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Chiral Discrimination via Nuclear Magnetic Shielding Polarisabilities from NMR Spectroscopy: Theoretical Study of (*R*_a)-1,3-Dimethylallene, (2*R*)-2-Methyloxirane, and (2*R*)-*N*-Methyloxaziridine

R. ZANASI,¹ S. PELLONI,² P. LAZZERETTI²

¹Dipartimento di Chimica, Università di Salerno, v. Ponte don Melillo, 84084 Fisciano,
Salerno, Italy

²Dipartimento di Chimica, Università degli Studi di Modena e Reggio Emilia, v. Campi 183,
41100 Modena, Italy

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Abstract: Three medium-size optically active molecules have been studied to make a guess at candidates suitable for chiral discrimination in an isotropic medium via nuclear magnetic resonance spectroscopy. The criterion for experimental detection is given by the magnitude of the isotropic part of nuclear magnetic shielding polarisability tensors, related to a pseudoscalar of opposite sign for the two enantiomers. The pseudoscalar shielding polarisability at the ¹⁷O nucleus in *N*-methyloxaziridine, calculated at the Hartree-Fock level, is $\approx 7.8 \times 10^{-17} \text{ mV}^{-1}$. To obtain an experimentally observable magnetic field induced at the ¹⁷O nucleus in *N*-methyloxaziridine, electric fields as large as $\approx 10^7\text{--}10^8 \text{ Vm}^{-1}$ should be applied to the probe. The molecular electric dipole moment induced by precession of the magnetic dipole of the ¹⁷O nucleus in a magnetic field of 10 T is, in absolute value, $\approx 8.8 \times 10^{-42} \text{ Cm}$. The estimated rf-voltage at a resonance circuit is $\approx 10 \text{ nV}$. Smaller values have been estimated for N, C, and H nuclei in 1,3-dimethylallene and 2-methyloxirane.

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Key words: NMR; chiral discrimination; shielding polarisability

Introduction

Optical rotatory dispersion and circular dichroism, i.e., differential absorption of left and right circularly polarized light, are customarily employed to differentiate the spectroscopic properties of the two mirror images of a chiral molecule.^{1–3} Nuclear magnetic resonance (NMR) spectroscopy can distinguish diastereoisomers, but conventional experimental sets-up are unable to recognize the two mirror images of a chiral species. The spectral parameters available via an experiment in disordered phase—chemical shift (i.e., the average magnetic shielding of a given nucleus referred to that of a standard compound) and nuclear spin–spin coupling constant—are one third the trace of second-rank tensor properties characterized by even parity, and they have the same sign and magnitude for left and right-handed enantiomers.

Chiral discrimination can be obtained in NMR by employing an environment *ad hoc* for either L or D mirror images, e.g., adding chiral reagents or solvents.^{4,5} Sears et al.⁶ have simulated creation of diastereoisomers by attaching helical partial charge

arrays to chiral complexes to remove “chiral blindness” of NMR. In principle, any chiral potential would be sufficient to break mirror symmetry.⁷ There exists a pseudoscalar component of total nuclear magnetic shielding arising from parity nonconservation, with the same magnitude but opposite sign for the two enantiomeric forms.^{8–10} However, the contributions arising from parity violating electroweak forces are extremely small.^{11,12} Theoretical studies show that the splitting in the ¹⁹F NMR spectrum between the left and right-handed CHFClBr molecules is $\sim 10^{-10} \text{ ppm}$.¹³ Therefore parity nonconserving effects cannot reasonably help discriminate the two mirror images.^{11–13}

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Correspondence to: P. Lazzeretti; e-mail: lazzeret@unimore.it

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On the other hand, the third-rank tensor $\sigma_{\alpha\beta\gamma}^I$ usually referred to as polarisability of the nuclear magnetic shielding of nucleus I ,¹⁴ or magnetic hypershielding, has odd parity and changes sign for the mirror images of a chiral species. Experiments for discriminating two enantiomers in an isotropic medium via NMR spectroscopy have been discussed recently by Buckingham¹⁵ and Buckingham and Fischer.¹⁶

The static $\sigma_{\alpha\beta\gamma}^I$ tensor contains diamagnetic and paramagnetic contributions that change in a transformation of the gauge of the vector potential in such a way that their sum stays the same for exact eigenstates to a model Hamiltonian.^{17–19}

