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Relaxation-Induced Polarization Transfer and the Determination of Methyl Group ^{13}C Chemical Shielding Anisotropy

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Numerous pathways by which nuclear spin polarization is transferred, rather than dissipated, through the spin relaxation process can be identified and exploited. In this study, application of relaxation-induced polarization transfer has been implemented to obtain the ^{13}C chemical shielding anisotropy (-23 ± 6 ppm) of the methyl group in methylcobalamin dissolved in D_2O (300 K).

I. Introduction

Nuclear spin relaxation results from site-specific fluctuations in electric and magnetic nuclear−extranuclear couplings. The fluctuations of these anisotropic interactions are induced by molecular rotation, translation, and exchange. Hence, studies of nuclear spin relaxation provide the chemical researcher with a discriminating probe of submicroscopic structures and dynamics. Perhaps the most powerful NMR relaxation methodologies monitor the transient behavior of relaxation-induced multispin order, an order most often induced by temporal correlations between competing relaxation pathways.[1−3] The characteristic signatures of multispin order are most easily recognized in spin systems where individual transitions are spectrally isolated and the study of scalar coupled spin systems has evolved into an important technique for the molecular scientist.[4]

A convenient framework used in analysis of relaxation-induced multispin order involves the concept of the "magnetization mode".[5−7] These "modes", which can be brought into direct spectral identification with various observables, provide an alternative operator basis which is more insightful than the basis defined by elements of the density matrix itself. Similar techniques have been employed to simplify descriptions of coherence and polarization transfer processes in multidimensional NMR.[8]

In general, the chosen magnetization modes have well-defined spin inversion symmetry. Modes which do not distinguish between symmetrically positioned multiplet components are antisymmetric with respect to spin inversion and can be identified with odd-spin order operators, whereas even-spin operators are symmetric with respect to spin inversion.[5−8] It is recognized that temporal correlation between two interactions of similar parity (e.g., dipole−dipole or quadrupole couplings) scramble polarizations but do not mix even and odd rank modes. Conversely, temporal correlation between two interactions of opposite parity (e.g., dipole−dipole and shielding anisotropy) can induce polarization transfer only between two modes of opposite parity. Recently, numerous experimental applications based upon these fundamental principles have been described.[9]

Utilization of these characteristics has rendered multiplet relaxation extremely useful for determination of electronic shielding anisotropies in solution-state studies. In this work, relaxation-induced polarization transfer will be used to investigate the ^{13}C-methyl chemical shielding anisotropy in methylcobalamin, where the methyl group is directly attached to cobalt.

II. Theory

Consider the four spin-1/2, AX_3 system. Spin "A" (^{13}C) is associated with the angular momentum operator, $\mathbf{I}$, whereas the three identical X spins (H, H', H'') are associated with the angular momentum operators $\mathbf{S}$, $\mathbf{S}'$, and $\mathbf{S}''$.

The magnetization modes chosen for the subsequent analysis are the modes originally defined and discussed in ref 10:

$$^{a}\nu_1 = \langle I_z\rangle - \langle I_z\rangle_{eq}$$

$$^{a}\nu_2 = \{\langle S_z + S_z' + S_z''\rangle - \langle S_z + S_z' + S_z''\rangle_{eq}\}/\sqrt{3}$$

$$^{a}\nu_3 = 4\langle I_z(S_zS_z' + S_zS_z'' + S_z'S_z'')\rangle/\sqrt{3}$$

$$^{a}\nu_4 = 4\langle S_zS_z'S_z''\rangle$$

$$^{a}\nu_5 = 2\langle S_z(S_+{}'S_-{}'' + S_-{}'S_+{}'') + S_z'(S_+S_-{}'' + S_-S_+{}'') + S_z''(S_+S_-{}' + S_-S_+{}'\rangle/\sqrt{6}$$

$$^{a}\nu_6 = 2\langle I_z(S_+{}'S_-{}'' + S_-{}'S_+{}'') + (S_+S_-{}'' + S_-S_+{}'') + (S_+S_-{}' + S_-S_+{}')\rangle/\sqrt{6}$$

$$^{s}\nu_7 = 2\langle I_z(S_z + S_z' + S_z'')\rangle/\sqrt{3}$$

$$^{s}\nu_8 = 8\langle I_zS_zS_z'S_z''\rangle$$

$$^{s}\nu_9 = 2\langle(S_zS_z' + S_zS_z'' + S_z'S_z'')\rangle/\sqrt{3}$$

$$^{s}\nu_{10} = \langle(S_+{}'S_-{}'' + S_-{}'S_+{}'') + (S_+S_-{}'' + S_-S_+{}'') + (S_+S_-{}' + S_-S_+{}')\rangle/\sqrt{6}$$

$$^{s}\nu_{11} = 4\langle I_z(S_z(S_+{}'S_-{}'' + S_-{}'S_+{}'') + S_z'(S_+S_-{}'' + S_-S_+{}'') + S_z''(S_+S_-{}' + S_-S_+{}'))\rangle/\sqrt{6} \quad (1)$$

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It is assumed that the three X spins are magnetically equivalent. Each of these modes is either symmetric (s) or antisymmetric (a) with respect to spin inversion. All modes are normalized with respect to I_z. For degenerate spin systems such as the AX_3 system discussed in this work, the choice of a complete set of magnetization modes is characterized by a certain arbitrariness for reasons discussed elsewhere.[11]

For studies performed in isotropic media, the set defined above includes all five independent measurables, ${}^{a}\nu_1(t)$, ${}^{a}\nu_2(t)$, ${}^{a}\nu_3(t)$, ${}^{s}\nu_7(t)$ and ${}^{s}\nu_8(t)$. Assuming the high-temperature limit is obtained, observables within the 1:3:3:1 ^{13}C quartet include ${}^{a}\nu_1(t)$, the summed intensity of the four members of the quartet minus their equilibrium intensities; ${}^{a}\nu_3(t)$, 3 times the intensities of the outermost lines minus the central lines; ${}^{s}\nu_7(t)$, the weighted sum of the two high-field components minus the two lower field components; ${}^{s}\nu_8(t)$, the highest field minus the lowest field component minus the higher field central component minus the lower field central component. These identifications assume a positive scalar coupling and like-signed gyromagnetic ratios for spins A and X.

