Manifestations of Slow Site Exchange Processes in Solution NMR: A Continuous Gaussian Exchange Model

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The effects of site exchange due to slow conformational changes in rapidly rotating molecules in solution are examined in detail. Significant gaps in the currently available theory are filled. The effects of site exchange on the lineshape, decay of a simple spin-echo, decay of the even echoes in a Carr–Purcell–Meiboom–Gill (CPMG) pulse-sequence, and decay of the transverse magnetization in a resonant spin-locking field are investigated. Both trajectory and stochastic operator approaches are formulated and shown to be completely equivalent whenever the dynamics of population transfers among the inequivalent sites is governed by either a stationary or a nonstationary Markov process. A nonstationary Markov process may result from Brownian dynamics (a stationary Markov process) in a larger conformational space that contains the subspace of inequivalent sites. A continuous Gaussian exchange model is formulated in which a nucleus undergoes continuous one-dimensional motion in a harmonic potential well that is located in a linear chemical shift gradient. The effects of this Gaussian exchange model on the lineshape, simple spin-echo decay, and decay of the even echoes of a CPMG pulse train are treated rigorously via the trajectory approach. Compact analytical expressions are obtained for the relevant correlation functions in each case. The relevant decays are found to be exponential in the very short time and long time limits, which are not necessarily experimentally significant in any given case. In the fast exchange limit the relevant decays are exponential at all times, and explicit formulas are given for their decay rates. In the long time limit, all discrete multisite models with the same intrinsic R_2^o at every site are shown to be completely equivalent to a continuous Gaussian model with appropriate relaxation time and variance of the Larmor frequency. The effects of this Gaussian exchange model on the decay of the transverse magnetization in a resonant spin-locking field are treated heuristically by a trajectory approach. The intrinsic contribution ($R_{1\rho}^o$) of rapid rotations and dipole–dipole interactions to relax the transverse magnetizations of two nuclei of the same kind in the presence of a (nearly) resonant spin-locking field is also derived and found to be practically the same as the intrinsic contribution, R_2^o, of those same rotations to the simple and CPMG spin-echo decay rates and linewidth. Literature data for the linewidth, decay rate of the CPMG even spin-echoes, and $R_{1\rho}$ decay rate for the A9-H2 protons of adenines at the central TpA step in the sequence, 5′-GCAGGTTTAAACCTCG-3′, are analyzed using the Gaussian exchange model to assess the time-scale and variance of the site exchange process as well as the intrinsic R_2^o rate. Although a single Gaussian exchange process with appropriate parameters can fit these three A9-H2 data rather well, this particular "solution" cannot be reconciled with NMR relaxation data on other protons in the same DNA molecule. Rather good agreement with all of the observations is obtained by using a model of two concurrent Gaussian exchange processes, whose relaxation times, $\tau = 7$ and 460 μs, differ in time-scale by a factor of 65. The insensitivity of $R_{1\rho}$ in the presence of a fast site exchange process to much slower concurrent site exchange processes is explicitly demonstrated. Protocols for detecting and characterizing a second slow site exchange process are suggested. © 1999 Academic Press

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INTRODUCTION

In solution NMR, the molecular motions responsible for (i) the shape and width of the spectrum, (ii) the decays of spin-echoes from either simple or complex pulse trains, and (iii) the decay of the transverse magnetization in a resonant spin-locking field can be divided into two categories, namely rotational motions that are normally very rapid and transitions between conformations wherein the Larmor frequency is altered. Such conformational transitions are called site exchange processes and are typically much slower than the rotations. Even though rotations of a particular group in the molecule may be slow in the molecular frame, perhaps because it proceeds via a slow conformational change, it will be superposed on the uniform (rigid-body) rotations and collective twisting and bending deformations when viewed from the laboratory frame. Consequently, the resultant motion in the lab frame will proceed at least as rapidly as the combined uniform rotations plus twisting and bending motions (*1, 2*). Dipole–dipole, quadrupolar, and chemical shift anisotropy (CSA) relaxation all require the reorientation of molecule-bound vectors or tensors in the lab frame. Provided that the rotational motions are sufficiently rapid compared to the rates of decay of the initial spin states, one may apply fast motion relaxation theory, for

