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Direct chiral discrimination in NMR spectroscopy

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Abstract

Conventional nuclear magnetic resonance spectroscopy is unable to distinguish between the two mirror-image forms (enantiomers) of a chiral molecule. This is because the NMR spectrum is determined by the chemical shifts and spin–spin coupling constants which – in the absence of a chiral solvent – are identical for the two enantiomers. We discuss how chirality may nevertheless be directly detected in liquid-state NMR spectroscopy: In a chiral molecule, the rotating nuclear magnetic moment induces an electric dipole moment in the direction perpendicular to itself and to the permanent magnetic field of the spectrometer. We present computations of the precessing electric polarization following a $\pi/2$ pulse. Our estimates indicate that the electric polarization should be detectable in favourable cases. We also predict that application of an electrostatic field induces a chirally sensitive magnetization oscillating in the direction of the permanent magnetic field. We show that the electric-field-perturbed chemical shift tensor, the nuclear magnetic shielding polarizability, underlies these chiral NMR effects.

Keywords: NMR; Nuclear magnetic shielding polarizability; Chiral molecules

1. Introduction

Nuclear magnetic resonance (NMR) spectroscopy is an important technique for determining the structure of molecules in solution. NMR can, however, not be used to determine the absolute configuration of chiral molecules in a pure liquid, as the chemical shifts and spin–spin coupling constants are identical for the two enantiomers of a chiral molecule. All NMR-based methods for chiral discrimination have therefore required that the chiral solute be in the presence of a chiral reagent or solvent [1–3].

A recent paper [4] shows that chirality may actually be directly observable in NMR spectroscopy without the need for a chiral auxiliary. The coherent precession of nuclear spins following the application of a $\pi/2$ pulse to a chiral sample is predicted to give rise to a rotating electric polarization. The electric polarization is due to molecular electric dipole moments induced by the rotating nuclear magnetic moment in the presence of the spectrometer's magnetic field. We show that the parity-odd nuclear-magnetic polarizability pseudoscalar that gives rise to the polarization in an optically active liquid has the same form as the isotropic part of the chemical shift tensor linearly perturbed by a uniform static electric field [5–7]. We use finite field calculations to compute its value for ^{1}H nuclei in hydrogen peroxide, H_2O_2, and for ^{1}H, ^{19}F, and ^{13}C nuclei in chlorofluoroacetic acid, CHClF(COOH). We deduce that the chiral electric polarization should be detectable in favourable cases.

We also show that in a chiral liquid application of an electrostatic field at right angles to the permanent magnetic field $B_z^{(0)}$ can give rise to an oscillating magnetization in the direction of $B_z^{(0)}$.

2. Theoretical background

In NMR, a $\pi/2$ pulse rotates the equilibrium magnetization from the direction of the magnetic field $B_z^{(0)}$ into the

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xy-plane at right angles to the field. The magnetization precesses around $B_z^{(0)}$ at the resonant angular frequency ω and its free induction decay is recorded by a coil whose axis we take to be parallel to the x-axis. The NMR spectrum is obtained through Fourier transformation of the signal. The NMR spin Hamiltonian is given by

$$H = -\sum_{\mathrm{N}} m_\alpha^{(\mathrm{N})}\left(\delta_{\alpha\beta} - \sigma_{\alpha\beta}^{(\mathrm{N})}\right)B_\beta^{(0)} + \sum_{\mathrm{N}<\mathrm{N}'} hJ_{\alpha\beta}^{(\mathrm{NN}')}I_\alpha^{(\mathrm{N})}I_\beta^{(\mathrm{N}')}, \quad (1)$$

where the magnetic moment of nucleus N is

$$m_\alpha^{(\mathrm{N})} = \hbar\gamma^{(\mathrm{N})}I_\alpha^{(\mathrm{N})}, \quad (2)$$

and where $\hbar I_\alpha^{(\mathrm{N})}$ is its angular momentum and $\gamma^{(\mathrm{N})}$ its magnetogyric ratio. $\sigma_{\alpha\beta}^{(\mathrm{N})}$ is the shielding tensor and $J_{\alpha\beta}^{(\mathrm{NN}')}$ is the spin–spin coupling tensor of the pair of nuclei N and N′. For isotropic media, Eq. (1) becomes

$$H = -\sum_{\mathrm{N}} m_z^{(\mathrm{N})}(1-\sigma^{(\mathrm{N})})B_z^{(0)} + \sum_{\mathrm{N}<\mathrm{N}'} hJ^{(\mathrm{NN}')}\boldsymbol{I}^{(\mathrm{N})}\cdot\boldsymbol{I}^{(\mathrm{N}')} \quad (3)$$

and the isotropic components of the shielding tensor and the spin–spin coupling tensor are:

$$\sigma^{(\mathrm{N})} = \frac{1}{3}\left(\sigma_{xx}^{(\mathrm{N})} + \sigma_{yy}^{(\mathrm{N})} + \sigma_{zz}^{(\mathrm{N})}\right) \equiv \frac{1}{3}\sigma_{\alpha\alpha}^{(\mathrm{N})}, \quad (4)$$