Using standard methods,[5,12] the time evolution of these modes can be described in master equation form as

$$-(\mathrm{d}/\mathrm{d}t)\nu_i(t) = \sum_j \Gamma_{ij}\, \nu_j(t) \qquad (2)$$

The chosen modes are orthonormal and hence $\Gamma_{ij} = \Gamma_{ji}$. In the absence of symmetry crossing interferences (e.g., dipolar-shielding anisotropy interference), Γ is block diagonal[6] and, as noted previously, polarization is transferred only between modes of similar parity.

Specific elements for the relaxation matrix, Γ, in various limits, have appeared elsewhere.[10,13] Assuming spin relaxation is induced by shielding anisotropies (SA_C, SA_H), mutual dipole–dipole couplings (D_{CH}, $D_{HH'}$), and uncorrelated random-field-like contributions (R_1^{C}, R_1^{H}), the various elements of Γ are reproduced in consistent notation in the Appendix. In general, each element of Γ is described as a linear combination of the following autocorrelation, $\mathbf{J}^{\eta}$, or cross-correlation, $\mathbf{K}^{\eta\cdot\eta'}$, spectral densitites ($\eta$, $\eta' = SA_C$, SA_H, D_{CH}, $D_{HH'}$):

$$\mathbf{J}^{\mathbf{D_{CH}}}(\omega) = (3/10)(\mu_o/4\pi)^2(\gamma_C\gamma_H h\langle r_{CH}{}^{-3}\rangle)^2\, f(\tau_c,\tau_i,\theta_{CH},\omega)$$

$$\mathbf{J}^{\mathbf{DD_{HH'}}}(\omega) = (3/10)(\mu_o/4\pi)^2(\gamma_H{}^2 h\langle r_{HH'}{}^{-3}\rangle)^2\, f(\tau_c,\tau_i,\theta_{HH'},\omega)$$

$$\mathbf{J}^{\mathbf{SA_{C(H)}}}(\omega) = (1/30)(\omega_{I(S)}\Delta\sigma_{C(H)})^2\, f(\tau_c,\tau_i,\theta_{C(H)},\omega)$$

$$\mathbf{K}^{\mathbf{D_{CH}D_{CH'}}}(\omega) = (3/10)(\mu_o/4\pi)^2(\gamma_C\gamma_H h\langle r_{CH}{}^{-3}\rangle)^2 f(\tau_c,\tau_i,\theta_{CH},\theta_{CH'},\omega)$$

$$\mathbf{K}^{\mathbf{D_{CH}D_{HH'}}}(\omega) = (3/10)(\mu_o/4\pi)^2(\gamma_C\gamma_H{}^3 h\langle r_{CH}{}^{-3}\rangle\langle r_{HH'}{}^{-3}\rangle)f(\tau_c,\tau_i,\theta_{CH},\theta_{HH'},\omega)$$

$$\mathbf{K}^{\mathbf{D_{CH}D_{H'H''}}}(\omega) = (3/10)(\mu_o/4\pi)^2(\gamma_C\gamma_H{}^3 h\langle r_{CH}{}^{-3}\rangle\langle r_{H'H''}{}^{-3}\rangle)f(\tau_c,\ \tau_i,\ \theta_{CH},\ \theta_{H'H''},\ \omega)$$

$$\mathbf{K}^{\mathbf{D_{HH'}\,D_{HH''}}}(\omega) = (3/10)(\mu_o/4\pi)^2(\gamma_H{}^2 h\langle r_{HH'}{}^{-3}\rangle)^2 f(\tau_c,\tau_i,\theta_{HH'},\theta_{HH''},\omega)$$

$$\mathbf{K}^{\mathbf{D_{HH'}SA_H}}(\omega) = (1/10)(\mu_o/4\pi)^2(\omega_H\Delta\sigma_H)(\gamma_H{}^2 h\langle r_{HH'}{}^{-3}\rangle)f(\tau_c,\tau_i,\theta_{HH'},\theta_H,\omega)$$

$$\mathbf{K}^{\mathbf{D_{HH'}SA_{H''}}}(\omega) = (1/10)(\mu_o/4\pi)^2(\omega_H\Delta\sigma_H)(\gamma_H{}^2 h\langle r_{HH'}{}^{-3}\rangle)f(\tau_c,\tau_i,\theta_{HH'},\theta_{H''},\omega)$$

$$\mathbf{K}^{\mathbf{D_{CH}\,SA_H}}(\omega) = (1/10)(\mu_o/4\pi)^2(\omega_H\Delta\sigma_H)(\gamma_C\gamma_H h\langle r_{CH}{}^{-3}\rangle)f(\tau_c,\tau_i,\theta_{CH},\theta_H,\omega)$$

$$\mathbf{K}^{\mathbf{D_{CH}\,SA_{H'}}}(\omega) = (1/10)(\mu_o/4\pi)^2(\omega_H\Delta\sigma_H)(\gamma_C\gamma_H h\langle r_{CH}{}^{-3}\rangle)f(\tau_c,\tau_i,\theta_{CH},\theta_{H'},\omega)$$

$$\mathbf{K}^{\mathbf{D_{CH}\,SA_C}}(\omega) = (1/10)(\mu_o/4\pi)^2(\omega_C\Delta\sigma_C)(\gamma_C\gamma_H h\langle r_{CH}{}^{-3}\rangle)f(\tau_c,\tau_i,\theta_{CH},\theta_C,\omega)$$

$$\mathbf{K}^{\mathbf{SA_H\,SA_{H'}}}(\omega) = (1/30)(\omega_H\Delta\sigma_H)^2 f(\tau_c,\tau_i,\theta_H,\theta_{H'},\omega) \qquad (3)$$

The interaction constants introduced include, r_{ij}, the appropriately averaged internuclear distance, γ_i, the gyromagnetic ratio of spin "i", and $\omega_i\Delta\sigma_i$, the shielding anisotropy of spin i.

The specfic form of the reduced spectral density terms, $f(\tau_c,\tau_i,\theta_\eta,\omega)$ or $f(\tau_c,\tau_i,\theta_\eta,\theta_{\eta'},\omega)$, is simplified by assuming that methyl group dynamics are described accurately with only two time constants: one time constant characterizing the fast motion about the triad axis, τ_i, and a second descsribisng the slower isotropic tumbling of the triad axis itself. This last motion is characterized by the reorientational correlation time, τ_c.

