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Measuring chirality in NMR in the presence of a static electric field

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The scalar Hamiltonian of nuclear spins in the presence of a static electric field supports chirality. However, the eigenvalues of the Hamiltonian are not chiral; hence, chirality is not manifested in the usual NMR experiment. In this work, we show that the magnetization response to certain radio frequency pulse sequences exhibits chirality as well as handedness. © *2008 American Institute of Physics*. [DOI: 10.1063/1.2888555]

I. INTRODUCTION

The magnetic responses of molecules are, as Buckingham put it, “blind” to chirality.[1] To be more precise, NMR parameters, such as the chemical shift[2] and spin-spin couplings, are in general identical for a given set of enantiomers (*L* and *R*) in a magnetic field. Only the presence of chiral influences such as other chiral molecules, chiral potentials, and/or parity violations can give rise to a pseudoscalar addition to the chemical shift and spin-spin coupling and thereby generate differences in the NMR parameters between enantiomers in a magnetic field.[3,4] Previously, the standard method of generating different magnetic responses for a given enantiomer was to create the diastereomer, where in a racemic mixture there would now be two resonances in the NMR spectrum (*LL*+*RR* and *LR*+*RL*) as opposed to one resonance. However, this is to be expected since diastereomers are not mirror images of each other; hence, the magnetic responses are not identical.

Recently Buckingham[1] and Buckingham and Fischer[5] suggested that the addition of a static as well as an ac electric field would remove the chiral blindness of NMR. Harris and Jameson gave a simple derivation of how a static electric field removes chiral blindness in NMR, where they obtained a scalar spin Hamiltonian that exhibited both a pseudoscalar chemical shift and a pseudoscalar spin-spin coupling constant using only simple parity and time reversal arguments.[6] In this article, the detection of the pseudoscalar (hence chiral) portion of the isotropic chemical shift and spin-spin coupling constants will be investigated, and a simple set of experiments will be proposed where the signal generated in the experiment arises only from the chiral terms in the spin Hamiltonian. In what follows, the problem of measuring the pseudoscalar chemical shift and spin-spin coupling for a given molecular species in an isotropic medium will be treated separately since the effects are additive.

II. MEASURING THE CHIRAL CHEMICAL SHIFT

In the presence of both a static electric and a magnetic field, the Hamiltonian, which exhibits chirality, is given by[6]

$$\frac{\hat{H}}{\hbar} = -(1-\sigma)\mathbf{B}\cdot\mathbf{S} + \sigma_C \mathbf{B}\times\mathbf{E}\cdot\mathbf{S}. \tag{1}$$

The pseudoscalar chemical shift σ_C vanishes for achiral molecules (unlike σ) and is of opposite sign for *L* and *R* enantiomers. Note that $\sigma_C|\mathbf{E}|$ has the same dimensions as σ.

The eigenvalues of $\hat{H}$ in Eq. (1) depend only on even powers of $\sigma_C|\mathbf{E}|$. This is because the pseudoscalar term in $\hat{H}$ is perpendicular to the Zeeman and scalar shift terms in $\hat{H}$. Since peaks in the observed spectrum correspond to transitions between eigenstates, both *L* and *R* enantiomers will produce peaks at the same transition frequency. Thus, the transition frequencies for $\hat{H}$ in Eq. (1) will exhibit chiral blindness and thus cannot be used to distinguish between *L* and *R* enantiomers. However, the eigenstates of $\hat{H}$ do depend on odd powers of $\sigma_C|\mathbf{E}|$. Therefore, in order to remove the chiral blindness in NMR, the portion of the eigenstates that is linear in the electric field must be measured.

Consider the case where the magnetic field is pointing along the $+\hat{z}$ axis and where the electric field is given by $\mathbf{E}=|\mathbf{E}|(\cos(\phi)\hat{y}+\sin(\phi)\hat{x})$. In this case, the Hamiltonian can be written as

$$\begin{aligned}\frac{\hat{H}}{\hbar} &= \omega_Z S_Z - \frac{|\mathbf{E}||\mathbf{B}|\sigma_c}{\hbar}(\cos(\phi)S_X - \sin(\phi)S_Y) \\ &= \omega_Z S_Z - \omega_c(\cos(\phi)S_X - \sin(\phi)S_Y),\end{aligned} \tag{2}$$

where $\hbar\omega_c = |\mathbf{E}||\mathbf{B}|\sigma_c$ and ω_Z is the sum of the Zeeman and the isotropic chemical shift terms.

