

# Evaluation of Spin Relaxation Induced by Chemical Shielding Anisotropy: A Comment on the Importance of the Antisymmetric Component

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**General comments related to the impact of the antisymmetric component of the electronic shielding tensor in context of nuclear magnetic relaxation studies are given. It is argued that in most conceivable applications of high field NMR, the effects associated with the antisymmetric component will be negligible. However, in certain situations, this conventional wisdom may fail and, as an extreme example, it is demonstrated that for highly nonaxially symmetric shieldings, motional anisotropy may accentuate dramatically the relative importance of the antisymmetry.** © 1997

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**Key Words:** antisymmetric shielding; shielding anisotropy; relaxation; anisotropic motion; *ab initio* calculations.

## INTRODUCTION

The NMR relaxation behavior at specific sites on isotopically labeled biopolymers provides a very powerful means to explore both structure and dynamics at the molecular level (1). Unfortunately, in contrast to simple molecules which are often characterized by certain local symmetries, the relative orientations of the molecular frame, the motional frame, and the coordinate frame diagonalizing the anisotropic interactions effecting nuclear spin relaxation are poorly defined for macromolecular systems. In general, the problem is underdetermined and this can lead to ambiguity.

Recently, there has been a significant interest shown in determination and subsequent interpretation of shielding anisotropies via NMR relaxation studies (2). When looked at more closely, this is a daunting task. Complex motions in the vicinity of the  $T_1$  minimum effecting nuclear spin relaxation through a nonaxially symmetric interaction have discouraged many workers. For those who have chosen to participate in this area of research, one of the “cleaner” approaches involves the measurement of relaxation-induced polarization and coherence transfer (3). However, even applications of this sensitive methodology can be plagued with ambiguity. The use of conventional relaxation rates in conjunction with these transfer rates can be helpful—but at the expense of introducing yet further uncertainty!

Moreover, there is one additional subtle feature which is generally ignored. For nuclei situated at sites with low local symmetry, the shielding tensor is characterized by an intrinsic antisymmetry (4, 5). Although only two experiments—one utilizing  $T_1/T_2$  ratios (6) and the other exploiting interference effects (7)—have detected this intriguing parameter, the fact that it has escaped experimental detection does not imply, necessarily, that it is small.

Frequently, each relaxation mechanism has its own characteristic signature which enables identification, isolation, and abstraction of molecular information. However, both shielding anisotropy and shielding antisymmetry have the same quadratic field dependence and only the most subtle differences distinguish between these two contributions (6, 7). Indeed, when chemical shielding anisotropies are determined from conventional NMR relaxation studies, there is a distinct possibility that a portion of the determined relaxation rate should be associated with the antisymmetry of the shielding. Of course such error may lead to an overestimation of the shielding anisotropy or flawed dynamic parameters deduced from the relaxation experiment.

In this note, errors resulting from ignoring antisymmetric shieldings are discussed quantitatively. In particular, we present estimates of the effects upon  $^{15}\text{N}$  spin relaxation by shielding anisotropy and antisymmetry under different motional conditions. In all the calculations, we assume a “model shielding tensor” based on the *ab initio* calculations for the nitrogen atom in formamide,  $\text{HCO-NH}_2$ . A brief comment on the possible role of shielding antisymmetry for the carbonyl  $^{13}\text{C}$  relaxation is given also.

## THE MODEL SHIELDING TENSOR

The nitrogen and carbon shielding tensors have been computed in the same way as the  $^{17}\text{O}$  shieldings reported in a recent paper by Jackowski *et al.* (8). The calculations have been done with the GIAO (gauge-including atomic orbitals) CCSD (coupled cluster singles and doubles) method (9, 10)