A frequency dependent magnetic hypershielding $\sigma_{\alpha\beta\gamma}^I(\omega_\sigma; \omega_1, \omega_2)$, with $\omega_\sigma = \omega_1 + \omega_2$, has also been considered, since the application of a laser polarized in a reference plane could in principle generate a rotating electric polarization and chiral chemical shift.^{15,16} However, such a dynamic shielding polarisability is not invariant in a gauge translation of the vector potential, which implies that other dynamic tensors referred to as magnetoelectric shielding^{20–22} and hypershielding should be taken into account to define observables independent of the origin of the coordinate system.²³

The Chiral Pseudoscalar

For an isotropic medium it is convenient to define the pseudoscalar

$$\overline{\sigma^{(1)}}^{(I)} = \frac{1}{6} \varepsilon_{\alpha\beta\gamma} \sigma_{\alpha\beta\gamma}^I \quad (1)$$

allowing for the Einstein summation convention and using the third-rank Levi-Civita skew-symmetric unit tensor.¹⁶ The isotropic part of the magnetic hypershielding tensor is $\overline{\sigma^{(1)}}^{(I)} \varepsilon_{\alpha\beta\gamma}$. The pseudoscalar (1) is the basic quantity with opposite sign for two mirror image molecules in solution or gas phase. Therefore, the magnetic field induced at nucleus I by a magnetic field with flux density \mathbf{B} , in the presence of an additional electric field \mathbf{E} , by quadratic response of the n electrons of a molecule in an isotropic environment, is^{15,16,23}

$$\Delta \langle \mathbf{B}_I^n \rangle = -\overline{\sigma^{(1)}}^{(I)} \mathbf{B} \times \mathbf{E} \quad (2)$$

denoting by \mathbf{B}_I^n the corresponding electronic operator. The electric dipole moment

$$\Delta \langle \boldsymbol{\mu} \rangle = -\overline{\sigma^{(1)}}^{(I)} \mathbf{m}_I \times \mathbf{B} \quad (3)$$

induced in the electron cloud by the permanent magnetic dipole \mathbf{m}_I at nucleus I and by the magnetic field is also defined via the intrinsic property.⁽¹⁾ Analogously,

$$\Delta \langle \mathbf{m} \rangle = -\overline{\sigma^{(1)}}^{(I)} \mathbf{E} \times \mathbf{m}_I \quad (4)$$

is the orbital magnetic dipole moment of the electrons, induced by the electric field and the intrinsic magnetic dipole at nucleus I .

The field (2) and the moments (3) and (4) are origin independent in the static case. If the fields \mathbf{E} and \mathbf{B} depend on time, and the nuclear magnetic dipole \mathbf{m}_I precesses at the Larmor frequency ω , the l. h. s. of eqs. (2)–(4) is not invariant to translation and other molecular tensors should be considered to obtain origin-

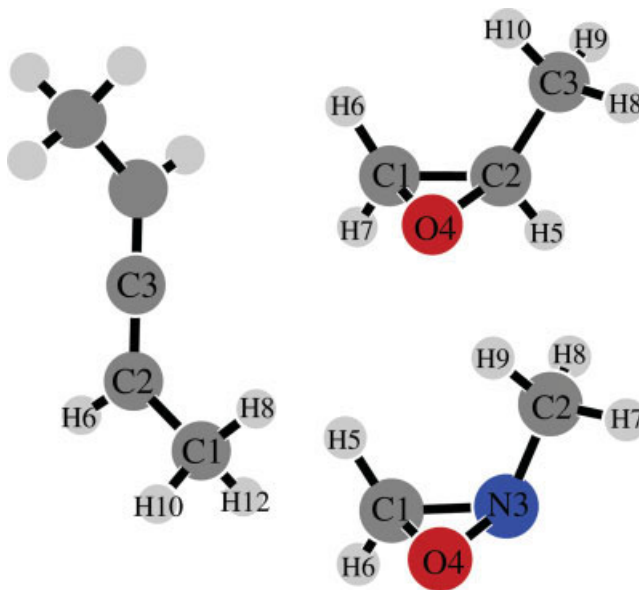
independent observables (2) and (3).²³ However, the precession frequency is of the order of 10^{-7} of the electronic excitation frequencies, so the zero-frequency limit formulae are appropriate.