example, Fermi's Golden Rule or the double commutator formula of Abragam (3). In that case, the relevant rate constants for relaxation of various magnetizations, or spin-orders, can be expressed in terms of spectral densities. These spectral densities are Fourier transforms of sums of correlation functions of particular rotation functions of the Euler angles that orient the relevant vectors or tensors in the lab frame (2–5). The contributions of cylindrically symmetric anisotropic uniform rotations, collective twisting and bending, and various local angular motions to the dipole–dipole, quadrupolar, and CSA R_1 and R_2 relaxation rates in this fast motion limit were described previously (2). In solutions with an isotropic equilibrium state, the relevant correlation functions in every case relax completely to zero, and exhibit a longest relaxation time that is equal to the longest rotational relaxation time (τ_L) of the molecule. Typically $\tau_L \leq 10^{-8}$ s. Consequently, molecular motions that take place on a longer time-scale than τ_L are not significantly manifested in dipole–dipole, quadrupolar, or CSA relaxation. Nevertheless, slow conformational transitions that cause the Larmor frequency to vary, specifically by altering the isotropic part of the chemical shift tensor, may still be manifested in (i) the lineshape, (ii) the decay of a simple spin-echo, (iii) the decay of the even spin-echoes of a Carr–Purcell–Meiboom–Gill (CPMG) pulse train, and (iv) the decay of the transverse magnetization in a spin-locking field, albeit in a somewhat different manner. Our ultimate objective is to characterize insofar as possible both the rapid local angular motions and the slow conformational transitions in which a given nucleus participates from measurements of the properties (i), (iii), and (iv) above together with an independent assessment of the uniform rotational dynamics by time-resolved fluorescence polarization anisotropy (FPA). Specifically, our intent is to estimate the rms amplitude of rapid local angular motion, the relaxation time(s) characterizing the slow conformational transitions, and the standard deviation of the Larmor frequencies among the accessible conformations. In order to do this, it is necessary to have a reasonably complete theory describing how both rapid rotations and slow site exchange processes contribute to each of these properties. However, there presently exist significant gaps in the available theory, much of which pertains only to two-site exchange models.

In the absence of any slow site exchange due to either slow conformational transitions or chemical exchange (e.g., exchange of protons with solvent), the rapid rotations provide "intrinsic" contributions, namely $\Delta\nu_{1/2}^{\circ}$, R_2°, and $R_{1\rho}^{\circ}$ to, respectively, the linewidth, decay rate of the even spin-echoes in a CPMG pulse sequence, and decay rate of the transverse magnetization in a resonant spin-locking field. The superscript o is used to distinguish these intrinsic contributions due to rapid rotations from the total contribution that is manifested when effects of site exchange are also included. Expressions for dipole–dipole, quadrupolar, and CSA contributions to R_2° are available for fairly general models (2), as noted above. Of course, $\Delta\nu_{1/2}^{\circ} = R_2^{\circ}/\pi$, as is well known. The dipole–dipole

contribution to $R_{1\rho}^{\circ}$ has been derived for the case when the two spins (I and S) are of different kinds and the spin-locking RF field is resonant with the I spin, but far off-resonance for the S spin (5, 6). A corresponding treatment of $R_{1\rho}^{\circ}$ for the case of two identical spins that experience different environments with slightly different Larmor frequencies, for which the RF power is nearly resonant with both spins, has evidently not been obtained previously. Such a result, which is necessary to interpret spin-locking experiments on protons that are dipolar relaxed by other protons, is derived in Appendix C.

Random variations of the dipole–dipole, quadrupolar, and CSA interactions that arise from rotational Brownian motions, and which mix spin eigenstates of the Zeeman Hamiltonian, are typically treated by second-order perturbation theory according to either Fermi's Golden Rule or Abragam's double commutator formulas. Consequently, those results for $\Delta\nu_{1/2}^{\circ}$, R_2°, and $R_{1\rho}^{\circ}$ are valid only in the fast-motion limit, wherein the longest rotational relaxation time τ_L of the molecule is much less than $T_2^{\circ} \equiv 1/R_2^{\circ}$. In contrast, random variations of the isotropic chemical shift, or Larmor frequency, due to site exchanges, which do not mix the spin eigenstates of the Zeeman Hamiltonian, can in principle be treated in a complete (nonperturbative) manner by the trajectory approach described below, so the results are valid regardless of whether the exchange process is fast or slow. A stochastic operator, or master equation, approach for treating site exchange processes has also been formulated and commonly used to calculate lineshapes and spin-echoes for both simple and CPMG pulse sequences (7–13). However, the validity of the stochastic operator approach has been substantiated only for *time-independent* stochastic operators in the space of the *inequivalent sites* (9). Such constant operators in that restricted space often cannot adequately account for the Brownian dynamics in any larger conformational space, of which the inequivalent sites constitute a subspace. Although Brownian motion in the full conformational space typically proceeds according to a *stationary* (*homogeneous*) Markov process with a time-independent stochastic operator, the resultant population dynamics within the subspace of inequivalent sites, after integrating over (or summing out) the conformational coordinates external to that subspace, generally follows a *nonstationary* (*nonhomogeneous*) Markov process with a *time-dependent* stochastic operator, for example a time-dependent rate matrix or a diffusion operator with time-dependent diffusion coefficients (15). The stochastic operator approach with a time-dependent stochastic operator is shown to be fully equivalent to the trajectory approach for the same nonstationary (nonhomogeneous) Markov process in Appendix A. Although the trajectory approach in principle remains valid even for non-Markovian dynamics, wherein inertial effects and memory are important, the stochastic operator approach very likely does not, because the present proof of equivalence fails in that case.