using the ACES II program (11). The geometry of formamide was taken from the literature (12). The TZ2P basis set of ACES II, originally taken from Dunning (13), was used. The resulting nitrogen shielding tensor, used for estimating the relaxation effects, is strongly nonaxial. The planarity of the molecule results in the antisymmetric part having only one single nonvanishing element (5). The principal components of the traceless symmetric shielding tensor equal  $-96.4$  ppm ( $\sigma_{zz}$ ),  $8.6$  ppm ( $\sigma_{xx}$ ) and  $87.8$  ppm ( $\sigma_{yy}$ ). We label the axes using the convention that the  $zz$  element of the traceless symmetric tensor is that with the largest absolute value and the  $xx$  element is that with the smallest absolute value. The isotropic, absolute shielding is  $169.9$  ppm and the antisymmetric component,  $\sigma_{yz} = -\sigma_{zy}$ , equals  $18.2$  ppm. The principal  $z$  axis lies in the plane of the molecule, and the principal  $x$  axis is perpendicular to the plane.

The corresponding values for the carbonyl  $^{13}\text{C}$  equal  $-97.4$  ppm ( $\sigma_{zz}$ ),  $22.9$  ppm ( $\sigma_{xx}$ ), and  $74.5$  ppm ( $\sigma_{yy}$ ). The isotropic, absolute shielding is  $35.2$  ppm, the  $y$  principal axis is perpendicular to the plane, and the antisymmetric component,  $\sigma_{xz} = -\sigma_{zx}$ , equals  $4.8$  ppm. Thus, the anisotropy of the symmetric tensor for  $^{13}\text{C}$  is similar to the case of nitrogen, while the antisymmetric part for carbon is much smaller. Hence, the impact of the antisymmetric component is expected to be considerably smaller for  $^{13}\text{C}$  in formamide than for  $^{15}\text{N}$ , and in the following development, we focus our attention on the  $^{15}\text{N}$  case. The isotropic shielding and the elements of the symmetric tensors for both nitrogen and carbon agree quite well with the results obtained using different methods by Vaara *et al.* (14).

## RELAXATION EFFECTS: ISOTROPIC MOTION

Possible nuclear spin relaxation resulting from antisymmetric shielding tensors was first discussed by Blicharski (15). Subsequently, other workers expounded upon this idea (16–18). An excellent review of this topic has been presented by Anet and O’Leary (19). In the limit of motional narrowing, it is easily demonstrated that the longitudinal and transverse relaxation rates,  $1/T_1$  and  $1/T_2$ , are defined in terms of the appropriate spectral densities,  $J_s$  and  $J_a$  (15)

$$(1/T_1) = 4J_s(\omega_0) + 4J_a(\omega_0) \quad [1]$$

$$(1/T_2) = (8/3)J_s(0) + 2J_s(\omega_0) + 2J_a(\omega_0), \quad [2]$$

where, for isotropic reorientations,

$$\begin{aligned} J_s(\omega) &= (\omega_0)^2 \tau_2 / (60(1 + (\omega\tau_2)^2)) \\ &\times \{(\sigma_{xx} - \sigma_{yy})^2 + (\sigma_{xx} - \sigma_{zz})^2 + (\sigma_{yy} - \sigma_{zz})^2\} \quad [3] \end{aligned}$$

and

$$\begin{aligned} J_a(\omega) &= (\omega_0)^2 \tau_1 / (24(1 + (\omega\tau_1)^2)) \\ &\times \{(\sigma_{xy} - \sigma_{yx})^2 + (\sigma_{xz} - \sigma_{zx})^2 + (\sigma_{yz} - \sigma_{zy})^2\}. \quad [4] \end{aligned}$$

$\omega_0$  is the relevant Larmor frequency,  $\tau_2$  is the standard second rank reorientational correlation time, and  $\tau_1$  is its first rank counterpart. For isotropic rotational diffusion,  $\tau_1 = 3\tau_2$  and we can express the longitudinal and transverse relaxation rates,  $T_1^{-1}$  and  $T_2^{-1}$  using only  $\tau_2$  (15):