The equilibrium density matrix for $\mathbf{E}=|\mathbf{E}|\hat{y}$ is given by the Boltzmann distribution

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$$\rho_{\mathrm{eq}} = \frac{\exp[\hat{H}/k_BT]}{\mathrm{trace}[\exp[\hat{H}/k_BT]]} \equiv \frac{1}{2}\hat{1} + \tanh\left(\frac{\hbar\lambda}{2k_BT}\right)(\cos(\theta_i)S_Z - \sin(\theta_i)S_X), \qquad (3)$$

where $\lambda = \sqrt{\omega_Z^2 + \omega_c^2}$ and $\cos(\theta_i) = \omega_Z/\lambda$ and $\sin(\theta_i) = \omega_c/\lambda$.

For detection due to induction in the receiver coil (typical in high-field NMR), the voltage induced in the receiver coil is proportional to the time derivate of the transverse magnetization (i.e., dc components of the magnetization do not contribute to the observed signal). After a θ_p pulse is applied about the $\hat{x}$ axis to the equilibrium density matrix, the time dependent transverse magnetization is given by

$$\begin{aligned}\langle S_X(t)\rangle_{E\hat{y}} &= \frac{\mathrm{trace}[U(t)U_p\rho_{\mathrm{eq}}U_p^\dagger U^\dagger(t)S_X]}{\mathrm{trace}[S_X^2]} \\ &= \tanh\left(\frac{\hbar\lambda}{2k_BT}\right)(\cos^2(\theta_i)\sin(\theta_i)\cos(\lambda t) \\ &\quad \times(\cos(\theta_p) - 1) + \sin(\lambda t)\cos^2(\theta_i)\sin(\theta_p)) \\ &\quad - \tanh\left(\frac{\hbar\lambda}{2k_BT}\right)(\sin^3(\theta_i) + \cos(\theta_p)\cos^2(\theta_i)\sin(\theta_i)),\end{aligned} \qquad (4)$$

$$\begin{aligned}\langle S_Y(t)\rangle_{E\hat{y}} &= \frac{\mathrm{trace}[U(t)U_p\rho_{\mathrm{eq}}U_p^\dagger U^\dagger(t)S_Y]}{\mathrm{trace}[S_Y^2]} \\ &= -\tanh\left(\frac{\hbar\lambda}{2k_BT}\right)\left(\sin(\lambda t)\sin(2\theta_i)\sin^2\left(\frac{\theta_p}{2}\right) \right. \\ &\quad \left. + \cos(\lambda t)\cos(\theta_i)\sin(\theta_p)\right),\end{aligned} \qquad (5)$$

where $[U_p = \exp(-i\theta_p S_X)]$ and $[U(t) = \exp(-it\hat{H}/\hbar)]$. The observed signal is proportional to the time derivate of the transverse magnetization [so the last, time-independent term in Eq. (4) for $\langle S_X(t)\rangle$ does not contribute]. Now the terms linear in $\sin(\theta_i) = \omega_c/\lambda$ contain the information about handedness. These "chiral terms" can be separated from the "achiral" terms by performing another experiment, this time with the electric field pointing along the negative $\hat{y}$ axis, $\mathbf{E} = -|\mathbf{E}|\hat{y}$. Subtracting the signals (or in this case the magnetizations) obtained from the two experiments gives

$$\begin{aligned}\overline{\langle S_X(t)\rangle} &= \frac{1}{2}(\langle S_X(t)\rangle_{E\hat{y}} - \langle S_X(t)\rangle_{-E\hat{y}}) \\ &= \tanh\left(\frac{\hbar\lambda}{2k_BT}\right)\cos^2(\theta_i)\sin(\theta_i)\cos(\lambda t)(\cos(\theta_p) - 1) \\ &= \tanh\left(\frac{\hbar\lambda}{2k_BT}\right)\frac{\omega_Z^2\omega_c}{\lambda^3}\cos(\lambda t)(\cos(\theta_p) - 1),\end{aligned} \qquad (6)$$

$$\begin{aligned}\overline{\langle S_Y(t)\rangle} &= \frac{1}{2}(\langle S_Y(t)\rangle_{E\hat{y}} - \langle S_Y(t)\rangle_{-E\hat{y}}) \\ &= -\tanh\left(\frac{\hbar\lambda}{2k_BT}\right)\sin(\lambda t)\sin(2\theta_i)\sin^2\left(\frac{\theta_p}{2}\right) \\ &= -2\tanh\left(\frac{\hbar\lambda}{2k_BT}\right)\frac{\omega_Z\omega_c}{\lambda^2}\sin(\lambda t)\sin^2\left(\frac{\theta_p}{2}\right).\end{aligned} \qquad (7)$$