The effects of two-site exchange on the lineshape and decays of both simple and CPMG spin-echoes have been formally

treated in a rather complete manner, valid for all times and exchange rates, by both trajectory (*12*) and stochastic operator (*10–14*) approaches. Unfortunately, there exists no comparable general treatment of the decay of the transverse magnetization in a resonant spin-locking field. In the presence of site exchange, relaxation of the transverse magnetization in a free-induction decay and the decays of both simple and CPMG spin echoes are generally nonexponential, although the deviation from single-exponential behavior may be rather slight in some cases, for example, (1) at very short times $t \ll \tau$ and $t \ll 1/\Delta\omega$, where τ is the exchange time and $\Delta\omega$ the difference in Larmor frequency between the two sites, whenever both sites exhibit the same intrinsic R_2° rate, or (2) at any time in the fast-exchange limit, defined by $\Delta\omega \cdot \tau \ll 1.0$ (*13*). Experimentally, very short times with respect to exchange ($t \ll \tau$ and $t \ll 1/\Delta\omega$) can be sampled by either CPMG measurements with very short cycle times or $R_{1\rho}$ measurements with very high precession frequencies ω_1 around the spin-locking field in the rotating frame. By such methods, the inhomogeneous dephasing due to differences in Larmor frequency can be reversed and refocused before exchange renders it irreversible (*11, 12*). Although it is possible to account for the effects of simultaneous spin–spin coupling (*13*), such effects can often be eliminated by the application of decoupling pulses in experiments performed on modern instruments and are not considered here.

In the fast site exchange limit, wherein the relaxation rate $k_{ex} = 1/\tau$ for two-site exchange greatly exceeds the difference $\Delta\omega$ in Larmor frequency between the two sites, the relaxation of the transverse magnetization in a free-induction decay and the decays of both simple and CPMG spin-echoes become single exponential (*10–13*). In this fast-exchange limit, the effects of two-site exchange on the linewidth, decay rates of both simple and CPMG spin-echoes, and decay rate of transverse magnetization in a resonant spin-locking field have been treated by simple second-order perturbation methods (*16–21, 28*). Such fast-exchange expressions were recently employed to analyze (1) a CPMG spin-echo decay as a function of the time-delay between π pulses (*19*), and (2) the decay of transverse magnetization in a spin-locking field as a function of the precession frequency ω_1 of the magnetization around the resonant RF spin-lock field (*19, 22*), and also as a function of the offset between the frequency of the RF spin-locking field and that of the coalesced nuclear resonance (*23*). These studies enabled the detection of site exchange processes and quantitative estimates of $k_{ex} = 1/\tau$ in the fast-exchange limit. However, such analyses provide little or no reliable information about any concurrent much slower site exchange processes that may lie outside the fast-exchange limit.

In some cases (*24, 25*), it was suggested that the conformational exchange involved more than two states, or even diffusive motion among a continuum of states, but there appears to be no comprehensive treatment of the effects of any continuous diffusive model of site exchange on any of the relaxation properties of interest. In the present work we formulate a continuous Gaussian model of diffusive site exchange and derive its contributions to the lineshape, simple and CPMG spin-echo decay(s), and $R_{1\rho}$. These derivations proceed by reckoning the appropriate accumulated phase of the transverse magnetization of a single spin relative to the zero of a phase in a rotating frame (resonant with the mean Larmor frequency) due to fluctuations in its Larmor frequency along a particular trajectory and then performing an ensemble average overall possible trajectories. Abragam provided an essentially identical treatment of the lineshape for an *ad hoc* scenario in which the fluctuating Larmor frequency was assumed to be a Gaussian random variable with an exponentially decaying correlation function (*3*). However, he was evidently unaware that such a scenario corresponds physically to overdamped one-dimensional Brownian motion of the nuclear spin in a harmonic potential well located in a linear chemical shift gradient. Abragam did not investigate the decay of either simple or CPMG spin-echoes or the decay of the transverse magnetization in a resonant spin-locking field for this model. The connection of this model to discrete multisite jump models also was not explored.

The plan of this paper is as follows. (1) The problem of how to incorporate the effects of slow site exchange processes on the spectrum, simple spin-echo decay, and even echoes of a CPMG pulse sequence is discussed, and both trajectory and stochastic operator approaches are formulated. Their equivalence, for the case when the system evolves according to a time-dependent stochastic operator over the subspace of inequivalent sites, is proved in Appendix A. (2) The continuous Gaussian model of site exchange is introduced, its Langevin equation solved, and the autocorrelation function of its Larmor frequency obtained. The effects of exchange in this Gaussian model are treated via the accumulated phase of the trajectory approach. The spectrum (via the autocorrelation function of the unperturbed transverse magnetization), the simple spin-echo decay, and the amplitudes of the even echoes of a CPMG pulse sequence are expressed simply in terms of the relaxation time and variance of the Larmor frequency, using formulas derived in Appendix B. The behavior predicted in different limits is considered in detail. (3) Certain relations between this Gaussian model and discrete multisite models are developed and analyzed. The equivalence of the continuous Gaussian model and all multisite models in the long time limit is proved in Appendix E. (4) The total decay of the transverse magnetization in a resonant spin-locking field is discussed. $R_{1\rho}^\circ$ is derived for the case of dipolar relaxation of two spins of the same kind with slightly different Larmor frequencies, which are both nearly resonant with the spin-locking field, in Appendix C. It is shown that $R_{1\rho}^\circ$ is practically identical to R_2°, when the rotational motions are rapid, as assumed. The contribution of site exchange in the Gaussian model to $R_{1\rho}$ is derived by a heuristic trajectory approach in Appendix D. (5) Experimental linewidth, CPMG spin-echo decay, and $R_{1\rho}$ data (*25*) for the H$_2$ proton of A9 of the duplex DNA sequence, 5′-CGAGGTTTA-