In this case,

$$f(\tau_c,\tau_i,\theta_\eta,\omega) = (1/4)(3\cos^2\theta_\eta - 1)^2\tau_c/(1 + \omega^2\tau_c{}^2) + [1 - (1/4)(3\cos^2\theta_\eta - 1)^2]\tau_i$$

and

$$f(\tau_c,\tau_i,\theta_\eta,\theta_{\eta'},\omega) = (1/4)(3\cos^2\theta_\eta - 1)(3\cos^2\theta_{\eta'} - 1)\tau_c/(1 + \omega^2\tau_c{}^2) + [(1/2)(3\cos^2\alpha - 1) - (1/4)(3\cos^2\theta_\eta - 1)(3\cos^2\theta_{\eta'} - 1)]\tau_i$$

where $\cos\alpha = \cos\theta_\eta\cos\theta_{\eta'} + \sin\theta_\eta\sin\theta_{\eta'}(\cos\phi_\eta\cos\phi_{\eta'} + \sin\phi_\eta\sin\phi_{\eta'})$ and the angular arguments, θ_η, ϕ_η, position the principal axis of the ηth interaction relative to the C–Co bond axis.

It can be argued that modeling the ^{13}C shielding tensor as axially symmetric introduces no significant error. Although the asymmetry in the methyl ^{13}C shielding tensor can be significant,[14] it can be demonstrated[15] that this asymmetry will play no role in methyl group relaxation if the conditions described above are obtained. At present, proton shielding tensors are poorly characterized. Further consideration of the proton shielding tensor will not prove important in subsequent development.

III. Experimental Section

^{13}C-enriched methylcobalamin (Figure 1) was prepared by standard methods.[16] The sample studied was produced by dissolving 20.0 mg of methylcobalamin in 2.5 mL D_2O (99.9 atom % D, Aldrich, Milwaukee). The pD of the solution was 5.8.

The following three perturbation-response measurements were performed: (i) carbon inversion, observe carbon recovery; (ii) proton inversion, observe proton recovery; (iii) proton inversion, observe carbon recovery. All experiments were done at a controlled temperature (300 K) on degassed samples. Data were obtained on a Bruker AM360 NMR spectrometer ($B_o = 8.45$ T; $\omega_C/2\pi = 90.3$ MHz, $\omega_H/2\pi = 360.1$ MHz) and a Bruker

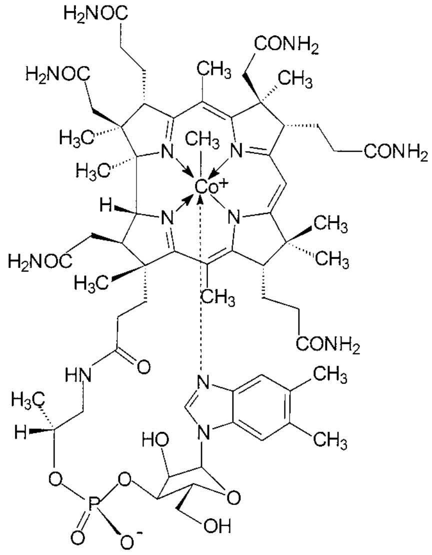

Figure 1. Structure of methylcobalamin.

TABLE 1

relaxation parameter	value at 8.46 T	value at 14.09 T
$\Gamma_{11} = 1/T_{1C}$	2.32 ± 0.2 s^{-1}	1.38 ± 0.2 s^{-1}
$\Gamma_{22} = 1/T_{1H}$	2.38 ± 0.2 s^{-1}	1.30 ± 0.2 s^{-1}
$\eta_{C-\{H\}}$	0.61 ± 0.05	0.40 ± 0.04
$\Delta\sigma_C$	-23 ± 8 ppm	-23 ± 7 ppm
τ_c	600 ± 60 ps	600 ± 50 ps
τ_i	<6 ps	

DMX 600 NMR spectrometer ($B_o = 14.09$ T; $\omega_C/2\pi = 150.5$ MHz, $\omega_H/2\pi = 600.1$ MHz). Typically, 12 different delay times were used to determine the recovery characteristics. Adequate signal-to-noise was achieved with 200−600 scans (DMX 600) or 2400 scans (AM 360). The time between subsequent scans always was greater than 5 times the longest "T_1" (largest Γ_{ii}^{-1}).

Deduction of the various spectral density functions from the raw relaxation data was accomplished by a nonlinear least-squares fitting routine described elsewhere.[17]

IV. Results and Discussion

In Table 1, the three basic NMR relaxation parameters characteristic of this system are reproduced. Γ_{11} is the conventional spin−lattice relaxation time of ^{13}C, Γ_{22} is the conventional spin−lattice relaxation time of the protons, and $\eta_{C-\{H\}}$ is the measured Overhauser enhancement. Also listed in this table are three important derived parameters, $\Delta\sigma$, τ_c, and τ_i. In Table 2, the various spectral densities obtained from the fits described in the Experimental Section are presented.

A typical ^{13}C quartet is reproduced in Figure 2. The time evolution of this quartet after an inversion perturbation is shown in Figure 3. It is apparent that there is substantial broadening of the multiplet components due to the rapid quadrupolar relaxation of ^{59}Co ($I = 7/2$, 100% abundant, $\gamma_{Co}/\gamma_H \approx 0.237$). However, this scalar relaxation of the second kind[18] does not contribute to relaxation of the modes considered in this study. Indeed, the rapid relaxation of ^{59}Co ensures that all multispin order involving Co will be nulled and hence, the ^{59}Co−^{13}C dipolar interaction can be treated rigorously as a random field contribution.[19] Given that the C−Co distance[20] is approximately 2.0 Å and $\gamma_{Co} \approx \gamma_C$, the magnitude of this random-field-like contribution, $21(\mu_o/4\pi)^2(\gamma_C\gamma_{Co}h\langle r_{CCo}{}^{3-}\rangle)^2\tau_c$, almost equals $\mathbf{J}^{D_{CH}}(\omega_c)$ for the regime probed by this study.

Actually, the fact that the "random" field is so well characterized in this system provides an additional check on internal consistency. It is expected that this contribution will dominate spin-internal rotation, the only other reasonable "random-field" source. Because the internuclear distance is well-known and the C−Co axis is collinear with the principal axis of rotation, this "random-field" term yields a very good, independent measure of τ_c.