$$\begin{aligned} (1/T_1) &= (\omega_0)^2 \tau_2 [ \frac{1}{2} \{ (\sigma_{xy} - \sigma_{yx})^2 + (\sigma_{xz} - \sigma_{zx})^2 \\ &+ (\sigma_{yz} - \sigma_{zy})^2 \} / (1 + 9(\omega_0\tau_2)^2) \\ &+ \frac{1}{15} \{ (\sigma_{xx} - \sigma_{yy})^2 + (\sigma_{xx} - \sigma_{zz})^2 \\ &+ (\sigma_{yy} - \sigma_{zz})^2 \} / (1 + (\omega_0\tau_2)^2) ] \quad [5] \end{aligned}$$

$$\begin{aligned} (1/T_2) &= (2(\omega_0)^2 \tau_2 / 45) \{ (\sigma_{xx} - \sigma_{yy})^2 + (\sigma_{xx} - \sigma_{zz})^2 \\ &+ (\sigma_{yy} - \sigma_{zz})^2 \} + (1/2T_1) \quad [6] \end{aligned}$$

Alternatively,  $\frac{1}{2} \{ (\sigma_{xx} - \sigma_{yy})^2 + (\sigma_{xx} - \sigma_{zz})^2 + (\sigma_{yy} - \sigma_{zz})^2 \} = \Delta\sigma^2(1 + \eta^2/3)$ , where the anisotropy and asymmetry are defined as  $\Delta\sigma = \sigma_{zz} - (\sigma_{xx} + \sigma_{yy})/2$  and  $\eta = 3(\sigma_{xx} - \sigma_{yy})/2\Delta\sigma$  respectively. For the model shielding tensor,  $\Delta\sigma = -144$  ppm and  $\eta = 0.82$ . Likewise,  $\{ (\sigma_{xy} - \sigma_{yx})^2 + (\sigma_{xz} - \sigma_{zx})^2 + (\sigma_{yz} - \sigma_{zy})^2 \} / 4 = \delta\sigma^2$ . For our model shielding tensor,  $\delta\sigma^2 = 3.31 \times 10^{-10}$  and the  $\Delta\sigma^2(1 + \eta^2/3) = 2.56 \times 10^{-8}$ .

In the absence of other competing mechanisms of relaxation, for isotropic diffusional rotators in extreme narrowing, accurate determinations of  $T_1/T_2$  ratios enable one to identify and isolate the shielding anisotropy and shielding asymmetry (6). Obviously, if extreme narrowing fails, a certain ambiguity is introduced.

Again, in extreme narrowing, the anisotropy of the model shielding tensor (the  $J_s$  terms) is responsible for 84% of the total shielding tensor contribution to  $1/T_1$ , while the antisymmetry (the  $J_a$  terms) yields 16%. Even though the shielding antisymmetry is much smaller than the shielding anisotropy, a significant portion of  $T_1$  is associated with the antisymmetry. When the motions become slow, so that  $\omega_0^2 \tau_2^2 \gg 1$ , then the relative contributions become 98 and 2%, for the anisotropy and antisymmetry, respectively. In Fig. 1, the motional dependence of the ratio,  $(1/T_1)_a / (1/T_1)_s$ , for the model shielding tensor is shown. Note that the antisymmetric contribution fails to satisfy extreme nar-