AACCTCG-3′, are analyzed under the assumption of a single Gaussian exchange process and again under the assumption that two Gaussian exchange processes, one fast and one much slower, take place concurrently. The model of two Gaussian exchange processes is shown to be most consistent with all of the NMR relaxation data. (6) The problem of detecting and characterizing a second site exchange process is discussed in detail, and a particular example is explicitly demonstrated.

THE PROBLEM

We consider a simple spin-$\frac{1}{2}$ system in which each spin resides in a site designated by the index Ω, which may be either discrete or continuous. In the presence of the main magnetic field, a spin in site Ω has Larmor frequency $\omega(\Omega) = \omega_o + \delta\omega(\Omega)$, where

$$\omega_o = \langle\omega(\Omega)\rangle = \sum_\Omega f^o_\Omega \omega(\Omega) = \int d\Omega P_o(\Omega)\omega(\Omega) \quad [1]$$

is the equilibrium average Larmor frequency, and $\delta\omega(\Omega)$ is the deviation from that. The quantity f^o_Ω is the equilibrium fraction of spins in the discrete site Ω, or $P_o(\Omega)$ is the equilibrium distribution of spins among continuous sites Ω. We consider the $M_\pm = M_x \pm iM_y$ components of the transverse magnetization operator. The quantum mechanical average magnetizations of the spins in site Ω at time t are denoted by $\langle M_+(\Omega, t)\rangle$ and $\langle M_-(\Omega, t)\rangle$. When the spins are *fixed* in the site at Ω, the transverse magnetization operators are assumed to obey the Bloch-type Heisenberg equations,

$$\frac{dM_\pm(\Omega, t)}{dt} = [\mp i(\omega_o + \delta\omega(\Omega)) - R^o_2]M_\pm(\Omega, t), \quad [2]$$

where R^o_2 is the contribution of rapid motions associated with the site to relax the transverse magnetization. It is essential that the correlation functions of all motions contributing to R^o_2 relax on a time-scale much less than $T^o_2 = 1/R^o_2$, because the Golden Rule or double-commutator formulas used to calculate R^o_2 no longer apply when the relevant relaxation times exceed $T^o_2/10$. Any slower motion can in principle be regarded as a transfer of spins among different sites, which could represent different molecular orientations when the molecules rotate extremely slowly. However, in the usual circumstance, which is assumed here, the relevant relaxation times for molecular reorientations are extremely small compared to T^o_2. Consequently, the slower motions correspond exclusively to either conformational fluctuations or chemical exchanges that alter the isotropic chemical shifts and Larmor frequencies of the nuclei involved. It is assumed throughout this work that R^o_2 is the same for all sites.

One can envision two alternative approaches to treating intersite transfer.

1. Trajectory Approach

One can regard the index $\Omega(t)$ as time-dependent along the trajectory of a single spin. With this modification, Eq. [1] can be rewritten as

$$\frac{dM_\pm(\Omega(t), t)}{dt} = [\mp i(\omega_o + \delta\omega(\Omega(t))) - R^o_2]M_\pm(\Omega(t), t),$$

[3]

which can be formally solved to yield

$$M_\pm(\Omega(t), t) = e^{-R^o_2 t \mp i\omega_o t \mp i \int_0^t dt' \delta\omega(\Omega(t'))}M_\pm(\Omega(0), 0). \quad [4]$$

In general, the absorption spectrum is proportional to the imaginary part of the susceptibility, namely (26)

$$\chi_i(\omega) = \frac{\omega}{k_B T} \text{Re} \int_0^\infty dt \langle\langle M_x(\Omega(0), 0) M_x(\Omega(t), t)\rangle\rangle e^{i\omega t},$$

[5]

where the double angular brackets denote first a quantum mechanical average and then a trajectory average for the unperturbed (by RF power) system. Because $M_x = (\frac{1}{2})(M_+ + M_-)$, the correlation function in Eq. [5] can be written as

$$\langle\langle M_x(\Omega(0), 0) M_x(\Omega(t), t)\rangle\rangle$$
$$= [\langle\langle M_x(\Omega(0), 0) M_+(\Omega(t), t)\rangle\rangle$$
$$+ \langle\langle M_x(\Omega(0), 0) M_-(\Omega(t), t)\rangle\rangle]/2. \quad [6]$$