Buckingham and Fischer¹⁶ have estimated $\overline{\sigma^{(1)}}^{(I)}$ to be ≈ 3 ppm au = 5.834×10^{-18} m/V for hydrogen in HOOH. Values 10 times larger were obtained for fluorine and carbon in chloro-fluoroacetic acid CHClF(COOH).¹⁶

In the present article, coupled Hartree-Fock (CHF) calculations of the pseudoscalar (1) of nuclear magnetic shielding polarisabilities are reported for three small, rigid chiral molecules, namely (*R*_a)-1,3-dimethylallene (**1**), (2*R*)-2-methyloxirane (**2**), and (2*R*)-*N*-methyloxaziridine (**3**) shown in Scheme 1. Shielding polarisabilities have been obtained by a finite field perturbation scheme, computing second-rank nuclear magnetic shielding tensors in the presence of an external uniform electric field formally retained in the unperturbed Fock Hamiltonian. The continuous transformation of the origin of the current density (CTOCD) method,²⁴ within the numerical DZ2 variant,²⁵ has been used to get results that are origin independent for any electronic wave function, irrespective of the approximation adopted.^{17–19,26} Such a procedure provides a simple and effective, easy-to-code route, alternative to methods using gauge-including atomic orbitals (GIAO).

Results and Discussion

Molecular geometries have been optimized at the B3LYP/6-31G* level using GAUSSIAN03.²⁷ Nuclear magnetic shielding polarisabilities and pseudoscalar term (1) have been computed by the SYSMO package.²⁸ The results are shown in Tables 1–3. Four basis sets, i.e., Pople 6-31G** available in GAUS-



Scheme 1. (*R*_a)-1,3-dimethylallene (**1**), (2*R*)-2-methyloxirane (**2**), (2*R*)-*N*-methyloxaziridine (**3**). [Color scheme can be viewed in the online issue, which is available at www.interscience.wiley.com.]

Table 1. CTOCD-DZ2/CHF Pseudoscalar of Magnetic Shielding Polarizability of (*R_a*)-1,3-Dimethylallene Nuclei from Four Basis Sets.^a

Nuc. ^b	6-31G**	Sadlej	aug-cc-pVDZ	aug-cc-pVTZ
C1	1.532	−4.749	−3.296	−4.270
C2	−0.080	−3.044	−2.557	−3.018
C3	1.611	−7.541	−6.118	−6.292
H6	0.235	0.553	0.748	0.737
H8	−0.222	−0.576	−0.504	−0.436
H10	−0.060	0.274	0.222	0.140
H12	−0.123	−0.998	−0.896	−0.846

^aIn ppm au.^bSee Scheme 1 for nucleus identification.

SIANO3,²⁷ Sadlej basis sets developed for electric polarizabilities,²⁹ Dunning and Woon aug-cc-pVDZ and aug-cc-pVTZ^{30,31} have been employed in the calculations (see the Supporting Information for the full set of computed tensor components of the nuclear magnetic shielding polarizability).

The 6-31G** basis set does not seem flexible enough to guarantee reliable results. As can be observed in the tables and throughout the supporting information, the pseudoscalar (1) predicted via this basis is smaller, in absolute value, than that obtained via the other basis sets in a number of cases, e.g., for C1 in (2*R*)-2-methyloxirane and for C1 and O4 of (2*R*)-*N*-methyloxaziridine. The estimates for C1 and C3 of (*R_a*)-1,3-dimethylallene, and for O4 of (2*R*)-2-methyloxirane have opposite sign with respect to those from larger basis sets. Sadlej, aug-cc-pVDZ and aug-cc-pVTZ basis sets yield similar estimates for all the nuclei in the molecules considered. Most calculated values are close to one another, a discrepancy being observed only for the Sadlej prediction of the pseudoscalar for C3 in (*R_a*)-1,3-dimethylallene. However, assuming that the aug-cc-pVTZ gives the best results in the present study, we can observe that the overall performance of the Sadlej basis is superior to that of aug-cc-pVDZ in most cases. In fact, Gaussian basis sets employed to calculate magnetic shielding polarizabilities should include diffuse functions for improved description of the tail regions of a molecule, that is, functions suitable for accurate prediction of second-rank electric dipole polarizability.¹⁹

We have noticed that computed $\overline{\sigma_{(1)}^{(I)}}$ mean values are usually much smaller than the six individual components of the shielding polarizability tensor from which they have been obtained by contraction with the Levi-Civita skew-symmetric tensor, according to the definition, eq. (1). The addenda of this sum are characterized by different sign, typically three positive and three negative, so that partial cancellation takes place. The situation resembles that usually occurring in the calculation of the optical rotatory power tensor, for which small trace and big diagonal components of different sign are frequently evaluated.

Previous investigations have shown the extreme difficulty of obtaining nuclear magnetic shielding polarizabilities close to the limit of a given approximate method. However, we think that the substantial agreement of the theoretical predictions arrived at by three basis sets within the coupled Hartree-Fock CTOCD-DZ2 scheme indicates that the order of magnitude of $\overline{\sigma_{(1)}^{(I)}}$ in

the molecules investigated is correctly estimated. The GIAO approach has also been used to make a comparison, using the same basis sets with functions multiplied by gauge factors. The corresponding estimates, reported as supplementary material, are in good agreement with CDOCD-DZ2. Saturation of basis set does not seem to be achieved by either approaches, and further studies are needed to make the point.