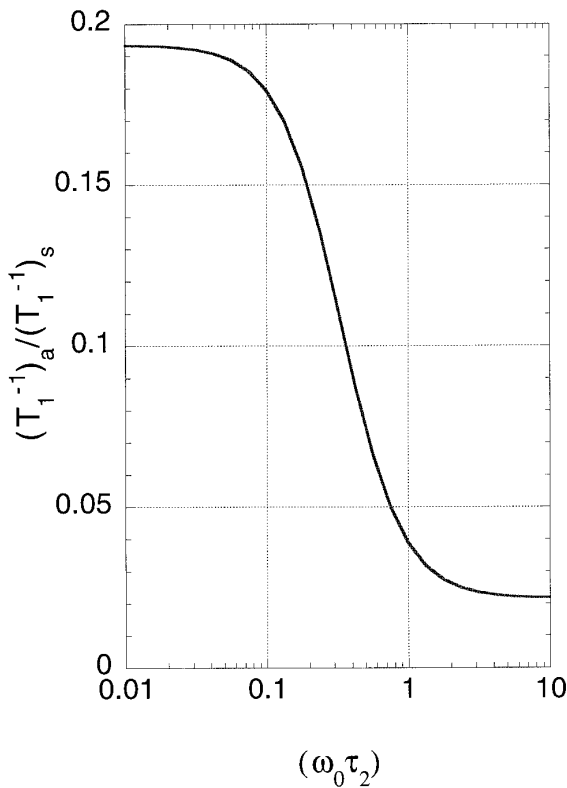


FIG. 1. Plot of the ratio,  $(1/T_1)_a/(1/T_1)_s$ , for the model shielding tensor versus  $\omega_0\tau_2$ .

rowing much sooner than expected; for example, if  $\omega_0\tau_2 = 0.2$ , the antisymmetric contribution is already selectively suppressed. For  $\omega_0 = 2\pi(100 \text{ MHz})$ , this corresponds to  $\tau_2 \approx 300 \text{ ps}$ .

For the spin–spin relaxation rate, the role of the antisymmetric terms is smaller: 8% in extreme narrowing and essentially zero when  $\omega_0\tau_2 \gg 1$ .

In studies of biological macromolecules, it is common to use the model, proposed by Lipari and Szabo (20), in which the spectral density consists of two Lorentzians. The first term is weighted by  $S^2$ , the so-called generalized order parameter squared, and contains (for rank-two tensorial interactions) the correlation time corresponding to the  $\tau_2$  introduced earlier. The second term is weighted by  $1-S^2$  and depends on a correlation time describing fast, local motions. If the dynamics are described by this model and the global motions lie outside of extreme narrowing, the relaxation rate contribution from the antisymmetric shielding will fall between the limits of fast and slow motions described above.

### RELAXATION EFFECTS: ANISOTROPIC MOTION

The constraints of isotropic rotational diffusion are rarely fulfilled, and we also wish to comment on the case of spin

relaxation being effected by symmetric-top-like diffusional reorientation of the molecule-fixed shielding tensor. It is assumed for simplicity that the  $x$  axis of the symmetric part of the model shielding tensor (the axis perpendicular to the molecular plane) coincides with the unique principal axis of the rotational diffusion tensor. Again, the shielding antisymmetry has only one nonvanishing pair of components ( $\sigma_{ij} = -\sigma_{ji} = \delta\sigma$ ), and this one pair of components orients the axis of this vector-like interaction along the  $x$  axis ( $\sigma_{yz} \neq 0$ ) defined by the diagonalized rank-two shielding tensor. These simplifying assumptions can be eliminated easily but the resulting expressions are unwieldy (18).

Given this scenario, one can define the spectral densities associated with each of these two contributions to the relaxation process

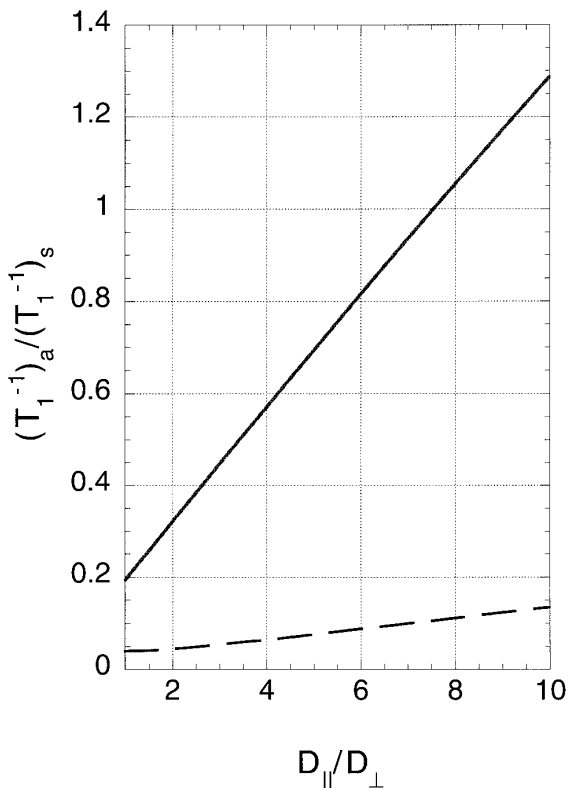
$$J_a(\omega) = ((\omega_0\delta\sigma)^2/6) \{ \cos^2\theta_{yz}(\tau_{10}/(1 + (\omega\tau_{10})^2)) + \sin^2\theta_{yz}\tau_{11}/(1 + (\omega\tau_{11})^2) \} \quad [7]$$