Multiplying Eq. [4] by $M_x(\Omega(0), 0)$, performing the quantum mechanical and trajectory averages, and using $\langle\langle M_x(\Omega(0), 0) M_y(\Omega(0), 0)\rangle\rangle = 0$ gives

$$\langle\langle M_x(\Omega(0), 0) M_\pm(\Omega(t), t)\rangle\rangle$$
$$= e^{\mp i\omega_o t - R^o_2 t}\langle e^{\mp i \int_0^t dt' \delta\omega(\Omega(t'))}\langle M_x(\Omega(0), 0)^2\rangle\rangle_T, \quad [7]$$

where the subscript T indicates a trajectory average. For a spin-$\frac{1}{2}$ system, $\langle M_x(\Omega(0), 0)^2\rangle = (\mu^2/4)\langle\sigma_x^2\rangle = \mu^2/4$, where σ_x is the corresponding Pauli matrix, $\mu = \gamma_n\hbar$ is the nuclear magnetic moment, and γ_n is the magnetogyric ratio, regardless of the spin site $\Omega(0)$, so it can be removed from the trajectory average of the phase factor. The correlation function $\langle\langle M_x(\Omega(0), 0) M_-(\Omega(t), t)\rangle\rangle$ contains the factor $e^{+i\omega_o t}$ and thus does not make a "resonance" contribution to the integral in Eq. [5], so its contribution to the spectrum is negligibly small. As is customary, this nonresonant term is ignored in the sequel. In view of these considerations, the relevant correlation function for the NMR spectrum is now

$$\langle\langle M_x(\Omega(0),\,0)\,M_x(\Omega(t),\,t)\rangle\rangle$$

$$= (\mu^2/8)e^{-(i\omega_o + R_2^o)t}\langle e^{-i\int_0^t dt'\,\delta\omega(\Omega(t'))}\rangle_T. \qquad [8]$$

For a simple spin-echo experiment in which the $\pi/2$ pulse establishes the positively rotating transverse magnetization, namely $\langle M_+(\Omega(0),\,0)\rangle$, at $t = 0$, and the π pulse is delivered at time t, the normalized magnetization at the time $2t$ of the "echo" is obtained from Eq. [4] as

$$\frac{\langle\langle M_+(\Omega(2t),\,2t)\rangle\rangle}{\langle\langle M_+(\Omega(0),\,0)\rangle\rangle}$$

$$= e^{-(i\omega_o + R_2^o)2t}\langle e^{+i(\int_0^t dt'\,\delta\omega(\Omega(t')) - \int_t^{2t} dt''\,\delta\omega(\Omega(t'')))}\rangle_T. \qquad [9]$$

To obtain Eq. [9], the accumulated phase relative to ω_o, namely $\int_0^t dt'\,\delta\omega(\Omega(t'))$, is reversed effectively instantaneously by the π pulse at t, after which the phase continues to evolve in the usual way until $2t$.

Similarly, the amplitudes of the even echoes in a CPMG pulse sequence, $\pi/2 - (t - \pi - t - t - \pi - t)_n$, are given by

$$\frac{\langle\langle M_+(\Omega(n4t),\,n4t)\rangle\rangle}{\langle\langle M_+(\Omega(0),\,0)\rangle\rangle} = e^{-(i\omega_o + R_2^o)n4t}\langle e^{-i\Delta\gamma(0,n4t)}\rangle_T, \quad [10]$$

where

$$\Delta\gamma(0,\,n4t) \equiv \int_0^{4t} dt'\,\delta\omega(\Omega(t'))\,z(t')$$

$$+ \int_{4t}^{8t} dt''\,\delta\omega(\Omega(t''))\,z(t'' - 4t) + \ldots$$

$$+ \int_{(n-1)4t}^{n4t} dt'''\,\delta\omega(\Omega(t'''))\,z(t''' - (n-1)4t)$$

$$[11]$$

is the net accumulated phase from 0 to $n4t$, and $z(x) = +1$ for $0 \le x \le t$, -1 for $t \le x \le 3t$, and $+1$ for $3t \le x \le 4t$. That is, if $\delta\omega(\Omega(t))$ is positive, then the accumulated phase is positive during the first quarter of each $4t$ cycle, negative during the second and third quarter cycles, and positive during the final quarter cycle of each $4t$ cycle.

Equations [3]–[11] are fundamental and can be employed whenever trajectories of $\Omega(t)$ are available, for example from molecular or Brownian dynamics simulations (27). Equations [5] and [8] of this section are the principal results pertaining to the spectrum, [9] is the principal result for the simple spin-echo decay, and [11], [12] are the principal results for the even echoes of a CPMG pulse sequence.