$$J^{(\mathrm{NN}')} = \frac{1}{3}J_{\alpha\alpha}^{(\mathrm{NN}')}. \quad (5)$$

The equilibrium magnetization along the direction of the field of the spectrometer is

$$\left\langle M_z^{(\mathrm{N})}\right\rangle = N^{(\mathrm{N})}\hbar\gamma^{(\mathrm{N})}(1-\sigma^{(\mathrm{N})})\left\langle I_z^{(\mathrm{N})}\right\rangle, \quad (6)$$

where

$$\left\langle I_z^{(\mathrm{N})}\right\rangle \approx I^{(\mathrm{N})}(I^{(\mathrm{N})}+1)\hbar\gamma^{(\mathrm{N})}B_z^{(0)}/(3kT) \quad (7)$$

and $N^{(\mathrm{N})}$ is the number density of N-containing molecules. For protons at a resonance frequency $\omega/2\pi$ of 600 MHz, $B_z^{(0)} = 14.1$ T and at 300 K $\langle I_z^{(\mathrm{H})}\rangle \approx 2.4\times10^{-5}$ and $\langle M_z^{(\mathrm{H})}\rangle \approx 7\times10^{-3}\,\mathrm{A\,m^{-1}}$, where we have assumed that the number density in a pure liquid is $N^{(\mathrm{N})} \approx 10^{28}\,\mathrm{m}^{-3}$.

After application of the $\pi/2$ pulse, the magnetization precesses around $B_z^{(0)}$, such that the mean nuclear magnetization at time t has x and y components:

$$M_x^{(\mathrm{N})}(t) = -\left\langle M_z^{(\mathrm{N})}\right\rangle \sin\omega t\exp(-t/T_2), \quad (8)$$

$$M_y^{(\mathrm{N})}(t) = \left\langle M_z^{(\mathrm{N})}\right\rangle \cos\omega t\exp(-t/T_2), \quad (9)$$

T_2 is the dephasing relaxation time and is of the order of 1 s for a proton in a liquid. The exact resonance frequency $\omega/2\pi = |\gamma^{(\mathrm{N})}|B_z^{(\mathrm{N})}/2\pi$ depends on the chemical environment of the nucleus:

$$B_z^{(\mathrm{N})} = (1-\sigma^{(\mathrm{N})})B_z^{(0)}. \quad (10)$$

The shielding tensor $\boldsymbol{\sigma}^{(\mathrm{N})}$ ($\sigma^{(\mathrm{N})} \approx 10^{-5}$ for protons) can be thought of as giving either the reduction of the magnetic field at N due to the surrounding electrons or the reduction of the magnetic moment of the molecule $\Delta\boldsymbol{m}^{(\mathrm{N})}$ from the nuclear magnetic moment $\boldsymbol{m}^{(\mathrm{N})}$ due to the current induced in the electronic cloud by $\boldsymbol{m}^{(\mathrm{N})}$:

$$\Delta B_\alpha^{(\mathrm{N})} = -\sigma_{\alpha\beta}^{(\mathrm{N})}B_\beta^{(0)}, \quad (11)$$

$$\Delta m_\alpha^{(\mathrm{N})} = -\sigma_{\beta\alpha}^{(\mathrm{N})}m_\beta^{(\mathrm{N})}. \quad (12)$$

Perturbation theory may be used to derive expressions for the diamagnetic (dia) and the paramagnetic (para) components of the shielding tensor [8]. For a closed-shell molecule in the state $|0\rangle$,

$$\sigma_{\alpha\beta}^{(\mathrm{N})} = \sigma_{\alpha\beta}^{(\mathrm{N})(\mathrm{dia})} + \sigma_{\alpha\beta}^{(\mathrm{N})(\mathrm{para})}, \quad (13)$$

$$\sigma_{\alpha\beta}^{(\mathrm{N})(\mathrm{dia})} = \frac{\mu_0}{4\pi}\frac{e^2}{2m_\mathrm{e}}\langle 0|\sum_i\left(r_i^2\delta_{\alpha\beta} - r_{i_\alpha}r_{i_\beta}\right)r_i^{-3}|0\rangle = \langle 0|\hat{\sigma}_{\alpha\beta}^{(\mathrm{N})(\mathrm{dia})}|0\rangle, \quad (14)$$

$$\sigma_{\alpha\beta}^{(\mathrm{N})(\mathrm{para})} = -\frac{\mu_0}{4\pi}\frac{e^2\hbar}{m_\mathrm{e}^2}\sum_{p\neq0}\frac{\omega_p\,\mathrm{Re}\left\{\langle 0|\sum_j l_{j_\alpha}/r_j^3|p\rangle\langle p|\sum_i l_{i_\beta}|0\rangle\right\}}{\omega_p^2-\omega^2}, \quad (15)$$

where $\hbar\boldsymbol{l}_i$ is the orbital angular momentum operator of electron i about the origin of coordinates at nucleus N, $\hbar\omega_p$ is the excitation energy from $|0\rangle$ to $|p\rangle$, and where $\omega_p/(\omega_p^2-\omega^2)$ may be approximated by ω_p^{-1} since $\omega/\omega_p \sim 10^{-8}$.