TABLE 2[a]

spectral density	$T = 300$ K; $B_o = 8.46$ T (s^{-1})	$T = 300$ K; $B_o = 14.09$ T (s^{-1})
$\mathbf{J}^{D_{CH}}(\omega_C)$	0.36 ± 0.04	0.31 ± 0.04
$\mathbf{J}^{D_{CH}}(\omega_C + \omega_H)$	0.11 ± 0.02	0.04 ± 0.02
$\mathbf{J}^{D_{CH}}(\omega_H - \omega_C)$	0.20 ± 0.04	0.11 ± 0.04
$\mathbf{K}^{D_{CH}\cdot D_{CH'}}(\omega_C)$	0.37 ± 0.02	0.30 ± 0.03
$\mathbf{J}^{D_{HH'}}(\omega_H)$	0.32 ± 0.04	0.16 ± 0.04
$\mathbf{J}^{D_{HH'}}(2\omega_H)$	0.14 ± 0.04	0.05 ± 0.02
$\mathbf{K}^{D_{HH'}D_{H'H''}}(\omega_H)$	0.30 ± 0.04	0.15 ± 0.04
$\mathbf{K}^{D_{HH'}D_{H'H''}}(2\omega_H)$	0.12 ± 0.04	0.04 ± 0.02
$\mathbf{K}^{D_{CH}D_{HH'}}(\omega_H)$	0.09 ± 0.04	0.03 ± 0.02
$\mathbf{K}^{D_{CH}D_{H'H''}}(\omega_H)$	0.10 ± 0.04	0.03 ± 0.02
$\mathbf{K}^{D_{CH}SA_C}(\omega_C)$	0.024 ± 0.004	0.038 ± 0.006
$\mathbf{J}^{SA_C}(\omega_C)$	0.003 ± 0.001	0.008 ± 0.002
$\mathbf{J}^{SA_H}(\omega_H)$	<0.002	<0.002
$\mathbf{R}_1{}^{C}(\omega_C)$	0.34 ± 0.05	0.33 ± 0.04
$\mathbf{R}_1{}^{H}(\omega_H)$	0.18 ± 0.08	0.18 ± 0.06

[a] All other spectral densities [s^{-1}], $\mathbf{K}^{D_{HH'}\ SA_H}(\omega_H)$, $\mathbf{K}^{D_{HH'}\ SA_{H''}}(\omega_H)$, $\mathbf{K}^{D_{CH}\ SA_{H'}}(\omega_H)$, $\mathbf{K}^{SA_H\ SA_{H'}}(\omega_H)$, and $\mathbf{K}^{D_{CH}\ SA_H}(\omega_H)$, could not be determined.

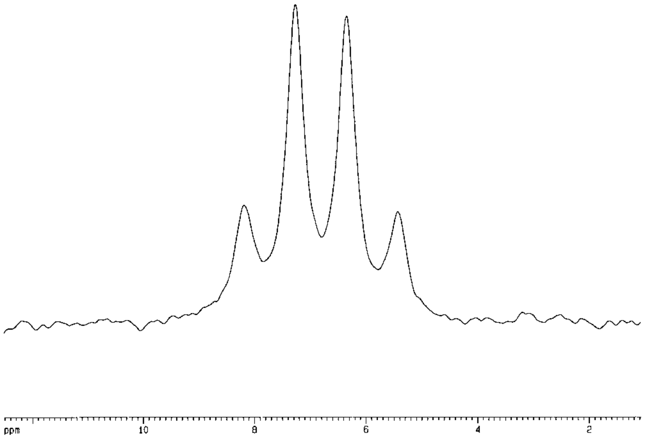

Figure 2. ^{13}C spectrum of the methyl group in methylcobalamine obtained at 300 K and 14.09 T in D_2O solution.

In Figure 4, the time evolution of the various ^{13}C modes is shown for the experiments performed at the higher applied magnetic field strength (14.09 T). It is clear from these figures that both two-spin ($^s\nu_7$) and three-spin order ($^a\nu_3$) is generated throughout the course of the relaxation process. A least-squares fit of these data to eq 2 yielded the spectral densities summarized in Table 1. Of particular interest is the behavior of two-spin ($^s\nu_7$) order.

In the system under study, the C−H scalar coupling constant is positive and the two nuclei have like-signed gyromagnetic ratios. Hence, the appropriately weighted high-field lines minus low-field lines define mode ($^s\nu_7$). The data clearly indicates that the high-field lines recover more slowly and hence this mode is negative. If $\tau_c \gg \tau_i$ and $\tau_c\tau_i\omega^2 \ll 1$, then the anisotropic shielding and dipolar interactions will be strongly anticorrelated, $f(\tau_c,\tau_i,\theta_{CH},\theta_C,\omega) \approx (-\tau_c/3)/(1 + \omega^2\tau_c^2)$. However, because the dipolar and CSA interactions are oppositely signed, the shielding anisotropy must be negative to explain the experimental data. These data determine, quite precisely, the chemical shielding anisotropy of the methyl group in methylcobalamin to be −23 ppm.

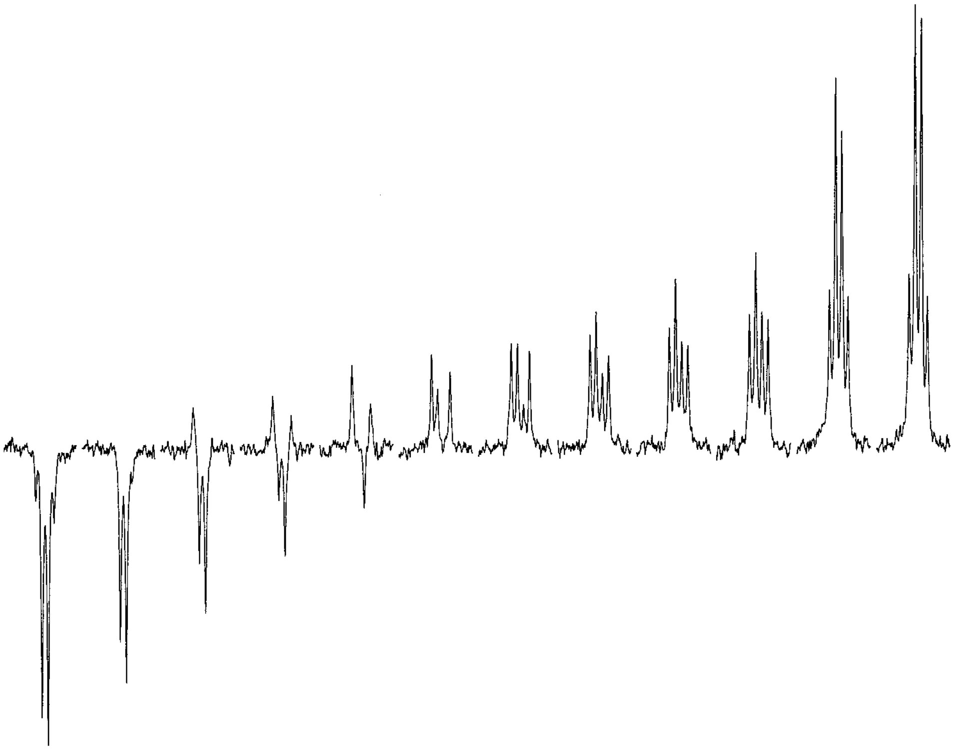

Figure 3. ^{13}C inversion recovery spectrum (delay 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 2.0, 5.0 from left to right).

