly rotat-
ing around the z-axis, the time-averaged coupling tensor has only the single xy-component
which is scaled by the degree of orientation (see Supplemental Material):

\[
\overline{J}^{(1)} \propto \begin{pmatrix}
0 & \pm J_{xy} & 0 \\
\mp J_{xy} & 0 & 0 \\
0 & 0 & 0
\end{pmatrix},
\]

where the constant of proportionality comes from the degree of orientation and the sign depends on the handedness of the molecule. A measurement of the sign of \( J_{xy} \), which is equal to \( J_0^{(1)} \) in the spherical basis, yields the chiral signal. We note that \( \overline{J}_0^{(1)} \) is the projection of \( J^{(1)} \) along the director axis, scaled by the degree of orientation. Since the orientation is defined by the molecular electric dipole moment, the measured quantity is proportional to \( J^{(1)} \cdot E \), which gives a pseudoscalar term in the Hamiltonian. The remainder of this work outlines methods to observe the sign of \( J_0^{(1)} \).

The antisymmetric \( J \)-coupling Hamiltonian does not commute with the Zeeman Hamiltonian unless the spins have the same Larmor frequency. In typical high-field NMR an identical Larmor frequency would imply that the spins be chemically equivalent, which is incompatible with local \( C_1 \) symmetry.

We therefore propose an experiment based on zero-field NMR \([29]\) of two coupled unlike spin-\( \frac{1}{2} \) nuclear spins in a chiral molecule oriented by an electric field. Zero-field NMR spectroscopy is the detection of NMR signals generated by spin-spin couplings in the absence of an applied magnetic field, thus giving an identical Larmor frequency of zero for all spins. The spin-spin coupling signals are generally in the sub-kHz regime and are detected through means such as atomic vapor cell magnetometers. In isotropic media, the signal corresponds to \( J^{(0)} \). We show how an additional signal, whose sign and magnitude depend on \( J_0^{(1)} \), may be observed along an axis orthogonal to the usual signal. The general principle is that the three axes defined by the initial spin state, detector axis, and electric field form a coordinate system with a definite handedness that yields chiral information (Fig. 2).

We define bilinear spherical tensor operators for coupled spins \( I_1 \) and \( I_2 \):

\[
T_k^{(q)} = \sum_{k_1=-1}^{1} \sum_{k_2=-1}^{1} C_{q,k_1,k_2,k_1,k_2}^{q,k} J_1^{(1)} I_1^{(1)} J_2^{(1)} I_2^{(1)},
\]

where \( C_{q,k_1,k_2,k_1,k_2}^{q,k} \) are Clebsch-Gordan coefficients. With these definitions, we can write the time-averaged coupling Hamiltonian in a more useful form:
FIG. 1. a) Schematic chiral molecule and $J^{(1)}$ tensor components for the $^1{H}^{13}{C}$ J-coupling. $\mu$ is the molecular electric dipole which is oriented along the z-axis by an applied electric field. b) After reflection through the xz plane, the electric dipole is unchanged, but the xy-component of $J^{(1)}$ has now gained a negative sign. In both situations the molecule is rapidly rotating around the z-axis, so only the xy (red) component of $J^{(1)}$ is observable.

$$H = I_1 \cdot \bar{J} \cdot I_2 = \sum_{q=0}^{2} \sum_{k=-q}^{q} (-1)^k J^{(q)}_k T^{(q)}_{-k}.$$  \hfill (6)

However, since there is rapid motion around the z-axis, this reduces to (see Supplemental Material):

$$H = \sum_{q=0}^{2} J^{(q)}_0 T^{(q)},$$ \hfill (7)

where the sign of $J^{(1)}_0$ depends on the handedness of the molecule as shown above. As will be shown in the simulations, the presence of rank-2 couplings (either from the rank-2 $J$ tensor or residual dipolar couplings) give small first-order frequency shifts \cite{28} while $J^{(1)}_0$
FIG. 2. Schematic representation of a zero-field NMR experiment for chiral discrimination. a) Without electric field orientation, we have pure singlet and triplet states and no signal emerges. b) With electric field orientation, the singlet and $|0\rangle$ states mix and the coherences become observable as oscillating transverse magnetization along the x-axis. The choice of initial magnetization, electric field vector, and transverse detector vector define a handed coordinate system that yields chiral information in the sign of the detected signal. The $\alpha$ and $\beta$ states exhibit small energy shifts from $J^{(1)}_0$ and residual dipolar couplings.