Because $\boldsymbol{\sigma}^{(\mathrm{N})}$ and $\boldsymbol{J}^{(\mathrm{NN}')}$ are even under parity (space-inversion), it follows that NMR is unable to distinguish between the enantiomers of a chiral molecule (except in a chiral solvent). In order to achieve direct chiral discrimination in NMR spectroscopy, an odd-parity property needs to be linked to the magnetic moment of the nucleus.

3. Chirality in NMR

We consider whether a nuclear magnetic moment can induce an electric dipole moment, and whether the converse, the application of an electric field, has an effect on NMR spectra.

3.1. Induced rotating electric moment

Let us enquire if a nuclear magnetic moment $\boldsymbol{m}^{(\mathrm{N})}$ can induce an electric dipole moment $\Delta\boldsymbol{\mu}^{(\mathrm{N})}$ in the molecule [4]:

$$\Delta\mu_\alpha^{(\mathrm{N})} = \xi_{\alpha\beta}^{(\mathrm{N})}m_\beta^{(\mathrm{N})} + \xi_{\alpha\beta}^{\prime(\mathrm{N})}\dot{m}_\beta^{(\mathrm{N})}/\omega. \quad (16)$$

Perturbation expressions for the nuclear-magnetic polarizabilities are:

$$\xi_{\alpha\beta}^{(\mathrm{N})} = -\frac{\mu_0}{4\pi}\frac{2e}{m_\mathrm{e}}\sum_{p\neq0}\frac{\omega_p\,\mathrm{Re}\left\{\langle 0|\mu_\alpha|p\rangle\langle p|\sum_j l_{j_\beta}/r_j^3|0\rangle\right\}}{\omega_p^2-\omega^2}, \quad (17)$$

$$\xi_{\alpha\beta}^{\prime(\mathrm{N})} = \frac{\mu_0}{4\pi}\frac{2e\omega}{m_\mathrm{e}}\sum_{p\neq0}\frac{\mathrm{Im}\left\{\langle 0|\mu_\alpha|p\rangle\langle p|\sum_j l_{j_\beta}/r_j^3|0\rangle\right\}}{\omega_p^2-\omega^2}. \quad (18)$$

Equations equivalent to the transpose of (17) and (18) were derived by Lazzeretti and Zanasi [9] for their magnetoelectric shielding tensors $\lambda_{\alpha\beta}$ and $\hat{\lambda}_{\alpha\beta}$ that give the magnetic field induced at a nucleus by an oscillating electric field.

Time-reversal symmetry requires that $\xi^{(\mathrm{N})}_{\alpha\beta}$ is zero for closed-shell molecules, but in a magnetic field $\boldsymbol{B}^{(0)}$

$$\xi^{(\mathrm{N})}_{\alpha\beta}(\boldsymbol{B}^{(0)}) = \xi^{(\mathrm{N})}_{\alpha\beta\gamma}B^{(0)}_{\gamma} \tag{19}$$

is non-vanishing. The operator for the magnetic field at the nucleus N is

$$B^{(\mathrm{N})}_{\alpha} = B^{(0)}_{\alpha} - \frac{\mu_0}{4\pi}\frac{e\hbar}{m_\mathrm{e}}\sum_j l_{j_\alpha}/r_j^3 - \hat{\sigma}^{(\mathrm{N})(\mathrm{dia})}_{\alpha\beta}B^{(0)}_{\beta}, \tag{20}$$

$\xi^{(\mathrm{N})}_{\alpha\beta\gamma}$ can be obtained from Eq. (20) and the formula (17) for $\xi^{(\mathrm{N})}_{\alpha\beta}$ using wavefunctions and energies perturbed by the static magnetic field:

$$|p\rangle_{\boldsymbol{B}^{(0)}} = |p\rangle + \sum_{q\neq p}\frac{\langle q|\boldsymbol{m}|p\rangle\cdot\boldsymbol{B}^{(0)}}{\hbar\omega_{qp}}|q\rangle + \cdots, \tag{21}$$

$$\hbar(\omega_p)_{\boldsymbol{B}^{(0)}} = \hbar\omega_p - \langle p|\boldsymbol{m}|p\rangle\cdot\boldsymbol{B}^{(0)} + \cdots, \tag{22}$$

where the magnetic moment operator $\boldsymbol{m} = -\frac{e\hbar}{2m_\mathrm{e}}\sum_j \boldsymbol{l}_j$, and where $\hbar\omega_{qp} = \hbar(\omega_q - \omega_p)$ is the excitation energy of the transition $q \leftarrow p$. The contamination of the wavefunctions $|0\rangle$ and $|p\rangle$ in Eq. (17) by the strong field $B^{(0)}_z$ of the NMR spectrometer is $\sim 10^{-3}$ to 10^{-4}. If we neglect $\xi'^{(\mathrm{N})}$ [4], Eq. (16) becomes