Thus, by measuring the transverse magnetization, the sign of the signal will be different for different enantiomers. Note, however, that the amplitude of the signal is scaled by a factor of ω_c/ω_Z relative to the signal obtained after a single 90° excitation pulse (a 90°-acquire experiment). Thus, in order to get the same signal to noise ratio as that obtained from a simple 90°-acquire experiment, the measurement would have to be performed $(\omega_Z/\omega_c)^2$ times, which in general would be prohibitively large. For example, if $\omega_Z/\omega_c \approx 10^7$, 10^{14} experiments would be required to get the same signal to noise ratio as from a single 90°-acquire experiment. Assuming a reduction in the signal to noise ratio of a factor of 100 relative to the 90°-acquire experiment would still be satisfactory and assuming a repetition time of 1 s for each experiment, the total experimental time would be approximately 317.1 years! In order to observe the pseudoscalar chemical shift, the repetition times would need to be reduced to the order of microseconds to tens of microseconds, which would then require experimental times on the order of 2.77–27.7 h. This would require using spin systems with incredibly short T_1 relaxation times or, conversely, systems with very long relaxation times where many measurements could be performed as the system relaxes, similar to recent Carl-Purcell-Meiboom-Gill (CPMG) pulse sequences which were used to increase sensitivity[7] (such experiments should be feasible in this case since it is only the sign of the signal that one is interested in). Finally, for $\omega_c/\omega_Z \geqslant 10^{-8}$, measurement of the slight deviation of the bulk magnetization from the direction of the static magnetic field caused by the pseudoscalar chemical shift in Eq. (3) could be performed by using a radiation damping spin amplifier.[8] It should be noted that the measurement of magnetization derivatives of enantiomers is akin to measuring circular dichroism and that the chiral portion of the response vanishes for a racemic mixture.[9]

III. MEASURING THE CHIRAL HOMONUCLEAR SPIN-SPIN COUPLING CONSTANT IN HIGH-FIELD NMR

We now consider two homonuclear but chemically inequivalent $I=1/2$ spins (e.g., the two ^{13}C nuclei in ^{13}CClFH$-^{13}$CH$_3$) which are scalar coupled in the presence of a static electric and a magnetic field. The Hamiltonian is given by (neglecting the pseudoscalar chemical shift terms)[5]

$$\begin{aligned}\frac{\hat{H}}{\hbar} &= -(1-\sigma_1)\mathbf{I}_1\cdot\mathbf{B} - (1-\sigma_2)\mathbf{I}_2\cdot\mathbf{B} + J\mathbf{I}_1\cdot\mathbf{I}_2 \\ &\quad + J_{\mathrm{chiral}}\mathbf{E}\cdot\mathbf{I}_1\times\mathbf{I}_2,\end{aligned} \qquad (8)$$

where $J_{\mathrm{chiral}}|\mathbf{E}|$ has the same units as J.

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The eigenvalues of $\hat{H}$ in Eq. (8) again contain only even powers of J_{chiral} and, hence, the frequencies of all spectroscopic transitions measured in a NMR spectrum will not exhibit chirality. However, the eigenstates of $\hat{H}$, as in the previous section on the pseudoscalar chemical shift, do contain odd powers of J_{chiral}, which can be used to remove the chiral blindness of NMR. In the following, a simple pulse sequence will be presented where the signal is proportional $J_{\text{chiral}}|\mathbf{E}|$. The sign of the signal can therefore determine the handedness of the sample being measured.