Electron correlation effects on nuclear hypershielding are known to be quite large,^{32–34} but hopefully not so large to change magnitude and sign of the individual components of nuclear magnetic hypershielding. Buckingham and Fischer employed second-order Møller-Plesset (MP2) procedures to calculate static $\sigma'_{\alpha\beta\gamma}$ and $\overline{\sigma_{(1)}^{(I)}}$ for the nuclei of hydrogen peroxide.¹⁶ They claim that MP2 overemphasizes components of the nuclear magnetic shielding polarizability. In fact, at the MP2 level, electron correlation changes the estimates of the pseudoscalar for the hydrogen nucleus in HOOH by about a factor of two.¹⁶ These authors expect inclusion of correlation contributions via multiconfigurational self-consistent-field (MCSCF) methods to reduce the magnitude of nuclear magnetic shielding polarizability components by $\approx 10\%$.¹⁶ This and other relevant aspects, concerning, e.g., vibrational averaging and solvent effects, will be examined by us in future investigations.

The values reported in the tables may help assess a possible connection between magnitude of $\overline{\sigma_{(1)}^{(I)}}$ and local symmetry. In 1,3-dimethylallene, the pseudoscalars (1) calculated for C1, C2, and C3 are slightly different. C3 lies on the asymmetry centre and is characterized by the biggest $\overline{\sigma_{(1)}^{(I)}}$ in absolute value. C2 is bonded to C3, and it is closer to the asymmetric centre than C1, but $\overline{\sigma_{(1)}^{(I)}}$ for *I* = C2 is smaller than that calculated for *I* = C1. Therefore, the magnitude of the pseudoscalar does not seem to depend on the degree of local asymmetry. Neither does it depend on the distance from the asymmetry centre. At any rate, the dimethylallene molecule is comparatively less interesting, as the pseudoscalar (1) of its nuclei is very small. In 2-methyloxirane, the basin of C2 is less symmetric than C1's, but $\overline{\sigma_{(1)}^{(I)}}$ of C2 is significantly smaller than that of C1. In this molecule the value predicted for *I* = O is comparable with that of C2. Analogously, the oxygen in (2*R*)-*N*-methyloxaziridine is characterized by the biggest computed pseudoscalar (1). Comparison

Table 2. CTOCD-DZ2/CHF Pseudoscalar of Magnetic Shielding Polarizability of (2*R*)-2-Methyloxirane Nuclei.^a

Nuc. ^b	6-31G**	Sadlej	aug-cc-pVDZ	aug-cc-pVTZ
C1	−15.50	−19.04	−17.64	−20.04
C2	5.217	7.473	8.984	8.935
C3	3.653	0.257	0.038	−0.568
O4	−6.786	9.784	8.883	8.878
H5	−2.670	−2.573	−2.657	−2.584
H6	−2.232	−1.558	−1.829	−1.794
H7	2.808	2.802	2.985	2.962
H8	1.213	1.126	1.175	1.285
H9	0.079	0.088	0.095	−0.040
H10	0.485	0.226	0.387	0.376

^aSee footnotes to Table 1.^bSee Scheme 1 for nucleus identification.

Table 3. CTOCD-DZ2/CHF Pseudoscalar of Magnetic Shielding Polarizability of (2*R*)-*N*-Methyloxaziridine Nuclei.^a

Nuc. ^b	6-31G**	Sadlej	aug-cc-pVDZ	aug-cc-pVTZ
C1	-17.66	-25.44	-25.84	-24.93
C2	2.864	0.476	0.889	-0.031
N3	1.481	25.95	21.13	25.32
O4	14.11	39.92	40.88	39.50
H5	-0.369	1.181	1.048	0.987
H6	0.425	0.114	0.285	0.150
H7	-0.024	0.044	0.026	0.056
H8	-0.870	-0.663	-0.419	-0.413
H9	0.382	0.443	0.443	0.639

^aSee footnotes to Table 1.^bSee Scheme 1 for nucleus identification.

with the values obtained for nitrogen and carbon seems to indicate that the polarizability of local charge distribution plays a dominant role, e.g., the magnitude of $\sigma^{(1)(I)}$ is mainly biased by the number of electron lone pairs at nucleus *I*. The local symmetry seems to be comparatively less important.