2. Stochastic Operator Approach

An alternative approach is to write a separate Heisenberg equation for the spins at each site, or at each value of Ω, which is regarded as *fixed*, but to take account of the transport between sites by an appropriate stochastic evolution operator (10, 11). In that case, when Ω is discrete,

$$\frac{dM_+(\Omega,\,t)}{dt} = -[i(\omega_o + \delta\omega(\Omega)) + R_2^o]M_+(\Omega,\,t)$$

$$+ \sum_{\Omega'} \Gamma(\Omega,\,\Omega',\,t)\,M_+(\Omega',\,t)$$

$$= \sum_{\Omega'} R(\Omega,\,\Omega',\,t)\,M_+(\Omega',\,t), \qquad [12]$$

where $\Gamma(\Omega,\,\Omega',\,t)$ is an element of the stochastic evolution matrix, $\Gamma(t)$, which operatores on the vector, $\mathbf{M}_+(t)$, of magnetization operators, $M_+(\Omega',\,t)$, for the different sites, and

$$R(\Omega,\,\Omega',\,t) = -(i\omega_o + R_2^o)\delta_{\Omega,\Omega'} - i\delta\omega(\Omega)\delta_{\Omega,\Omega'}$$

$$+ \Gamma(\Omega,\,\Omega',\,t) \qquad [13]$$

is an element of the total evolution matrix, $\mathbf{R}(t)$. If $\Omega,\,\Omega'$ are continuous, then the sums in Eq. [12] must be replaced by integrals and the Kronecker deltas in Eq. [13] must be replaced by Dirac delta functions, $\delta(\Omega,\,\Omega')$. In discrete form, $\Gamma(\Omega,\,\Omega',\,t)$ is the instantaneous rate constant for transfer from Ω' to Ω at time t.

In general, $\Gamma(\Omega,\,\Omega',\,t)$ may depend on the time, although commonly it does not, as in the case of multisite jump models or uniform (rigid-body) rotational diffusion. When it does depend upon the time, the origin of time must be taken to coincide with the moment of "selection" of the spins for study, e.g., the instant of the $\pi/2$ pulse. The selection of such a special time has been discussed previously (15).

The formal solution of the matrix equation [12] is

$$M_+(\Omega,\,t) = \sum_{\Omega'} (Te^{\int_0^t dt'\,\mathbf{R}(t')})_{\Omega\Omega'}M_+(\Omega',\,0), \qquad [14]$$

where T is the time-ordering operator. It is assumed that $M_+(\Omega',\,0)$ is just the initial fraction, $f(\Omega',\,0)$, of spins in state Ω' times the total magnetization operator $(M_+(0))$ at $t = 0$, which is just the Schrödinger operator for the spin in question. That is

$$M_+(\Omega',\,t) = f(\Omega',\,t)M_+(0) = f(\Omega',\,t)(\mu/2)\sigma_+, \quad [15]$$

where $\sigma_+ = \sigma_x + i\sigma_y$ is the appropriate Pauli matrix. The total magnetization operator at time t is

$$M_+(t) = \sum_\Omega M_+(\Omega, t). \qquad [16]$$

In this case, the relevant correlation function for the NMR spectrum in Eq. [5] is

$$\langle\langle M_x(0) M_x(t)\rangle\rangle = (1/2)\langle\langle M_x(0) M_+(t)\rangle\rangle, \qquad [17]$$

where the double angular brackets now denote first a quantum mechanical average and then an ensemble average over initial conditions. In this approach a trajectory average is not taken, because such a trajectory average is assumed to be already implicit in the stochastic matrix $\Gamma(t)$ and in the evolution factor, $T \exp[\int_0^t dt' \mathbf{R}(t')]$, in Eq. [14]. In Eq. [17], the nonresonant term has again been neglected. Making use of Eqs. [14]–[17] and performing the ensemble average over initial conditions gives

$$\langle\langle M_x(0) M_x(t)\rangle\rangle$$
$$= (1/2) \sum_\Omega \sum_{\Omega'} (Te^{\int_0^t dt' \mathbf{R}(t')})_{\Omega\Omega'} f^o(\Omega') \mu^2/4, \qquad [18]$$

where $f^o(\Omega') = \langle f(\Omega', 0)\rangle$ is the equilibrium fraction of spins in site Ω'. In Eq. [18] the relations $\langle M_x(0) M_+(0)\rangle = \langle M_x(0)^2\rangle = (\mu^2/4)\sigma x^2 = \mu^2/4$ have been employed. One can write

$$\mathbf{R} = -(i\omega_o + R_2^o)\mathbf{1} + \mathbf{Q}(t), \qquad [19]$$

where from Eq. [13],

$$(\mathbf{Q}(t))_{\Omega\Omega'} = -i\delta\omega(\Omega)\delta_{\Omega,\Omega'} + \Gamma(\Omega, \Omega', t). \qquad [20]$$

Since $\mathbf{1}$ commutes with $\mathbf{Q}(t)$,

$$Te^{\int_0^t dt' \mathbf{R}(t')} = Te^{\int_0^t dt'[-(i\omega_o+R_2^o)\mathbf{1}+\mathbf{Q}(t)]}$$
$$= e^{-(i\omega_o+R_2^o)\mathbf{1}t}Te^{\int_0^t dt'\mathbf{Q}(t')}. \qquad [21]$$

Use of Eq. [21] in [18] gives finally

$$\langle\langle M_x(0) M_x(t)\rangle\rangle = (1/2)e^{-(i\omega_o+R_2^o)t} \sum_\Omega \sum_{\Omega'}$$
$$\times (Te^{\int_0^t dt'\mathbf{Q}(t')})_{\Omega\Omega'} f^o(\Omega')\mu^2/4. \qquad [22]$$