Consider a magnetic field pointing along the $+\hat{z}$ axis and an electric field $\mathbf{E}=|\mathbf{E}|\hat{z}$. The Hamiltonian is given by

$$\frac{\hat{H}}{\hbar}=\omega_1 I_{Z1}+\omega_2 I_{Z2}+J\mathbf{I}_1\cdot\mathbf{I}_2+J_{\text{chiral}}|\mathbf{E}|(I_{X1}I_{Y2}-I_{Y1}I_{X2}), \tag{9}$$

where ω_1 and ω_2 are the resonance frequencies (chemical shifts plus Zeeman) for spins 1 and 2, respectively. Note that the homonuclear pseudoscalar spin-spin coupling in Eq. (9) has the same form as the antisymmetric spin-spin coupling.[10]

The initial density matrix in high field can be approximated as

$$\rho_i\approx\left(\frac{\hat{1}}{2}+\lambda_1 I_{Z1}\right)\left(\frac{\hat{1}}{2}+\lambda_2 I_{Z2}\right)$$

$$\approx\frac{\hat{1}}{4}+\frac{\lambda_{\text{av}}}{2}(I_{Z1}+I_{Z2})+\frac{\lambda_\Delta}{2}(I_{Z1}-I_{Z2}), \tag{10}$$

where

$$\lambda_{\text{av}}=\tfrac{1}{2}(\lambda_1+\lambda_2),\quad \lambda_\Delta=\tfrac{1}{2}(\lambda_1-\lambda_2),$$

and

$$\lambda_{1(2)}=\tanh(\hbar\omega_{1(2)}/(2k_BT)).$$

Note that $|\lambda_{\text{av}}/\lambda_\Delta|\approx|(\omega_1+\omega_2)/(\omega_1-\omega_2)|\gg 1$. In writing ρ_i in Eq. (10), terms like $J\mathbf{I}_1\cdot\mathbf{I}_2$, $\lambda_1\lambda_2 I_{Z1}I_{Z2}$, etc., have been neglected. Signal arising from these two-spin terms can be removed by using a generalized "phase" cycle, so they will not be considered in the following. Since λ_{av} is much greater than λ_Δ, we at least want part of the desired signal to originate from the λ_{av} term in Eq. (10).

Now consider the following experiment: A selective inversion pulse is initially applied to spin 2, $P(\pi)_X^2\equiv\exp(-i\pi I_{X2})$, followed by a $P(\pi/2)_Y$ on both spins to create the initial density matrix

$$\rho(0)=\frac{\lambda_{\text{av}}}{2}(I_{X1}-I_{X2})+\frac{\lambda_\Delta}{2}(I_{X1}+I_{X2}). \tag{11}$$

Note that in order to selectively excite either spin, the chemical shift difference should be greater than the inverse relaxation time, i.e., $|(\omega_1-\omega_2)/2\pi|\gg 1/T_2\approx 1$ Hz.

As before, the signal is proportional to the transverse magnetization,

$$\langle I_{X(Y)}(t)\rangle=\frac{\text{trace}[(I_{X1(Y1)}+I_{X2(Y2)})U(t)\rho(0)U^\dagger(t)]}{\text{trace}[(I_{X1(Y1)}+I_{X2(Y2)})^2]}. \tag{12}$$

The propagator, $U(t)=\exp(-it\hat{H}/\hbar)$, is given by

$$U(t)=\begin{pmatrix}\exp\left(-it\left(\omega_\Sigma+\frac{J}{4}\right)\right) & 0 & 0 & 0\\ 0 & \exp\left(i\frac{Jt}{4}\right)\nu^*(t) & \exp\left(i\frac{Jt}{4}\right)\sin\left(\frac{J_Dt}{2}\right)\zeta^* & 0\\ 0 & -\exp\left(i\frac{Jt}{4}\right)\sin\left(\frac{J_Dt}{2}\right)\zeta & \exp\left(i\frac{Jt}{4}\right)\nu(t) & 0\\ 0 & 0 & 0 & \exp\left(-it\left(\frac{J}{4}-\omega_\Sigma\right)\right)\end{pmatrix}, \tag{13}$$

where $\omega_\Sigma=(\omega_1+\omega_2)/2$, $\Delta\omega=\omega_1-\omega_2$, and

$$J_D=\sqrt{(J_{\text{chiral}}|\mathbf{E}|)^2+J^2+(\Delta\omega)^2},$$

$$\nu(t)=\left(\cos\left(\frac{J_Dt}{2}\right)+i\sin\left(\frac{J_Dt}{2}\right)\frac{\Delta\omega}{J_D}\right), \tag{14}$$