$$\Delta\mu^{(\mathrm{N})}_{\alpha} = \xi^{(\mathrm{N})}_{\alpha\beta\gamma}m^{(\mathrm{N})}_{\beta}B^{(0)}_{\gamma}, \tag{23}$$

where for $\omega \ll \omega_p$

$$\begin{aligned}\xi^{(\mathrm{N})}_{\alpha\beta\gamma} = &-\frac{2}{\hbar}\sum_{p\neq 0}\frac{1}{\omega_p}\mathrm{Re}\left[\langle 0|\mu_\alpha|p\rangle\langle p|\hat{\sigma}^{(\mathrm{N})(\mathrm{dia})}_{\beta\gamma}|0\rangle\right]\\ &-\frac{\mu_0}{4\pi}\frac{2e}{m_\mathrm{e}\hbar}\sum_{p\neq 0}\left\{\frac{\langle p|m_\gamma|p\rangle}{\omega_p^2}\mathrm{Re}\left[\langle 0|\mu_\alpha|p\rangle\langle p|\sum_j l_{j_\beta}/r_j^3|0\rangle\right]\right.\\ &+\sum_{q\neq 0}\frac{1}{\omega_p\omega_q}\mathrm{Re}\left[\langle q|m_\gamma|0\rangle(\langle 0|\mu_\alpha|p\rangle\langle p|\sum_j l_{j_\beta}/r_j^3|q\rangle\right.\\ &\left.+\langle 0|\sum_j l_{j_\beta}/r_j^3|p\rangle\langle p|\mu_\alpha|q\rangle)\right] + \sum_{q\neq p}\frac{1}{\omega_p\omega_{qp}}\\ &\times\mathrm{Re}\left[\langle p|m_\gamma|q\rangle(\langle 0|\mu_\alpha|p\rangle\langle q|\sum_j l_{j_\beta}/r_j^3|0\rangle\right.\\ &\left.\left.+\langle 0|\sum_j l_{j_\beta}/r_j^3|p\rangle\langle q|\mu_\alpha|0\rangle)\right]\right\}.\end{aligned} \tag{24}$$

In an optically active liquid $\xi^{(\mathrm{N})}_{\alpha\beta\gamma}$ has an isotropic part $\bar{\xi}^{(\mathrm{N})}\varepsilon_{\alpha\beta\gamma}$, and the corresponding pseudoscalar

$$\begin{aligned}\bar{\xi}^{(\mathrm{N})} &= \frac{1}{6}\left(\xi^{(\mathrm{N})}_{\alpha\beta\gamma}\varepsilon_{\alpha\beta\gamma}\right)\\ &= \frac{1}{6}\left(\xi^{(\mathrm{N})}_{xyz} - \xi^{(\mathrm{N})}_{xzy} + \xi^{(\mathrm{N})}_{yzx} - \xi^{(\mathrm{N})}_{yxz} + \xi^{(\mathrm{N})}_{zxy} - \xi^{(\mathrm{N})}_{zyx}\right)\end{aligned} \tag{25}$$

is non-zero for a chiral molecule. Hence, the induced rotating electric dipole moment in an optically active liquid is given by

$$\Delta\boldsymbol{\mu}^{(\mathrm{N})} = \bar{\xi}^{(\mathrm{N})}\boldsymbol{m}^{(\mathrm{N})}\times\boldsymbol{B}^{(0)}. \tag{26}$$

Note that the diamagnetic contribution to $\xi^{(\mathrm{N})}_{\alpha\beta\gamma}$ in Eq. (24) is symmetric in $\beta\gamma$ and therefore does not contribute to $\bar{\xi}^{(\mathrm{N})}$.

3.2. Application of an electric field in NMR

Let us similarly enquire if a static electric field $\boldsymbol{E}^{(0)}$ can cause a magnetic field at the nucleus:

$$\Delta B^{(\mathrm{N})}_{\alpha} = -\sigma^{(\mathrm{N})}_{\alpha\beta}B^{(0)}_{\beta} - \sigma^{(1)(\mathrm{N})}_{\alpha\beta\gamma}B^{(0)}_{\beta}E^{(0)}_{\gamma}, \tag{27}$$

where $\sigma^{(1)(\mathrm{N})}_{\alpha\beta\gamma}$ is the chemical shift tensor perturbed by a uniform static electric field [5–7]. After taking an isotropic average, we obtain

$$\Delta\boldsymbol{B}^{(\mathrm{N})} = -\sigma^{(\mathrm{N})}\boldsymbol{B}^{(0)} - \overline{\sigma^{(1)}}^{(\mathrm{N})}\boldsymbol{B}^{(0)}\times\boldsymbol{E}^{(0)}, \tag{28}$$

where the pseudoscalar $\overline{\sigma^{(1)}}^{(\mathrm{N})}$ is given by an expression similar to Eq. (25). By comparing $\xi^{(\mathrm{N})}_{\alpha\beta\gamma}$ in Eq. (23) with $\sigma^{(1)(\mathrm{N})}_{\alpha\beta\gamma}$ in Eq. (27) it becomes evident that both tensors depend on an electric-dipole, a magnetic-dipole, and a magnetic-field operator. Should the tensors have the same frequency argument, then it follows from consideration of the energy in $E^{(0)}_{\alpha}m^{(\mathrm{N})}_{\beta}B^{(0)}_{\gamma}$ that $\xi^{(\mathrm{N})}_{\alpha\beta\gamma} = -\sigma^{(1)(\mathrm{N})}_{\beta\gamma\alpha}$ and hence that $\bar{\xi}^{(\mathrm{N})} = -\overline{\sigma^{(1)}}^{(\mathrm{N})}$.