$$J_s(\omega) = (\omega_0^2/120) [ (\sigma_{xx} - \sigma_{zz})^2 \times \{ (3\cos^2\theta_x - 1)^2\tau_{20}/(1 + (\omega\tau_{20})^2) + 12\sin^2\theta_x\cos^2\theta_x\tau_{21}/(1 + (\omega\tau_{21})^2) + 3\sin^4\theta_x\tau_{22}/(1 + (\omega\tau_{22})^2) \} + (\sigma_{yy} - \sigma_{zz})^2 \{ (3\cos^2\theta_y - 1)^2\tau_{20}/(1 + (\omega\tau_{20})^2) + 12\sin^2\theta_y\cos^2\theta_y\tau_{21}/(1 + (\omega\tau_{21})^2) + 3\sin^4\theta_y\tau_{22}/(1 + (\omega\tau_{22})^2) \} + 2(\sigma_{xx} - \sigma_{zz})(\sigma_{yy} - \sigma_{zz}) \{ (3\cos^2\theta_x - 1) \times (3\cos^2\theta_y - 1)\tau_{20}/(1 + (\omega\tau_{20})^2) + 12\sin\theta_x\cos\theta_x\sin\theta_y\cos\theta_y\cos(\phi_x - \phi_y) \times \tau_{21}/(1 + (\omega\tau_{21})^2) + 3\sin^2\theta_x\sin^2\theta_y\cos(2\phi_x - 2\phi_y) \times \tau_{22}/(1 + (\omega\tau_{22})^2) \} ], \quad [8]$$

where  $\tau_{Lk}$  can be defined in terms of the two diffusion constants,  $D_{\parallel}$  and  $D_{\perp}$ ,  $1/\tau_{Lk} = L(L+1)D_{\perp} + k^2(D_{\parallel} - D_{\perp})$ . The angular arguments,  $\theta_x (= \theta_{yz})$ ,  $\phi_x$ ,  $\theta_y$  and  $\phi_y$ , position the  $x$  and  $y$  axes of the diagonalized shielding tensor in the diffusion frame.

For the geometry exemplified,  $\theta_x = \theta_{yz} = 0$ ,  $\theta_y = \pi/2$ , these spectral densities simplify accordingly

$$J_a(\omega) = ((\omega_0\delta\sigma)^2/6) \{ (\tau_{10}/(1 + (\omega\tau_{10})^2)) \} \quad [9]$$



**FIG. 2.** Plot of the ratio,  $(1/T_1)_a/(1/T_1)_s$ , for the model shielding tensor versus  $D_{\parallel}/D_{\perp}$  for  $\omega_0\tau_2 \ll 1$  (solid curve) and  $\omega_0\tau_2 = 1$  (dashed curve).

$$\begin{aligned}
 J_s(\omega) &= (1/30)\omega_0^2 \{ \Delta\sigma^2(1 + \eta^2/3)\tau_{20}/(1 + (\omega\tau_{20})^2) \\
 &\quad - (3/4)(\sigma_{yy} - \sigma_{zz})^2[\tau_{20}/(1 + (\omega\tau_{20})^2) \\
 &\quad - \tau_{22}/(1 + (\omega\tau_{22})^2)] \} \\
 &= (1/30)\omega_0^2\Delta\sigma^2(1 + \eta^2/3)\tau_{20}/(1 + (\omega\tau_{20})^2) \\
 &\quad \times \{ 1 - (3/4)(\sigma_{yy} - \sigma_{zz})^2/\Delta\sigma^2(1 + \eta^2/3) \\
 &\quad \times [1 - \tau_{22}(1 + (\omega\tau_{20})^2)/\tau_{20}(1 + (\omega\tau_{22})^2)] \}.
 \end{aligned}
 \tag{10}$$