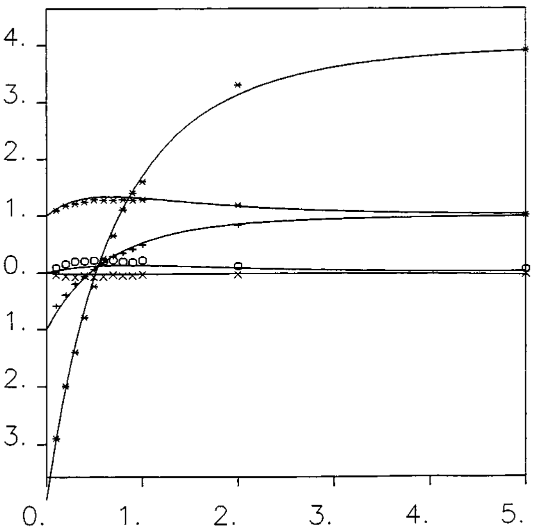

Figure 4. Experimentally determined values of the single spin order ($^{a}\nu_1$) are [+] signs, the two spin order ($^{s}\nu_7$) are [×] signs, and three spin order ($^{a}\nu_3$) are [○] signs; the calculated values appear as lines.

Comparison of the various dipole auto- and cross-correlated spectral densities is equally informative. It is apparent that all dipolar interactions are highly correlated, $\mathbf{J}^{D_{CH}}(\omega) \approx \mathbf{K}^{D_{CH}\cdot D_{CH'}}(\omega)$ and $\mathbf{J}^{D_{HH'}}(\omega) \approx \mathbf{K}^{D_{HH'}\cdot D_{HH''}}(\omega)$. This is clear evidence that $\tau_c \gg \tau_i$. Also, because $\gamma_C\langle r_{CH}{}^{-3}\rangle/\gamma_H\langle r_{HH}{}^{-3}> \approx 0.92$, $\mathbf{K}^{D_{CH}\cdot D_{HH'}}(\omega) \approx (3/10)\mathbf{K}^{D_{HH'}\cdot D_{HH''}}(\omega)$. Utilizing standardized curves,[21] it is deduced that motions about the triad axis are at least 2 orders of magnitude more rapid than the overall motion of the molecular framework. Again, using tetrahedral geometry, it is seen from eqs 3 that $30\mathbf{J}^{D_{CH}}(\mu_o/4\pi)^{-2}(\gamma_C\gamma_H h\langle r_{CH}{}^{-3}\rangle)^{-2} = \tau_c/(1 + \omega^2\tau_c{}^2)$. The experimental value obtained for $\mathbf{J}^{D_{CH}}(\omega_C)$ yields $\tau_c \approx 600 \pm 50$ ps. In addition, this value has been cross-checked by determination of T_1 values for carbons belonging to the hydrated phthalocyanine moiety (e.g., T_1 for carbon 10 is 0.82 s). The measured NOE enhancement at 4.69 T ($\eta = 0.80$) again confirms the data is fit nicely with one, overall, isotropic time constant, τ_c.

V. Conclusion

It has been demonstrated that the approach described in this study can be used to determine, quickly and accurately, shielding anisotropies of methyl groups in isotropic fluids. Similarly, it has been shown that the methyl group attached to the central Co atom in the cobalamin undergoes very rapid internal rotation resulting in complete correlation of the various interactions responsible for inducing nuclear spin relaxation. It is also interesting to note that, in contrast to most C-13 shielding anisotropies of methyl carbons, the chemical shielding orthogonal to the C−Co bond is greater than the shielding parallel to this triad axis, resulting in a negative shielding anisotropy of −23 ppm. The overall correlation time of the methylcobalamin turned out to be $\tau_c \approx 600 \pm 50$ ps.

VI. Appendix

The perturbation-response characteristics of the 11 magnetizations assoicated with the AX_3 ($^{13}CH_3$) spin system can be written in the form shown in eq 2. Using the numbering scheme introduced in eq 1, the specific elements of Γ_{ij} ($=\Gamma_{ji}$) can be written in terms of the spectral densities introduced in eq 3. To simplify the following expressions, it is assumed that the random fields experienced by the protons are uncorrelated and nonrandom-field adiabatic terms are fully correlated (e.g., $\mathbf{J}^{D_{CH}}(0) = \mathbf{K}^{D_{CH}D_{CH'}}(0)$). This is equivalent to assuming that $\tau_c \gg \tau_i$. Utilizing the following recurring combinations of dipolar terms, $\rho_{CH} = (1/3)\mathbf{J}^{D_{CH}}(\omega_H - \omega_C) + \mathbf{J}^{D_{CH}}(\omega_C) + 2\mathbf{J}^{D_{CH}}(\omega_C + \omega_H)$, $\rho_{HC} = (1/3)\mathbf{J}^{D_{CH}}(\omega_H - \omega_C) + \mathbf{J}^{D_{CH}}(\omega_H) + 2\mathbf{J}^{D_{CH}}(\omega_C + \omega_H)$, $\rho_{HCH'}(C) = (1/3)\mathbf{K}^{D_{CH}\ D_{CH'}}(\omega_H - \omega_C) + \mathbf{K}^{D_{CH}\ D_{CH'}}(\omega_C) + 2\mathbf{K}^{D_{CH}\ D_{CH'}}(\omega_H + \omega_C)$, $\rho_{HCH'}(H) = (1/3)\mathbf{K}^{D_{CH}\ D_{CH'}}(\omega_H - \omega_C) + \mathbf{K}^{D_{CH}\ D_{CH'}}(\omega_H) + 2\mathbf{K}^{D_{CH}\ D_{CH'}}(\omega_H + \omega_C)$, $\sigma_{CH} = 2\mathbf{J}^{D_{CH}}(\omega_H + \omega_C) - (1/3)\mathbf{J}^{D_{CH}}(\omega_H - \omega_C)$, $\sigma_{HCH'} = 2\mathbf{K}^{D_{CH}D_{CH'}}(\omega_H + \omega_C) - (1/3)\mathbf{K}^{D_{CH}\ D_{CH'}}(\omega_H - \omega_C)$, $\delta_{CH} = \mathbf{J}^{D_{CH}}(\omega_C) + \mathbf{J}^{D_{CH}}(\omega_H)$, $\delta_{HCH'} = \mathbf{K}^{D_{CH}}$

$^{\mathrm{D_{CH'}}}(\omega_\mathrm{C}) + \mathbf{K}^{\mathrm{D_{CH}\,D_{CH'}}}(\omega_\mathrm{H})$, and $\rho_{\mathrm{HH'}} = \mathbf{J}^{\mathrm{D_{HH'}}}(\omega_\mathrm{H}) + 4\mathbf{J}^{\mathrm{D_{HH'}}}(2\omega_\mathrm{H})$, the following identifications result (more general expressions can be found in the original literature[10,13]).