Just as $\boldsymbol{\sigma}^{(\mathrm{N})}$ has two meanings (see Eqs. (11) and (12)), so $\boldsymbol{\sigma}^{(1)(\mathrm{N})}$ has three. In addition to

$$\Delta\mu^{(\mathrm{N})}_{\alpha} = -\sigma^{(1)(\mathrm{N})}_{\beta\gamma\alpha}m^{(\mathrm{N})}_{\beta}B^{(0)}_{\gamma} = \xi^{(\mathrm{N})}_{\alpha\beta\gamma}m^{(\mathrm{N})}_{\beta}B^{(0)}_{\gamma} \tag{29}$$

and

$$\Delta B^{(\mathrm{N})}_{\alpha} = -\sigma^{(\mathrm{N})}_{\alpha\beta}B^{(0)}_{\beta} - \sigma^{(1)(\mathrm{N})}_{\alpha\beta\gamma}B^{(0)}_{\beta}E^{(0)}_{\gamma}, \tag{27}$$

a magnetic moment may also be induced in a molecule by the nuclear magnetic moment in the presence of an electric field:

$$\Delta m^{(\mathrm{N})}_{\alpha} = -\sigma^{(\mathrm{N})}_{\beta\alpha}m^{(\mathrm{N})}_{\beta} - \sigma^{(1)(\mathrm{N})}_{\beta\alpha\gamma}m^{(\mathrm{N})}_{\beta}E^{(0)}_{\gamma}. \tag{30}$$

For an isotropic medium one obtains:

$$\Delta\boldsymbol{\mu}^{(\mathrm{N})} = -\overline{\sigma^{(1)}}^{(\mathrm{N})}\boldsymbol{m}^{(\mathrm{N})}\times\boldsymbol{B}^{(0)}, \tag{31}$$

$$\Delta\boldsymbol{B}^{(\mathrm{N})} = -\sigma^{(\mathrm{N})}\boldsymbol{B}^{(0)} - \overline{\sigma^{(1)}}^{(\mathrm{N})}\boldsymbol{B}^{(0)}\times\boldsymbol{E}^{(0)}, \tag{32}$$

$$\Delta\boldsymbol{m}^{(\mathrm{N})} = -\sigma^{(\mathrm{N})}\boldsymbol{m}^{(\mathrm{N})} + \overline{\sigma^{(1)}}^{(\mathrm{N})}\boldsymbol{m}^{(\mathrm{N})}\times\boldsymbol{E}^{(0)}. \tag{33}$$

The isotropic component of the nuclear magnetic shielding polarizability $\overline{\sigma^{(1)}}^{(\mathrm{N})}$ gives rise to the chiral NMR effects considered in this paper.

Another approach might be through the electric-field dependence of the spin–spin coupling tensor $J^{(\mathrm{NN}')}_{\alpha\beta}$:

$$J^{(\mathrm{NN}')}_{\alpha\beta}(\boldsymbol{E}) = J^{(\mathrm{NN}')}_{\alpha\beta} + J^{(1)(\mathrm{NN}')}_{\alpha\beta\gamma}E_{\gamma}. \tag{34}$$

Like $\sigma^{(1)(\mathrm{N})}_{\alpha\beta\gamma}$, $J^{(1)(\mathrm{NN}')}_{\alpha\beta\gamma}$ has a chirally sensitive isotropic part $\varepsilon_{\alpha\beta\gamma}\overline{J^{(1)}}^{(\mathrm{NN}')}$. A possible application could be to induce zero-quantum transitions by a time-dependent electric field $E_z(t)$ oscillating at the difference frequency $|\omega(\mathrm{N}) - \omega(\mathrm{N}')|/2\pi$.

4. Computation of $\overline{\sigma^{(1)}}^{(N)} = -\xi^{(N)}$

The nine-element nuclear magnetic shielding tensor can be computed using the Dalton program and a finite electric field can be applied [10,11]. We used electric fields in the *x*, *y* and *z* directions of $\pm 10^{-3}$ a.u. (1 a.u. = 5.14×10^{11} V/m), and thereby deduced the pseudoscalar $\overline{\sigma^{(1)}}^{(N)}$.