Equation [22] in conjunction with [5] gives the spectrum. Of course, when $\Gamma(t)$ commutes with $\Gamma(t')$ at any other time, then also $\mathbf{Q}(t)$ commutes with $\mathbf{Q}(t')$ at any other time, and the time-ordering operator, T, can be omitted in Eqs. [14], [18], and [22], and also [23] and [24] below. The equivalence of Eq. [12] and the more fundamental Eq. [3], or equivalently of Eq. [22] and the more fundamental Eq. [8], has apparently been proved for only a stationary (homogeneous) Markov process in the space of the inequivalent sites, which corresponds to the case when $\Gamma(\Omega, \Omega', t)$ is independent of the time (9). In general, Brownian dynamics applies whenever the velocity distribution relaxes in a time much less than that required for the system to move between significantly different conformations. Although Brownian dynamics in the full conformational space generally proceeds by a stationary (homogeneous) Markov process, the resultant population dynamics within the subspace of the inequivalent sites, after integrating over (or summing out) the conformational coordinates external to that subspace, generally does not. In such a case, the population dynamics within that subspace can generally be regarded as a nonstationary (nonhomogeneous) Markov process with a time-dependent stochastic operator. A proof of the equivalence of Eqs. [22] and [8] in this case is indicated in Appendix A, specifically in Eq. [A10]. For any system whose dynamics is satisfactorily characterized by Brownian dynamics, Eqs. [8] and [22] are completely identical. Moreover, all thermally driven motions on time-scales ≥ 30 ps in water (or aqueous solution) exhibit (overdamped) Brownian dynamics. Thus, Eqs. [22] and [8], or equivalently [12] and [3], should be equivalent for all cases wherein the significant changes in conformation occur on a time-scale ≥ 30 ps. The common neglect of the time-ordering operator is valid whenever the matrix operator $\Gamma(t)$ commutes with itself ($\Gamma(t')$) at any other time. This condition is satisfied whenever $\Gamma(\Omega, \Omega', t)$ is independent of time. It is also satisfied by diffusion operators with time-dependent diffusion coefficients, which have been frequently employed in connection with deformable macro-molecules (1, 15, 29–32).

The simple spin-echo signal in Eq. [9] can be rewritten using Eq. [A11] to obtain

$$\frac{\langle\langle M_+(\Omega(2t), 2t)\rangle\rangle}{\langle\langle M_+(\Omega(0), 0)\rangle\rangle} = e^{-(i\omega_o+R_2^o)2t} \sum_\alpha \sum_\zeta$$
$$\times (Te^{\int_0^t dt'\mathbf{Q}^*(t')}Te^{\int_t^{2t} dt''\mathbf{Q}(t'')})_{\alpha\zeta} f_\zeta^o$$
$$= \frac{\langle\langle M_+(2t)\rangle\rangle}{\langle\langle M_+(0)\rangle\rangle}, \qquad [23]$$

where the last line simply expresses this quantity in the notation of the stochastic operator approach. It is implicit in Eq. [23] that $\langle\langle M_x(0)\rangle\rangle$ is the magnetization immediately following the (nonselective) $\pi/2$-pulse. $\mathbf{Q}^*(t)$ is the complex conjugate (not the hermitian adjoint) of $\mathbf{Q}(t)$.

The amplitudes of the even echoes in a CPMG pulse sequence, $\pi/2-(t-\pi-t-t-\pi-t)_n$, in Eq. [11] can be written using Eq. [A13] to obtain

$$\frac{\langle\langle M_+(n4t)\rangle\rangle}{\langle\langle M_+(0)\rangle\rangle} = (1/2)e^{-(i\omega_o+R_2^o)t}\sum_\alpha\sum_\zeta$$

$$\times\,[(Te^{\int_{3t}^{4t}dt'\mathbf{Q}(t')}Te^{\int_t^{3t}dt''\mathbf{Q}^*(t'')}Te^{\int_0^t dt'''\mathbf{Q}(t''')})^n]_{\alpha\zeta}f_\zeta^o. \quad [24]$$

Because $\mathbf{Q}^*(t)$ does not generally commute with $\mathbf{Q}(t)$, their corresponding exponential factors in Eqs. [23] and [24] cannot be simply combined. In any case, Eqs. [23] and [24] of the stochastic operator approach correspond to Eqs. [9] and [10] of the trajectory approach. When $\mathbf{Q}^*(t)$ commutes with $\mathbf{Q}^*(t')$ at any other time, and $\mathbf{Q}(t)$ commutes with $\mathbf{Q}(t')$ at any other time, then the time ordering operators can be removed from each factor, but their corresponding exponential factors still cannot be combined.