1. Antisymmetric Manifold Couplings. *a. Diagonal Elements: Dissipative Rates.*

$$\Gamma_{1,1} = 3\rho_{\mathrm{CH}} + 4\mathbf{J}^{\mathrm{SA_C}}(\omega_\mathrm{C}) + R_1{}^{\mathrm{C}} = (1/T_{1\mathrm{C}})$$

$$\Gamma_{2,2} = \rho_{\mathrm{HC}} + 2\rho_{\mathrm{HH'}} + 4\mathbf{J}^{\mathrm{SA_H}}(\omega_\mathrm{H}) + R_1{}^{\mathrm{H}} = (1/T_{1\mathrm{H}})$$

$$\Gamma_{3,3} = \rho_{\mathrm{CH}} + 2\delta_{\mathrm{CH}} + 2\rho_{\mathrm{HH'}} + 2\mathbf{J}^{\mathrm{D_{HH'}}}(\omega_\mathrm{H}) + 4\mathbf{K}^{\mathrm{D_{HH'}\,D_{HH''}}}(\omega_\mathrm{H}) + 4\mathbf{J}^{\mathrm{SA_C}}(\omega_\mathrm{C}) + + 8\mathbf{J}^{\mathrm{SA_H}}(\omega_\mathrm{H}) + R_1{}^{\mathrm{C}} + 2R_1{}^{\mathrm{H}}$$

$$\Gamma_{4,4} = 3\rho_{\mathrm{HC}} + 6\mathbf{J}^{\mathrm{D_{HH'}}}(\omega_\mathrm{H}) + 12\mathbf{J}^{\mathrm{SA_H}}(\omega_\mathrm{H}) + 3R_1{}^{\mathrm{H}}$$

$$\Gamma_{5,5} = 2\rho_{\mathrm{CH}} + 2\mathbf{J}^{\mathrm{D_{CH}}}(\omega_\mathrm{H}) + 2\mathbf{J}^{\mathrm{D_{HH'}}}(\omega_\mathrm{H}) + 2\mathbf{J}^{\mathrm{D_{HH'}}}(2\omega_\mathrm{H}) + 2\mathbf{K}^{\mathrm{D_{HH'}\,D_{HH''}}}(\omega_\mathrm{H}) + 2\mathbf{K}^{\mathrm{D_{HH'}\,D_{HH''}}}(2\omega_\mathrm{H}) + 2\rho_{\mathrm{HCH'}}(\mathrm{H}) - 4\mathbf{K}^{\mathrm{D_{CH}\,D_{CH'}}}(\omega_\mathrm{C}) + 2\mathbf{K}^{\mathrm{D_{CH}\,D_{CH'}}}(\omega_\mathrm{H}) + 2\mathbf{J}^{\mathrm{D_{CH}}}(\omega_\mathrm{H}) + 8\mathbf{J}^{\mathrm{SA_H}}(\omega_\mathrm{H}) + 8\mathbf{K}^{\mathrm{SA_H.SA_{H'}}}(\omega_\mathrm{H}) + 3R_1{}^{\mathrm{H}}$$

$$\Gamma_{6,6} = \rho_{\mathrm{CH}} + \rho_{\mathrm{HC}} + \rho_{\mathrm{HCH'}\,(\mathrm{C})} + \rho_{\mathrm{HCH'}}(\mathrm{H}) - \delta_{\mathrm{HCH'}} \text{-}\ 2\mathbf{K}^{\mathrm{D_{CH}.D_{CH'}}}(\omega_\mathrm{C}) + 6\mathbf{J}^{\mathrm{D_{HH'}}}(\omega_\mathrm{H}) + 2\mathbf{J}^{\mathrm{D_{HH'}}}(2\omega_\mathrm{H}) - 2\mathbf{K}^{\mathrm{D_{HH'}\,D_{HH''}}}(\omega_\mathrm{H}) + 2\mathbf{K}^{\mathrm{D_{HH'}\,D_{HH''}}}(2\omega_\mathrm{H}) + 4\mathbf{J}^{\mathrm{SA_H}}(\omega_\mathrm{H}) + 4\mathbf{J}^{\mathrm{SA_C}}(\omega_\mathrm{C}) + R_1{}^{\mathrm{C}} + 2R_1{}^{\mathrm{H}}$$

b. Off-Diagonal Elements: Polarization Transfer Rates.

$$\Gamma_{1,2} = \sqrt{3}\sigma_{\mathrm{CH}}$$

$$\Gamma_{1,3} = 2\sqrt{3}\mathbf{K}^{\mathrm{D_{CH}\,D_{CH'}}}(\omega_\mathrm{C})$$

$$\Gamma_{1,4} = \Gamma_{1,5} = 0$$

$$\Gamma_{1,6} = \sqrt{6}\{\rho_{\mathrm{HCH'}}(\mathrm{C}) - \mathbf{K}^{\mathrm{D_{CH}\,D_{CH'}}}(\omega_\mathrm{C})\}$$

$$\Gamma_{2,3} = 4\mathbf{K}^{\mathrm{D_{CH}\,D_{HH'}}}(\omega_\mathrm{H})$$

$$\Gamma_{2,4} = 2\sqrt{3}\mathbf{K}^{\mathrm{D_{HH'}\,D_{HH''}}}(\omega_\mathrm{H})$$

$$\Gamma_{2,5} = 2\sqrt{2}\{2\mathbf{K}^{\mathrm{D_{HH'}\,D_{HH''}}}(2\omega_\mathrm{H}) - \mathbf{K}^{\mathrm{D_{HH'}\,D_{HH''}}}(\omega_\mathrm{H})\}$$