We have computed the nuclear magnetic shielding polarizability of hydrogen peroxide, H_2O_2. The ground state of hydrogen peroxide has C_2 symmetry with a dihedral angle ∠HOOH of about ±112° [12]. For dihedral angles of 0° and 180°, H_2O_2 is achiral and has, respectively, C_{2v} and C_{2h} symmetry. Fig. 1 shows that $\overline{\sigma^{(1)}}^{(H)}$ is of opposite sign for the two enantiomers and that it vanishes when H_2O_2 has C_{2h} symmetry. In practice inversion of the H_2O_2 molecule is sufficiently rapid to prevent chiral samples being isolated.

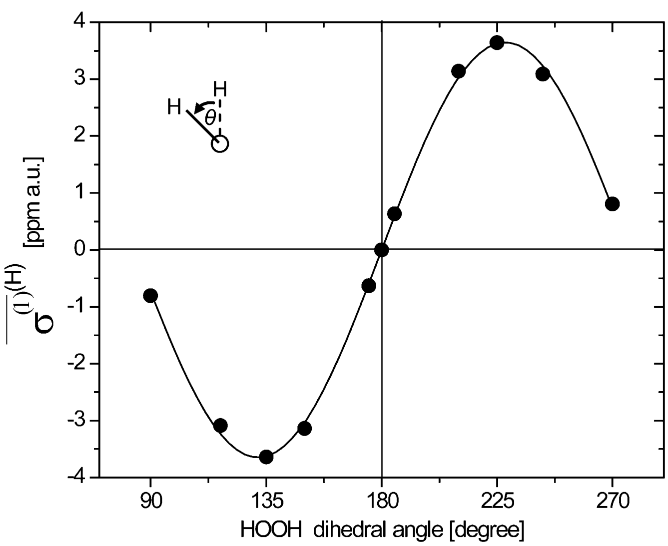

Fig. 1. The calculated isotropic component of the proton magnetic shielding polarizability for hydrogen peroxide (H_2O_2) is shown as a function of dihedral angle (θ, as defined in the inset). The two enantiomers are R-HOOH for dihedral angles <180° and S-HOOH for dihedral angles >180°. The equilibrium geometry has been determined using the 6-311+G(d,p) basis set. $\overline{\sigma^{(1)}}^{(H)}$ is obtained with the 6-311++G(3df,3pd) basis set from finite field calculations at the SCF level. The solid line is to guide the eye.

To ascertain the reliability of the ab initio results presented here, we have also calculated the shielding polarizabilities of water (results not shown), for which high-level calculations have been reported [11]. We find that the larger basis sets of Table 1 yield components of the shielding tensor and the nuclear magnetic shielding polarizability for H_2O that are in good agreement with self-consistent field (SCF) results reported by Rizzo et al. [11]. The results of self-consistent field (SCF) calculations of $\sigma^{(H)}$ and $\overline{\sigma^{(1)}}^{(H)}$ for chiral H_2O_2 shown in Table 1 may thus be close to the basis-set limit.

The importance of correlation in the calculation of $\overline{\sigma^{(1)}}^{(H)}$ is more difficult to ascertain. Whereas our second-order Møller–Plesset (MP2) results for the shielding tensor for H_2O are in good agreement with multiconfigurational self-consistent field (MCSCF) calculations by Rizzo et al., our MP2 calculations seem to overestimate components of the nuclear magnetic shielding polarizability $\sigma^{(1)(N)}_{\alpha\beta\gamma}$. Should correlation effects in H_2O_2 be of similar significance to those in H_2O, then the MCSCF study suggests that inclusion of correlation will reduce the magnitude of the nuclear magnetic shielding polarizability components by ~10% [11]. For our subsequent estimates, we take $|\overline{\sigma^{(1)}}^{(H)}|$ to be ~3 ppm a.u. = 5.834×10^{-18} m/V.

The nuclear magnetic shielding polarizability for an F atom and for a C atom in a chiral molecule may be larger than $|\overline{\sigma^{(1)}}^{(H)}|$. Table 2 indicates that for chlorofluoroacetic acid, CHClF(COOH), $|\overline{\sigma^{(1)}}^{(F)}|$ and $|\overline{\sigma^{(1)}}^{(C)}|$ are ~10 times larger.

5. Estimates of chiral NMR effects

Eqs. (31)–(33) suggest three means of observing $\overline{\sigma^{(1)}}^{(N)} = -\xi^{(N)}$.