Magnitude of Observable Quantities

The conversion factors for nuclear magnetic hypershielding, from atomic units to SI and cgs units, obtained from the CODATA recommended values of ref. 35 are 1 ppm au = $10^{-6} \frac{e a_0}{E_h} = 1.94469057 \times 10^{-18} \text{ mV}^{-1} = 5.83003566 \times 10^{-14} \text{ cm stat V}^{-1}$, respectively.

Buckingham and Fischer take $\sigma^{(1)(I)}$ to be $\approx 3 \text{ ppm au} = 5.834 \times 10^{-18} \text{ m/V}$ for hydrogen in HOOH. They report values ≈ 10 times larger for carbon and fluorine in chlorofluoroacetic acid CHClF(COOH).¹⁶

The largest value obtained in the present calculation for oxygen in (2*R*)-*N*-methyloxaziridine is as big as $\approx 40 \text{ ppm au}$, corresponding to $7.8 \times 10^{-17} \text{ mV}^{-1}$. An (unrealistic) electric field *E* of $\approx 1.3 \times 10^8 \text{ Vm}^{-1}$ should be applied to observe an induced magnetic field, eq. (2), perpendicular to the strong magnetic field *B* of an NMR spectrometer, corresponding to $\approx 0.01 \text{ ppm}$ for ¹⁷O. To measure the isotropic nuclear magnetic hypershielding in the presence of static electric fields, one would rather have to observe the rotating electric polarization, eq. (3). On the other hand, an electric field with very high strength is hard to reach for spectroscopical applications. Technical difficulties encountered operating with strong dc-fields has been discussed by Peshkovsy and McDermott, who applied field strengths of $\approx 10^6 \text{ Vm}^{-1}$. They resorted to ac-fields to minimize deleterious effects, e.g., corrosion of electrodes, electrolysis, and Ohmic heating of the sample.³⁶

Therefore, the tiny contribution provided by the shielding polarizability seems quite difficult to detect via NMR experiments in the presence of an additional electric field. Toroid cavity NMR detectors for *in situ* investigations in magnetic, electric, and centrifugal fields are employed by Gerald et al.³⁷ Such a device enables them to conduct NMR experiments in the presence

of an electric field, directed orthogonal to the applied magnetic field.³⁸

Moreover, the ¹⁷O nucleus, although displaying the largest isotropic magnetic hypershielding in the compounds studied here, is most likely all but an ideal probe, due to low receptivity and unfavourable nuclear spin (*I* = 5/2), which may cause undesirable lifetime broadening of signals. Therefore, either a proper experimental procedure is developed to differentiate the two enantiomers, or more suitable chemical compounds with high shielding polarizability (e.g., possessing low-lying electronic states) should be tested.

The magnetic dipole moment of ¹⁷O is -2.24077 nuclear magnetons.³⁶ The nuclear magneton from CODATA³⁵ is $\mu_N = 5.05078317 \times 10^{-27} \text{ J T}^{-1}$. Time-independent perturbation theory can be used to estimate the magnitude of the induced electric dipole via eq. (3). Then in a magnetic field $|B| = 10 \text{ T}$, the induced electric dipole moment is, in absolute value, $\approx 8.8 \times 10^{-42} \text{ Cm}$, or $2.6 \times 10^{-12} \text{ D}$, using the debye unit, $1 \text{ D} = 3.33564095 \times 10^{-30} \text{ Cm}$, or $1 \times 10^{-18} \text{ statC cm}$.

From eq. (4), the induced orbital magnetic dipole depends linearly on the external electric field. If $|\Delta\langle m \rangle|$ is expressed in J T^{-1} and $|E|$ in Vm^{-1} , the proportionality coefficient is $\approx 8.8 \times 10^{-43}$ for the magnetic dipole induced by the permanent magnetic dipole of the oxygen nucleus.

Buckingham and Fischer have estimated that a pseudoscalar shielding polarizability as big as 3 ppm au corresponds to an rf-voltage $\approx 1 \text{ nV}$ at a resonance circuit, see eqs. (35)–(37) of ref. 16. If the effect scales linearly with the magnitude of $\sigma^{(1)(I)}$, an rf-voltage $\approx 10\text{--}15 \text{ nV}$ would correspond to the value 40 ppm au for the oxygen atom in (2*R*)-*N*-methyloxaziridine, which compares unfavourably with the typical signal of $\approx 1 \text{ mV}$ from an inductor in NMR spectrometers.

Eventually, recent articles show that the magnitude of parity-odd electroweak shifts increases significantly in molecules with heavy nuclei,^{39,40} which might indicate the possibility of substantially larger effects on the $\sigma^{(1)(I)}$ pseudoscalar due to relativistic contributions. Therefore, compounds containing nuclei heavier than those examined here could be candidates for experimental detection of chirality via NMR.

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