$$\Gamma_{2,6} = \sqrt{2}\{\sigma_{\mathrm{HCH'}} - 2\mathbf{K}^{\mathrm{D_{CH}\cdot D_{HH'}}}(\omega_\mathrm{H})\}$$

$$\Gamma_{3,4} = \sqrt{3}\{\sigma_{\mathrm{CH}} + 4\mathbf{K}^{\mathrm{D_{CH}\cdot D_{HH'}}}(\omega_\mathrm{H})\}$$

$$\Gamma_{3,5} = -\sqrt{2}\{\sigma_{\mathrm{HCH'}} + 2\mathbf{K}^{\mathrm{D_{CH}D_{HH'}}}(\omega_\mathrm{H}) + 2\mathbf{K}^{\mathrm{D_{CH}D_{H'H''}}}(\omega_\mathrm{H})\}$$

$$\Gamma_{3,6} = -\sqrt{2}\{\mathbf{J}^{\mathrm{D_{HH'}}}(\omega_\mathrm{H}) + \mathbf{K}^{\mathrm{D_{CH}D_{CH'}}}(\omega_\mathrm{H}) + 3\mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(\omega_\mathrm{H}) + 3\mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(2\omega_\mathrm{H}) + 4\mathbf{K}^{\mathrm{SA_HSA_{H'}}}(\omega_\mathrm{H})\}$$

$$\Gamma_{4,5} = -\sqrt{6}\{\mathbf{J}^{\mathrm{D_{HH'}}}(\omega_\mathrm{H}) + \rho_{\mathrm{HCH'}}(\mathrm{H}) + \mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(\omega_\mathrm{H}) + 4\mathbf{K}^{\mathrm{SA_HSA_{H'}}}(\omega_\mathrm{H})\}$$

$$\Gamma_{4,6} = -\ 2\sqrt{6}\mathbf{K}^{\mathrm{D_{CH}D_{H'H''}}}(\omega_\mathrm{H})$$

$$\Gamma_{5,6} = \sigma_{\mathrm{CH}} + \sigma_{\mathrm{HCH'}} + 2\mathbf{K}^{\mathrm{D_{CH}D_{HH'}}}(\omega_\mathrm{H}) + 2\mathbf{K}^{\mathrm{D_{CH}D_{H'H''}}}(\omega_\mathrm{H})$$

2. Symmetric Manifold Couplings. *a. Diagonal Elements: Dissipative Rates.*

$$\Gamma_{7,7} = 2\rho_{\mathrm{CH}} + \delta_{\mathrm{CH}} + 2\rho_{\mathrm{HH'}} + 4\mathbf{K}^{\mathrm{D_{CH}D_{CH'}}}(\omega_\mathrm{C}) + 4\mathbf{J}^{\mathrm{SA_C}}(\omega_\mathrm{C}) + 4\mathbf{J}^{\mathrm{SA_H}}(\omega_\mathrm{H}) + R_1{}^{\mathrm{C}} + R_1{}^{\mathrm{H}} = (1/T_{1\mathrm{C}}) + (1/T_{1\mathrm{H}}) - \rho_{\mathrm{CH}} - \delta_{\mathrm{CH}} - \rho_{\mathrm{HC}} + 4\mathbf{K}^{\mathrm{D_{CH}D_{CH'}}}(\omega_\mathrm{C})$$

$$\Gamma_{8,8} = 3\delta_{\mathrm{CH}} + 6\mathbf{J}^{\mathrm{D_{HH'}}}(\omega_\mathrm{H}) + 4\mathbf{J}^{\mathrm{SA_C}}(\omega_\mathrm{C}) + 12\mathbf{J}^{\mathrm{SA_H}}(\omega_\mathrm{H}) + R_1{}^{\mathrm{C}} + 3R_1{}^{\mathrm{H}}$$

$$\Gamma_{9,9} = 2\rho_{\mathrm{HC}} + 2\rho_{\mathrm{HH'}} - 2\mathbf{J}^{\mathrm{D_{HH'}}}(\omega_\mathrm{H}) + 4\mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(\omega_\mathrm{H}) + 8\mathbf{J}^{\mathrm{SA_H}}(\omega_\mathrm{H}) + 2R_1{}^{\mathrm{H}}$$

$$\Gamma_{10,10} = \rho_{\mathrm{CH}} + \delta_{\mathrm{CH}} + 6\mathbf{J}^{\mathrm{D_{HH'}}}(\omega_\mathrm{H}) + 2\mathbf{J}^{\mathrm{D_{HH'}}}(2\omega_\mathrm{H}) - 2\mathbf{K}^{\mathrm{D_{CH}D_{CH'}}}(\omega_\mathrm{C}) - 2\mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(\omega_\mathrm{H}) + 2\mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(2\omega_\mathrm{H}) + 8\mathbf{J}^{\mathrm{SA_H}}(\omega_\mathrm{H}) - 4\mathbf{K}^{\mathrm{SA_HSA_{H'}}}(\omega_\mathrm{H}) + 2R_1{}^{\mathrm{H}}$$

$$\Gamma_{11,11} = \rho_{\mathrm{HC}} + \delta_{\mathrm{CH}} + 2\mathbf{K}^{\mathrm{D_{CH}D_{CH'}}}(\omega_\mathrm{H}) + 2[\mathbf{J}^{\mathrm{D_{HH'}}}(\omega_\mathrm{H}) + \mathbf{J}^{\mathrm{D_{HH'}}}(2\omega_\mathrm{H}) + \mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(\omega_\mathrm{H}) + \mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(2\omega_\mathrm{H})\ ] + 4\mathbf{J}^{\mathrm{SA_C}}(\omega_\mathrm{C}) + 8\mathbf{J}^{\mathrm{SA_H}}(\omega_\mathrm{H}) + 8\mathbf{K}^{\mathrm{SA_HSA_{H'}}} + R_1{}^{\mathrm{C}} + 3R_1{}^{\mathrm{H}}$$

b. Off-Diagonal Elements: Polarization Transfer Rates.