Table 1
The isotropic components of the shielding tensor $\sigma^{(H)}$ (ppm) and of the nuclear magnetic shielding polarizability $\overline{\sigma^{(1)}}^{(H)}$ (ppm a.u.) have been calculated for hydrogen peroxide (R-H_2O_2)

Basis-set	Number of basis functions		R-HOOH					
			Geometry 1		Geometry 2			
			SCF		SCF		MP2	
	H	O	$\overline{\sigma^{(1)}}^{(H)}$ (ppm a.u.)	$\sigma^{(H)}$ (ppm)	$\overline{\sigma^{(1)}}^{(H)}$ (ppm a.u.)	$\sigma^{(H)}$ (ppm)	$\overline{\sigma^{(1)}}^{(H)}$ (ppm a.u.)	$\sigma^{(H)}$ (ppm)
cc-pVDZ	5	14	−3.8	28.2	−4.2	26.5		
6-311G**	6	18	−4.1	26.5	−3.7	28.2	−6.1	25.6
6-311++G**	7	22	−4.1	26.5	−3.6	27.9	−5.9	24.5
aug-cc-pVDZ	9	23	−2.8	27.6	−3.2	26.0		
6-311++G(2d,2p)	10	27	−3.5	25.7	−3.0	27.4	−5.9	24.1
cc-pVTZ	14	30	−3.6	25.8	−3.1	27.5	−5.8	25.4
6-311++G(3df,3pd)	18	39	−3.2	25.4	−2.7	27.0	−5.6	24.6
aug-cc-pVTZ	23	59	−3.2	25.6	−2.7	27.3	−5.6	24.4
cc-pVQZ	30	55	−3.4	25.5	−2.9	27.2		

The number of basis functions is listed for the light and the heavy atoms. Two geometries were used in the calculations: geometry 1 has been optimized using the aug-cc-pVTZ basis: *R*(O–O) = 1.3866 Å, *R*(O–H) = 0.9426 Å, ∠OOH = 103.059°, ∠HOOH = 111.594°; geometry 2 represents a best estimate based on literature values [12]: *R*(O–O) = 1.452 Å, *R*(O–H) = 0.965 Å, ∠OOH = 100.0°, ∠HOOH = 112.0°.

Table 2
The isotropic components of the shielding tensor $\sigma^{(N)}$ (ppm) and of the nuclear magnetic shielding polarizability $\overline{\sigma^{(1)}}^{(N)}$ (ppm a.u.) have been calculated at the SCF level for the ^{1}H, ^{19}F, and ^{13}C nuclei in R-^{13}C^{1}HCl^{19}F(COOH)

Basis set	R-CHClF(COOH)					
	$\overline{\sigma^{(1)}}^{(H)}$ (ppm a.u.)	$\sigma^{(H)}$ (ppm)	$\overline{\sigma^{(1)}}^{(F)}$ (ppm a.u.)	$\sigma^{(F)}$ (ppm)	$\overline{\sigma^{(1)}}^{(C)}$ (ppm a.u.)	$\sigma^{(C)}$ (ppm)
cc-pVDZ	1.3	26.8	19.0	402.9	−19.5	116.9
6-311G**	1.2	27.1	10.0	389.2	−19.5	112.3
aug-cc-pVDZ	1.4	26.4	10.6	392.8	−19.9	117.8

The geometry has been optimized using the 6-311++G** basis.

5.1. Rotating chiral electric polarization

The electric polarization $\boldsymbol{P}^{(N)}$ induced by the precessing nuclear magnetization $\boldsymbol{M}^{(N)}$ is proportional to $(\gamma^{(N)}B_z^{(0)})^2$ and is given by [4]

$$P_x^{(N)} = -\overline{\sigma^{(1)}}^{(N)} M_y^{(N)} B_z^{(0)}, \tag{35}$$

$$P_y^{(N)} = \overline{\sigma^{(1)}}^{(N)} M_x^{(N)} B_z^{(0)}, \tag{36}$$

where we have neglected the contribution from $\xi'^{(N)}$ (see above). If a capacitor with plates at $\pm d/2$ on the y-axis is incorporated into the resonance circuit, then $P_y^{(N)}$ will generate an rf-voltage

$$V^{(N)} = P_y^{(N)} d/((\varepsilon - 1)\varepsilon_0), \tag{37}$$

where ε is the dielectric constant of the medium and ε_0 the permittivity of free space. The NMR frequency is far removed from any molecular resonances, and so we can use the values for the static nuclear magnetic polarizability to estimate $V^{(H)}$. The computational results of Section 4 suggest that for a small H-containing chiral molecule $|\overline{\sigma^{(1)}}^{(H)}| = |\bar{\xi}^{(H)}| \sim 3$ ppm a.u., such that $|V^{(H)}| \sim 1$ nV for a pure chiral liquid. This compares with a typical NMR signal from an inductor on the x-axis of 1 mV.

The electric polarization $\boldsymbol{P}^{(N)}$ induced by the precessing nuclei of a chiral sample oscillates at the resonance frequency, so new frequencies are not generated. Simultaneous observation of $P_y^{(N)}$ and $M_x^{(N)}$ would associate a signal with nuclei in a chiral environment and therefore facilitate spectral assignment.