gives a small second-order shift (Fig. 2b) but none of these interfere with chiral discrimination. We therefore neglect rank-2 terms in the analytical discussion and write the relevant Hamiltonian:

$$H = J^{(0)}_0 T^{(0)}_0 + J^{(1)}_0 T^{(1)}_0.$$  \hspace{1cm} (8)

In our NMR experiment, the observable quantity is the magnetization along the detector
axis, chosen here to be the x-axis, and represented by the operator $M_x$. Note that for this experiment there will also be a large achiral signal along the y-axis. In the spherical basis, the observable operator is:

$$ M_x = \sum_i \gamma_i I_{x,i} = \sum_i \gamma_i (I^{(1)}_{+1,i} + I^{(1)}_{-1,i}) $$  \hspace{1cm} (9)

and the observable signal which is given by:

$$ \langle M_x(t) \rangle(t) = \text{Tr}\{M_x^\dagger \rho(t)\}. $$ \hspace{1cm} (10)

In the absence of $J^{(1)}_0$, the energy eigenstates are three triplet states $|+1\rangle$, $|0\rangle$, $|-1\rangle$ and a singlet $|S\rangle$ (Fig. 2a). We consider $J^{(1)}_0$ as a perturbation, which is valid when $|J^{(1)}_0| << |J^{(0)}|$ as is the case for weakly oriented molecules. We note, however, that weak orientation is not a necessary condition for chiral discrimination. While the $|+1\rangle$ and $|-1\rangle$ states are not affected by the presence of $J^{(1)}_0$, the $|0\rangle$ and $|S\rangle$ states are mixed so that the first-order eigenstates are:

$$ |\alpha\rangle = (|S\rangle - i\frac{J^{(1)}_0}{2J^{(0)}}|0\rangle) \frac{1}{N} $$ \hspace{1cm} (11)

and

$$ |\beta\rangle = (|0\rangle - i\frac{J^{(1)}_0}{2J^{(0)}}|S\rangle) \frac{1}{N} $$ \hspace{1cm} (12)

where $N$ is a normalization factor. (See Fig. 2b with energy shifts from $J^{(1)}_0$ and residual dipolar couplings) The presence of a term linear in $J^{(1)}_0$ enables the creation of observable signals also linear in $J^{(1)}_0$. We choose an experimentally realizable initial condition containing coherences involving $|\alpha\rangle$ and $|\beta\rangle$ (arrows in Fig. 2b). Our chosen initial density operator is

$$ \rho(0) = \frac{1}{4} + \frac{B_p h}{4kT} \left[ \frac{\gamma_1 + \gamma_2}{2} (-I_{y,1} + I_{y,2}) + \frac{\gamma_1 - \gamma_2}{2} (-I_{y,1} - I_{y,2}) \right] $$ \hspace{1cm} (13)

which corresponds to prepolarization of spins in a field $B_p$ along the y-axis at temperature $T$ followed by inversion of spin 1. $k$ is the Boltzmann constant. This initial condition gives the following predicted signal in the zero-field NMR experiment (See Supplemental Material for a full calculation of matrix elements and coherence amplitudes):
\[
\langle M_x(t) \rangle = \frac{B_p \hbar \gamma_1 \gamma_2 J_0^{(1)}}{kTN^2J^{(0)}} \left[ \cos(\omega_\alpha t) - \cos(\omega_\beta t) \right],
\]

(14)

where \( \omega_\alpha = \frac{E_\alpha - E_{\pm 1}}{\hbar} \) and \( \omega_\beta = \frac{E_\beta - E_{\pm 1}}{\hbar} \).