$$\zeta=\frac{J_{\text{chiral}}|\mathbf{E}|+iJ}{J_D}.$$

The signal is given by

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$$\begin{aligned}\langle I_X(t)\rangle_{E\hat{z}} &= -\frac{\lambda_{\mathrm{av}}}{2}\sin(\omega_\Sigma t)\sin\left(\frac{J_D t}{2}\right)\left(\frac{J_{\mathrm{chiral}}|\mathbf{E}|}{J_D}\sin\left(\frac{Jt}{2}\right)+\frac{\Delta\omega}{J_D}\cos\left(\frac{Jt}{2}\right)\right)+\frac{\lambda_\Delta}{2}\cos(\omega_\Sigma t)\left(\cos\left(\frac{Jt}{2}\right)\cos\left(\frac{J_D t}{2}\right)\right.\\ &\quad\left.+\frac{J}{J_D}\sin\left(\frac{Jt}{2}\right)\sin\left(\frac{J_D t}{2}\right)\right),\\ \langle I_Y(t)\rangle_{E\hat{z}} &= \frac{\lambda_{\mathrm{av}}}{2}\cos(\omega_\Sigma t)\sin\left(\frac{J_D t}{2}\right)\left(\frac{J_{\mathrm{chiral}}|\mathbf{E}|}{J_D}\sin\left(\frac{Jt}{2}\right)+\frac{\Delta\omega}{J_D}\cos\left(\frac{Jt}{2}\right)\right)+\frac{\lambda_\Delta}{2}\sin(\omega_\Sigma t)\left(\frac{J}{J_D}\sin\left(\frac{Jt}{2}\right)\sin\left(\frac{J_D t}{2}\right)\right.\\ &\quad\left.+\cos\left(\frac{Jt}{2}\right)\cos\left(\frac{J_D t}{2}\right)\right).\end{aligned}\tag{15}$$

Thus, if the experiment is repeated again but this time with the electric field pointing along the negative $\hat{z}$ axis, $\mathbf{E}=-|\mathbf{E}|\hat{z}$, and this signal is subtracted from the previous signal in Eq. (15), the resulting signal is given by

$$\begin{aligned}\overline{\langle I_X(t)\rangle} &= \frac{1}{2}(\langle I_X(t)\rangle_{E\hat{z}}-\langle I_X(t)\rangle_{-E\hat{z}})\\ &= -\frac{\lambda_{\mathrm{av}}}{2}\frac{J_{\mathrm{chiral}}|\mathbf{E}|}{J_D}\sin(\omega_\Sigma t)\sin\left(\frac{J_D t}{2}\right)\sin\left(\frac{Jt}{2}\right),\\ \overline{\langle I_Y(t)\rangle} &= \frac{1}{2}(\langle I_Y(t)\rangle_{E\hat{z}}-\langle I_Y(t)\rangle_{-E\hat{z}})\\ &= \frac{\lambda_{\mathrm{av}}}{2}\frac{J_{\mathrm{chiral}}|\mathbf{E}|}{J_D}\cos(\omega_\Sigma t)\sin\left(\frac{J_D t}{2}\right)\sin\left(\frac{Jt}{2}\right).\end{aligned}\tag{16}$$

Thus, the sign of the signal is determined again by J_{chiral}, which will be opposite for different enantiomers. As in the case of σ_c, the signal is scaled by a factor of $J_{\mathrm{chiral}}|\mathbf{E}|/J_D$; however, since J_D does not contain the Zeeman energy (i.e., $J_D \approx J$), the scaling is not as serious as with the case of σ_c. This is due to the fact that the homonuclear pseudoscalar spin-spin coupling in Eq. (9) commutes with the Zeeman Hamiltonian (unlike the pseudoscalar chemical shift term).

IV. MEASURING THE CHIRAL HETERONUCLEAR SPIN-SPIN COUPLING CONSTANT IN LOW-FIELD NMR

We now consider the case of measuring the heteronuclear pseudoscalar spin-spin coupling. Applying the same pulse sequence as in the homonuclear case discussed in the previous section would produce a significantly smaller signal [Eq. (16)] since the difference in the Zeeman frequency is quite large for the heteronuclear case; for example, the resulting signal [Eq. (16)] for a ^{13}C-H system in a magnetic field of around 10 T would be at least a factor of 3×10^{-9} smaller than the signal from the homonuclear case since $|J_D/2\pi| \approx |\Delta\omega/2\pi| \approx 3\times10^{8}$ Hz. This is due to the fact that the heteronuclear pseudoscalar spin-spin coupling does not commute with the Zeeman interaction. To avoid this reduction in signal, the spins would need to evolve in a low magnetic field such that $|\Delta\omega| \leqslant J$, which would require performing the experiment in a magnetic field of less than 0.03 G (as a point of reference, the earth's magnetic field is currently around 0.3–0.6 G).