5.2. Chiral chemical shifts

A change of the magnetic field at the nucleus due to $\overline{\sigma^{(1)}}^{(N)}$ would result in a shift of the resonance frequency. However, Eq. (32) indicates that no such chemical shift can occur to first order, as the induced magnetic field at the nucleus would be perpendicular to the magnetic field of the spectrometer. Application of a laser polarized in the xy-plane could in principle give rise to a chiral chemical shift

$$\begin{aligned} \Delta\boldsymbol{B}^{(N)} &= -\overline{\sigma^{(1)}}^{(N)}(0;\omega,-\omega)\boldsymbol{B}\times\boldsymbol{E}, \\ \Delta B_z^{(N)} &= -\overline{\sigma^{(1)}}^{(N)}(0;\omega,-\omega)(B_xE_y - B_yE_x), \end{aligned} \tag{38}$$

where $\boldsymbol{E}$ and $\boldsymbol{B}$ are, respectively, the electric and magnetic fields of the laser. The light-induced chiral chemical shifts could arise even if the laser is linearly polarized and even if the solution is racemic [13]. To estimate the effect, one has to consider the frequency dependence of the nuclear magnetic shielding polarizability. The effect is likely to be too small to be observed, even if the optical field is resonant with an electronic transition in the molecule [14–16]. For a continuous-wave laser with an intensity of 10 W/cm^2, we estimate that near optical resonance the chiral chemical shift for protons $<10^{-12}$ Hz.

5.3. Oscillating chiral magnetization

An electrostatic field $\boldsymbol{E}^{(0)}$ will induce a magnetization according to Eq. (33)

$$\Delta\boldsymbol{M}^{(N)} = \overline{\sigma^{(1)}}^{(N)}\boldsymbol{M}^{(N)}\times\boldsymbol{E}^{(0)}. \tag{39}$$

Hence a field $E_y^{(0)}$ applied to the precessing nuclear magnetic moments will induce an oscillating magnetization in the z-direction:

$$\Delta M_z^{(N)} = \overline{\sigma^{(1)}}^{(N)} M_x^{(N)} E_y^{(0)}. \tag{40}$$

For a pure chiral liquid, we estimate that $|\Delta M_z^{(H)}/M_x^{(H)}|$ is of the order of 10^{-11}, where we have taken $|\overline{\sigma^{(1)}}^{(H)}| = |\bar{\xi}^{(H)}| \approx 3$ ppm a.u. and $E_y^{(0)} = 10^6$ V/m.

Since most chiral molecules are dipolar (those of D_n symmetry are not), there is an additional temperature-dependent orientational term $\Delta_T\boldsymbol{M}^{(N)}$, such that

$$\begin{aligned} \Delta_T\boldsymbol{M}^{(N)} = \frac{1}{6kT}\Big[\Big(\sigma_{xy}^{(N)} - \sigma_{yx}^{(N)}\Big)\mu_z^{(0)} + \Big(\sigma_{yz}^{(N)} - \sigma_{zy}^{(N)}\Big)\mu_x^{(0)} \\ + \big(\sigma_{zx}^{(N)} - \sigma_{xz}^{(N)}\big)\mu_y^{(0)}\Big]\boldsymbol{M}^{(N)}\times\boldsymbol{E}^{(0)} \end{aligned} \tag{41}$$

where $\boldsymbol{\mu}^{(0)}$ is the permanent dipole moment of the molecule. For HOOH, we compute a permanent dipole moment of 1.89 debye for geometry 2 (see Table 1), and using the same aug-ccpVTZ basis set we estimate that $|\frac{\Delta M_z^{(H)}}{M_x^{(H)}}| \approx 10^{-9}$.

Should the applied electric field be modulated at a low frequency $f/2\pi$, then the induced magnetization $\Delta M_z^{(N)}$ oscillates at a unique angular frequency $\omega \pm f$.

Methods to enhance the signal/noise ratio such as cooling the detector, narrowing the bandwidth, and extending the time of detection, may all be necessary to observe the effect. Use of a rf-SQUID may be required [17].

6. Discussion

We show that the electric-field-perturbed chemical shift tensor, the nuclear magnetic shielding polarizability $\bar{\xi}^{(N)} = -\overline{\sigma^{(1)}}^{(N)}$, gives rise to chiral NMR effects in a liquid that make it possible to discriminate directly between the enantiomers of a chiral molecule without the need for a chiral solvent. The pseudoscalar $\bar{\xi}^{(N)} = -\overline{\sigma^{(1)}}^{(N)}$ depends on electric-dipole, magnetic-dipole and magnetic-field operators and only exists for chiral molecules. It may give rise to three chiral NMR effects: The coherent precession of nuclear spins following application of a $\pi/2$ pulse to an optically active liquid will lead to a rotating macroscopic *electric* polarization; a laser polarized in the plane perpendicular to the field of the magnet may in principle give rise to chiral chemical shifts; and in a chiral liquid the application of an (oscillating) electric field at right angles to the magnetic field of the spectrometer may give rise to a magnetization oscillating (at a unique frequency) in the direction of the permanent magnetic field.

Using finite field calculations on small chiral molecules, we estimate the magnitude of the nuclear magnetic shielding polarizability and quantify the chiral NMR effects. Of the three chiral NMR effects, the rotating electric polarization [4] is most promising for experimental observation and should be detectable in favourable cases, particularly for heavier nuclei at or near asymmetric sites. The effect could facilitate assignment of NMR spectral peaks, as it could identify chiral centres in an NMR spectrum.

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