In our simulations, we consider the case of a chiral molecule with two spin-\( \frac{1}{2} \) nuclei (\(^{13}\)C and \(^{1}\)H) with \( J^{(0)} = 100 \) Hz, typical of a one-bond \(^{1}\)H-\(^{13}\)C \(J\)-coupling. Since antisymmetric \(J\)-couplings are similar in magnitude to the isotropic rank-0 term [23], we assume a residual \(J_0^{(1)} \) of 1 Hz, corresponding to a orientational order parameter of \( \sim 10^{-2} \), typical of electric-field orientation experiments[27]. For a one-bond \(^{13}\)C-\(^{1}\)H coupling with this degree of orientation, the alignment induced by the electric field results in a residual dipolar coupling of \( \sim 0.7 \) Hz (Supplemental Material) which results in small frequency shifts. Oscillating magnetization emerges along the x-axis with the sign of the signal determined by the sign of \(J_0^{(1)} \) (Fig. 3a,b), thereby distinguishing right and left enantiomers. The two curves in Fig. 3a sum to zero at all points, meaning that no signal will be observed in a racemic mixture.
FIG. 3. a) Predicted x-magnetization for positive (black) and negative (red) $J_0^{(1)}$ with a magnitude of 1 Hz, $J_0^{(0)} = 100$ Hz, and a residual dipolar coupling of 0.7 Hz. High frequency oscillations result from coherences between the $|\pm 1\rangle$ and $|\beta\rangle$ states while low frequency oscillations result from coherences between $|\pm 1\rangle$ and $|\alpha\rangle$. b) Fourier transform of (a) shows the phase relationship between peaks in the frequency spectrum for each enantiomer.
The signal predicted by Eqn. 14 is proportional to \( \frac{J^{(1)}}{J^{(0)}} \), which scales the signal by the degree of orientation. It is useful to compare the amplitude of this chiral signal to the achiral signal that evolves along the y-axis. This achiral signal is the “usual” zero-field NMR signal [29] and is given by:

\[
\langle M_y(t) \rangle = -\frac{(\gamma_1^2 - \gamma_2^2)(1 + \left(\frac{J^{(1)}}{J^{(0)}}\right)^2)}{N^2} \left[ \cos(\omega_\alpha t) + \cos(\omega_\beta t) \right]
\]

so that the relative amplitude of \( M_x \) and \( M_y \) is \( \frac{4\gamma_1 \gamma_2 \frac{J^{(1)}}{J^{(0)}}}{(\gamma_1^2 - \gamma_2^2)(1 + (\frac{J^{(1)}}{J^{(0)}})^2)} \). For our experiment this ratio is 0.0108, essentially in agreement with the exact value of 0.0106 (Supplemental Material). Therefore we expect a signal reduced by a factor of \( 10^{-2} \) compared to standard zero-field NMR. A typical 100 \( \mu \)L sample contains \( \sim 10^{21} \) \(^1\)H-\(^{13}\)C pairs and, assuming a spherical geometry, the standard zero-field signal signal corresponds to a field of \( \sim 50 \) fT at a distance of 0.5 cm from the center of the sphere when prepolarized in 2 Tesla field at 300 K. Given a magnetometer sensitivity of 15 fT/\( \sqrt{\text{Hz}} \) [30], and accounting for the \( 10^{-2} \) factor, we expect an acquisition time of approximately 5 minutes to achieve a signal to noise ratio greater than one.

We note that systematic errors may occur when the three axes (magnetizing field, electric field, and detector) are not orthogonal or when the pulse field is not collinear with the detector. In this case, some component of the large achiral signal will emerge along the detector axis. Such systematic errors could potentially overwhelm the desired chiral signal. However, we note that the desired signal is proportional to produce \( J^{(1)} \cdot E \), whose sign can be changed by reversal of the electric field. The spurious achiral signal has no such dependence and thus may be cancelled by subtracting spectra acquired with reversed electric fields.

In conclusion, we demonstrate that molecular chirality is a directly observable property in NMR spectroscopy through antisymmetric terms in the spin-spin coupling Hamiltonian. Electric-field orientation in liquids provides a method to observe these terms, owing to the interplay between the pseudovector nature of the antisymmetric coupling and the polar vector nature of a molecular electric dipole. The apparent sign change of the spin coupling directly determines the sign of observed NMR signals, enabling chiral discrimination without adding additional chiral agents to the sample. Since the signal depends on pairwise spin-spin couplings, the spectrum gives local information and shows to what extent the
local electronic structure is enantiomer-dependent. Furthermore, the observation of anti-symmetric J-couplings will provide a new technique to search for molecular parity violation. This proposal combines previously established methods and in principle requires no new techniques. However, design constraints of our current zero-field NMR spectrometers do not allow the use of electric-field orientation cells. We therefore present this work as a guide to the design of future experiments.

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