$$\Gamma_{7,8} = 2\sqrt{3}\{\mathbf{K}^{\mathrm{D_{CH}D_{CH'}}}(\omega_\mathrm{C}) + \mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(\omega_\mathrm{H})\}$$

$$\Gamma_{7,9} = 4\mathbf{K}^{\mathrm{D_{CH}\cdot D_{HH'}}}(\omega_\mathrm{H}) - 2\sigma_{\mathrm{CH}}$$

$$\Gamma_{7,10} = -\sqrt{2}\{\rho_{\mathrm{HCH'}}(\mathrm{C}) + 2\mathbf{K}^{\mathrm{D_{CH}D_{HH'}}}(\omega_\mathrm{H})\}$$

$$\Gamma_{7,11} = \sqrt{2}\{\rho_{\mathrm{HCH'}}(\mathrm{C}) - \mathbf{K}^{\mathrm{D_{CH}D_{CH'}}}(\omega_\mathrm{C}) - 2\mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(\omega_\mathrm{H}) + 4\mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(2\omega_\mathrm{H})\}$$

$$\Gamma_{7,11} = \sqrt{2}\{\rho_{\mathrm{HCH'}}(\mathrm{C}) - \mathbf{K}^{\mathrm{D_{CH}D_{CH'}}}(\omega_\mathrm{C}) - 2\mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(\omega_\mathrm{H}) + 4\mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(2\omega_\mathrm{H})\}$$

$$\Gamma_{7,11} = \sqrt{2}\{\rho_{\mathrm{HCH'}}(\mathrm{C}) - \mathbf{K}^{\mathrm{D_{CH}D_{CH'}}}(\omega_\mathrm{C}) - 2\mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(\omega_\mathrm{H}) + 4\mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(2\omega_\mathrm{H})\}$$

$$\Gamma_{8,9} = 4\sqrt{3}\mathbf{K}^{\mathrm{D_{CH}\cdot D_{HH'}}}(\omega_\mathrm{H})$$

$$\Gamma_{8,10} = 2\sqrt{6}\mathbf{K}^{\mathrm{D_{CH}\cdot D_{H'H''}}}(\omega_\mathrm{H})$$

$$\Gamma_{8,11} = -\sqrt{6}\{\mathbf{J}^{\mathrm{D_{HH'}}}(\omega_\mathrm{H}) + \mathbf{K}^{\mathrm{D_{CH}D_{CH'}}}(\omega_\mathrm{H}) + \mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(\omega_\mathrm{H}) - 4\mathbf{K}^{\mathrm{SA_H\cdot SA_{H'}}}(\omega_\mathrm{H})\}$$

$$\Gamma_{9,10} = -\sqrt{2}\{\mathbf{J}^{\mathrm{D_{HH'}}}(\omega_\mathrm{H}) + \rho_{\mathrm{HCH'}}(\mathrm{H}) + 3\mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(\omega_\mathrm{H}) + 4\mathbf{K}^{\mathrm{D_{HH'}D_{HH''}}}(2\omega_\mathrm{H}) + 4\mathbf{K}^{\mathrm{SA_HSA_{H'}}}(\omega_\mathrm{H})\}$$

$$\Gamma_{9,11} = \sqrt{2}\{\sigma_{\mathrm{HCH'}} - 2\mathbf{K}^{\mathrm{D_{CH}D_{HH'}}}(\omega_\mathrm{H}) - 2\mathbf{K}^{\mathrm{D_{CH}D_{H'H''}}}(\omega_\mathrm{H})\}$$

$$\Gamma_{10,11} = -\sigma_{\mathrm{HCH'}} + 2\mathbf{K}^{\mathrm{D_{CH}D_{HH'}}}(\omega_\mathrm{H}) + 2\mathbf{K}^{\mathrm{D_{CH}D_{H'H''}}}(\omega_\mathrm{H})$$

3. Symmetric/Antisymmetric Polarization Transfer Rates.

$$\Gamma_{1,7} = -4\sqrt{3}\mathbf{K}^{\mathrm{D_{CH}\cdot SA_C}}(\omega_\mathrm{C})$$

$$\Gamma_{1,8} = \Gamma_{1,9} = \Gamma_{1,10} = \Gamma_{1,11} = 0$$

$$\Gamma_{2,7} = -4\mathbf{K}^{\mathrm{D_{CH}\cdot SA_H}}(\omega_\mathrm{H})$$

$$\Gamma_{2,9} = -\sqrt{2}\Gamma_{2,10} = -8\mathbf{K}^{\mathrm{D_{HH'}SA_H}}(\omega_\mathrm{H})$$

$$\Gamma_{2,8} = \Gamma_{2,11} = 0$$

$$\Gamma_{3,7} = -8\{\mathbf{K}^{D_{CH}SA_{C}}(\omega_{C}) + \mathbf{K}^{D_{HH'}SA_{H}}(\omega_{H})\}$$

$$\Gamma_{3,8} = -4\sqrt{3}\{\mathbf{K}^{D_{CH}SA_{C}}(\omega_{C}) + 2\mathbf{K}^{D_{HH'}SA_{H}}(\omega_{H})\}$$

$$\Gamma_{3,9} = (-\sqrt{2})\Gamma_{3,10} = (1/\sqrt{2})\Gamma_{3,11} = -8\mathbf{K}^{D_{HH'}SA_{H}}(\omega_{H})$$

$$\Gamma_{4,7} = \Gamma_{5,7} = 0$$

$$\Gamma_{4,8} = (\sqrt{6}/2)\Gamma_{4,11} = -12\mathbf{K}^{D_{CH}SA_{H}}(\omega_{H})$$

$$\Gamma_{4,9} = -\sqrt{2}\Gamma_{4,10} = 4\sqrt{6}\mathbf{K}^{D_{HH}SA_{H}}(\omega_{H})$$

$$\Gamma_{5,8} = (\sqrt{3}/2)\Gamma_{5,9} = (-\sqrt{6}/2)\Gamma_{5,10} = 4\sqrt{6}\mathbf{K}^{D_{HH'}SA_{H}}(\omega_{H})$$

$$\Gamma_{5,11} = -16\mathbf{K}^{D_{CH}SA_{H}}(\omega_{H})$$

$$\Gamma_{6,7} = (1/\sqrt{3})\Gamma_{6,8} = 4\sqrt{2}\mathbf{K}^{D_{HH'}SA_{H}}(\omega_{H})$$

$$\Gamma_{6,9} = 4\sqrt{2}\mathbf{K}^{D_{CH}\cdot SA_{H'}}(\omega_{H})$$

$$\Gamma_{6,10} = -4\mathbf{K}^{D_{CH}\cdot SA_{H}}(\omega_{H})$$

$$\Gamma_{6,11} = -4\{\mathbf{K}^{D_{CH}SA_{C}}(\omega_{C}) + 2\mathbf{K}^{D_{HH'}SA_{H}}(\omega_{H})\}$$

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