For this specific geometrical arrangement, it is seen that prolate motional anisotropy ( $D_{\parallel} > D_{\perp}$ ;  $\tau_{20} > \tau_{21}, \tau_{22}$ ) reduces the effective strength of the shielding anisotropy,  $\Delta\sigma$ , while leaving the antisymmetry unchanged, whereas for oblate motional anisotropy ( $D_{\parallel} < D_{\perp}$ ;  $\tau_{20} < \tau_{21}, \tau_{22}$ ), the influence of the shielding anisotropy is increased. For rapid anisotropic motions ( $1/\omega_0 \gg \tau_{20}$ ;  $D_{\parallel} \gg D_{\perp}$ ),  $J_s$  is strongly suppressed and the  $J_a$  term is expected to dominate  $1/T_1$  even though  $(\delta\sigma)^2/\Delta\sigma^2(1 + \eta^2/3) < 0.01!$  In Fig. 2,  $(1/T_1)_a/(1/T_1)_s$  versus  $D_{\parallel}/D_{\perp}$  is plotted for  $\omega_0\tau_{20} \ll 1$  and  $\omega_0\tau_{20} = 1$ . As clearly seen, in certain situations, even small motional anisotropies may enhance dramatically the effects associated with shielding antisymmetry.

Incredibly, the behavior noted above is always true whenever the shielding tensor is highly asymmetric ( $\eta \rightarrow 1$ ) and the  $x$  axis reorients slowly compared with the reorientation of the  $y$  and  $z$  axes (with all motions in extreme narrowing). The use of this novel aspect of ‘‘cross-correlation’’ for exacting determination of motional dynamics will be pursued elsewhere.

On the slow motion side of the  $T_1$  minimum, the effects attributable to the antisymmetric components are once again quenched dramatically. Of course, there are numerous other situations which can be envisioned where the orientation of the shielding tensor and diffusion axes may be equally effective at reducing or accentuating the importance of shielding anisotropy relative to the shielding asymmetry. As always, it is important that one be cognizant of the intriguing interplay between dynamics and structure when analyzing nuclear spin relaxation phenomena.

## CONCLUSIONS

At the present, the effects attributable to antisymmetric components of the shielding tensor are poorly understood and ill-characterized. Numerous theoretical investigations have demonstrated that the antisymmetric components can be quite large (21). In this study, a simple spin system has been discussed. The antisymmetry of the nitrogen shielding is modest and may be considered ‘‘typical.’’ It is argued that in extreme narrowing, a sizable fraction of any relaxation rate attributable to ‘‘shielding anisotropy’’ may be more properly associated with the shielding antisymmetry. Isolation and identification of each separate contribution will prove challenging. Anisotropic motions may greatly exaggerate (or in some cases, suppress) the relative importance of the antisymmetric contribution, and the investigator should proceed with due caution.

However, if spin relaxation measurements are made out of extreme narrowing, say for  $^{15}\text{N}$  or for carbonyl  $^{13}\text{C}$  in a biopolymer, the impact of the antisymmetric component is greatly diminished and can generally be ignored. Although certainly true for any parameter associated with dissipation of coherence, it appears that this statement is equally valid for  $T_1$  related studies. Furthermore, it is important to appreciate that failure of the extreme narrowing criterion sets in much sooner than normally anticipated.

Because the antisymmetric interaction transforms under molecular reorientation as a rank-one spherical harmonic, interferences with dipole–dipole or quadrupole interactions are absent (7, 22). If determination of the shielding tensor anisotropy is effected by relaxation-induced polarization or coherence transfer methods, then one can rigorously exclude from consideration the antisymmetric contribution. However, it must be recognized that polarization and coherence

transfer rates are much more sensitive to motional anisotropies than commonly believed.

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