Magnetic resonance experiments performed at such low-field strengths run into two significant problems. First, the initial polarization that is used in a NMR experiment is in general proportional to the magnetic field strength [Eq. (10)]. Second, the sensitivity of Faraday detection is quite poor at low magnetic field strengths since it is also proportional to the Zeeman frequency. One experimentally feasible resolution to the above two problems would be to use a NMR shuttling experiment.[11] In such an experiment, the spins, which are initially polarized by a large magnetic field (say, pointing along the $+\hat{z}$ axis), are adiabatically removed from the large magnetic field to a small fringe field (although the Zeeman energy in the fringe field is still large compared to the spin-spin coupling strength). Next, an additional "canceling" magnetic field is nonadiabatically turned on to cancel the fringe magnetic field for a time t, during which time the spin system evolves under zero- or low-field conditions. The canceling field is then nonadiabatically turned off, and the spin system is then shuttled adiabatically back up to high field for detection. During the shuttling process, only the component of the magnetization along the static magnetic field direction is preserved. Once in high field, an excitation pulse can be applied in order to measure the stored magnetization, which contains information about the zero- or low-field spin dynamics. Such spin shuttling experiments have been used in the past for obtaining zero-field NMR and NQR spectra.[11,12]

Application of a NMR shuttling experiment can be used to measure the heteronuclear pseudoscalar spin-spin coupling as follows: First, the spins, which are initially polarized in the presence of a large magnetic field pointing high field, are shuttled out of the magnet to zero- or low-field magnetic field. Once in low or zero field, a $P(\pi/2)_Y$ is applied to both spins, which then evolve for a time t_1 under $\hat{H}$ (making the substitutions $\omega_1=\omega_I$, $\omega_2=\omega_S$, $\mathbf{I}_1=\mathbf{I}$, and $\mathbf{I}_2=\mathbf{S}$ in Eq. (9)]. It should be noted that during the low- or zero-field evolution period, zero-field composite pulses[13] would have to be used in order that the same rotation can be applied to both spins due to their different gyromagnetic ratios. After evolving under $\hat{H}$, a $P(\pi/2)_X$ is applied to both spins in order to store the

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$\hat{y}$ magnetization (which contains a term linear in the heteronuclear pseudoscalar spin-spin coupling) along the $+\hat{z}$ axis, and the spins are shuttled back to high field. Any residual transverse magnetization is assumed to be dephased during the shuttling back to high field (if not, such magnetization can be readily phase cycled away). Once back in high field, the I and/or the S magnetization can be detected after application of an excitation pulse. The magnetization after the shuttling back to high field for such an experiment is given by

$$\begin{aligned}\langle I_Z(t)\rangle_{E\hat{z}} &= \frac{\text{trace}[I_Z\rho(t_1)]}{\text{trace}[(I_Z)^2]}\\ &= \frac{\lambda_I}{2}\cos\left(\frac{Jt_1}{2}\right)\left(\sin(\omega_\Sigma t_1)\cos\left(\frac{J_Dt_1}{2}\right)\right.\\ &\quad\left.+\frac{\Delta\omega}{J_D}\sin\left(\frac{J_Dt_1}{2}\right)\cos(\omega_\Sigma t_1)\right)\\ &\quad+\frac{\lambda_S}{2}\sin\left(\frac{Jt_1}{2}\right)\sin\left(\frac{J_Dt_1}{2}\right)\\ &\quad\times\left(\frac{J}{J_D}\sin(\omega_\Sigma t_1)-\frac{J_{\text{chiral}}|\mathbf{E}|}{J_D}\cos(\omega_\Sigma t_1)\right),\end{aligned} \tag{17}$$

$$\begin{aligned}\langle S_Z(t_1)\rangle_{E\hat{z}} &= \frac{\text{trace}[S_Z\rho(t_1)]}{\text{trace}[(S_Z)^2]}\\ &= \frac{\lambda_S}{2}\cos\left(\frac{Jt_1}{2}\right)\left(\sin(\omega_\Sigma t_1)\cos\left(\frac{J_Dt_1}{2}\right)\right.\\ &\quad\left.-\frac{\Delta\omega}{J_D}\sin\left(\frac{J_Dt_1}{2}\right)\cos(\omega_\Sigma t_1)\right)\\ &\quad+\frac{\lambda_I}{2}\sin\left(\frac{Jt_1}{2}\right)\sin\left(\frac{J_Dt_1}{2}\right)\\ &\quad\times\left(\frac{J_{\text{chiral}}|\mathbf{E}|}{J_D}\cos(\omega_\Sigma t_1)+\frac{J}{J_D}\sin(\omega_\Sigma t_1)\right),\end{aligned}$$

where

$$\begin{aligned}\rho(t_1) &= \tfrac{1}{2}P(\pi/2)_X U(t_1)P(\pi/2)_Y\\ &\quad\times(\lambda_I I_Z+\lambda_S S_Z)P(\pi/2)_{-Y}U^\dagger(t_1)P(\pi/2)_{-X}\end{aligned} \tag{18}$$

and where the propagator, $U(t)$, is given in Eq. (13) after making the appropriate substitutions. Note that $\Delta\omega$ in Eq. (17) is the difference in Zeeman frequency while at low- or zero-field conditions during the t_1 interval; thus, the chiral terms in Eq. (17) are not scaled that severely by the difference in Zeeman energy. If the experiment is repeated again but this time with the electric field pointing along the negative $\hat{z}$ axis, $\mathbf{E}=-|\mathbf{E}|\hat{z}$, and this signal is subtracted from the previous signal in Eq. (17), the resulting signal is given by

$$\begin{aligned}\overline{\langle I_Z(t_1)\rangle} &= \frac{1}{2}(\langle I_Z(t_1)\rangle_{E\hat{z}}-\langle I_Z(t_1)\rangle_{-E\hat{z}})\\ &= -\frac{\lambda_S}{2}\frac{J_{\text{chiral}}|\mathbf{E}|}{J_D}\cos(\omega_\Sigma t_1)\sin\left(\frac{J_Dt_1}{2}\right)\sin\left(\frac{Jt_1}{2}\right),\end{aligned} \tag{19}$$

$$\begin{aligned}\overline{\langle S_Z(t_1)\rangle} &= \frac{1}{2}(\langle S_Z(t_1)\rangle_{E\hat{z}}-\langle S_Z(t_1)\rangle_{-E\hat{z}})\\ &= \frac{\lambda_I}{2}\frac{J_{\text{chiral}}|\mathbf{E}|}{J_D}\cos(\omega_\Sigma t_1)\sin\left(\frac{J_Dt_1}{2}\right)\sin\left(\frac{Jt_1}{2}\right).\end{aligned}$$

Thus, the sign of the signal is determined again by J_{chiral}, which will be opposite for different enantiomers. By evolving the system under zero- or low-field conditions, the scaling of the signal in Eq. (19) will be of the same order as the homonuclear case [Eq. (16)].

V. CONCLUSIONS

In the presence of a static, homogeneous, electric field, a nuclear spin Hamiltonian supports chirality. Chirality is manifested in both a pseudoscalar chemical shift and a pseudoscalar spin-spin coupling. However, the eigenvalues of the Hamiltonian contain only even powers of the pseudoscalar parameters and hence do not exhibit chirality. Therefore, chiral blindness is not removed by the usual NMR experiments.

Using simple pulse sequences, we have shown how the component of the magnetization vector linear in the chiral parameters can be isolated and measured separately, thereby enabling one to determine if a sample is handed using NMR. Although measurement of the pseudoscalar chemical shift would be rather experimentally demanding, measurement of the homonuclear pseudoscalar spin-spin couplings might be more experimentally feasible since they commute with the Zeeman interaction when the electric field is applied parallel to the magnetic field. For heteronuclear spin systems, the heteronuclear pseudoscalar spin-spin coupling does not commute with the Zeeman interaction, which requires using a NMR shuttling experiment in order for the spin system to evolve under low- or zero-field conditions. Finally, because the signal from the proposed experiments is signed, like circular dichroism and unlike diastereoisomerism, a racemic mixture will show no evidence of chirality.

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[2] In a NMR experiment, the chemical shift, determined with respect to some reference substance, is related to the nuclear magnetic shielding σ: Chemical shift$=(\sigma_{\text{ref}}-\sigma)/(1-\sigma_{\text{ref}})$. In this paper, we seek the observable and use "chemical shift" while expressing relations in terms of the nuclear magnetic shielding σ.

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