Equations [22], [23], and [24] are the principal results of this section for the spectrum, simple spin-echo decay, and decay of the even echoes of a CPMG sequence via the stochastic operator approach. They are readily generalized to admit a different intrinsic R_2^o rate for each site. For the case when $\Gamma(t)$ and, hence, also $\mathbf{Q}(t)$ and $\mathbf{Q}^*(t)$ are independent of t, the time-ordering operators can be omitted, and Eqs. [23] and [24] are equivalent to the corresponding results of Gutowsky *et al.* (*13*) and Allerhand and Thiel (*14*) for discrete multisite exchange of uncoupled spins. In that case, Eqs. [22], [23], and [24] can be put in computationally tractable forms by substituting the relation

$$e^{\int_{t_1}^{t_2}dt'\mathbf{Q}(t')} = \mathbf{S}e^{\boldsymbol{\lambda}(t_2-t_1)}\mathbf{S}^{-1} \quad [25]$$

and the corresponding complex conjugate relation wherein $\mathbf{S}$ is a matrix that diagonalizes $\mathbf{Q}$ by similarity transformation, $\mathbf{S}^{-1}\mathbf{Q}\mathbf{S} = \boldsymbol{\lambda}$, and $\boldsymbol{\lambda}$ is the diagonal matrix of complex eigenvalues. In the event that $\mathbf{Q}$, which is nonhermitian, is nondiagonalizable (i.e., $\mathbf{S}^{-1}$ does not exist), the protocol of Allerhand and Thiel (*14*) may provide a useful alternative approach, although it is still necessary to evaluate an exponential function of the $\mathbf{Q}$ matrix by some (unspecified) means. In any case, we are aware of no physically realistic examples for which $\mathbf{Q}$ is nondiagonalizable. Extensive elaboration of the effects of two-site exchange on the spectrum and decays of both simple and CPMG spin-echoes can be found in the works of Gutowsky *et al.* (*13*) and Allerhand and Thiel (*14*).

BASIC THEORY OF A CONTINUOUS GAUSSIAN MODEL

We now consider a situation where, instead of discrete jumps, a nucleus undergoes continuous translational Brownian motion (diffusion) in the x direction in the molecular frame in a harmonic potential well centered at x_o and also experiences a linear gradient of (rotationally averaged) chemical shielding along x. Thus, if the Larmor frequency of a nucleus at x_o is denoted by ω_0, then the incremental frequency associated with

its displacement from x_o is $\delta\omega(x(t)) = \theta(x(t) - x_o)$, where θ is the magnitude of the gradient in Larmor frequency along x.

Let $\delta x(t) = x(t) - x_o$ denote the instantaneous displacement of the nucleus from x_o. This displacement coordinate is assumed to obey an overdamped Langevin equation of the form

$$f\frac{d\delta x(t)}{dt} + g\,\delta x(t) = F(t), \quad [26]$$

where f is an effective friction factor, g is the force constant for the potential well, and $F(t)$ is a very rapidly fluctuating force exerted by the environment on the atom or group of atoms of which the nucleus is a part and along with which it moves. We are concerned here with exchange processes that take place on the Brownian or slower time-scale, long after the velocity autocorrelation function has relaxed. In that case the motion is over-damped and the inertial (acceleration) term can be omitted from the Langevin equation, as was done in Eq. [26]. The friction factor is related to $F(t)$ by the fluctuation–dissipation expression, $f = (1/k_BT)\int_o^\infty dt\langle F(0)F(t)\rangle$, where the angular brackets denote an equilibrium trajectory average of the force on a *stationary* atom or group bearing the nucleus (*33*). $F(t)$ is further assumed to be a Gaussian random variable, which should be a good approximation, since it contains contributions from many system coordinates. Because the differential equation is linear, both $\delta x(t)$ and $\delta\omega(x(t)) = \theta\delta x(t)$ are also Gaussian random variables. When Eq. [26] is multiplied by $\delta x(0)$ and ensemble averaged, there results

$$f\frac{d\langle\delta x(0)\delta x(t)\rangle}{dt} + g\langle\delta x(0)\delta x(t)\rangle = 0. \quad [27]$$

It is fundamental to linear response Langevin theory that $F(t)$ is not correlated with $\delta x(t')$ at any earlier time, so $\langle\delta x(0)F(t)\rangle = 0$. The straightforward solution is

$$\langle\delta x(0)\delta x(t)\rangle = \langle\delta x(0)^2\rangle e^{-t/\tau}, \quad [28]$$

where $\tau = f/g$ is the relaxation time for Brownian motion in the harmonic well, and $\langle\delta x(0)^2\rangle = k_BT/g$ is the mean-squared displacement in the harmonic well. Similarly, the autocorrelation function for the frequency shift of a spin is

$$\langle\delta\omega(0)\delta\omega(t)\rangle = \delta^2 e^{-t/\tau}, \quad [29]$$

where $\delta^2 = \langle\delta\omega(0)^2\rangle = \theta^2 k_BT/g$ is the variance of the chemical shift over the equilibrium distribution of spins at the different positions in the harmonic well. This model might be expected to apply to circumstance where particular fluctuations in molecular conformation translate one subunit relative to another over a small distance, so the variation in chemical shift with translation is nearly linear. In order to realize long relax-

ation times, when g is sufficiently large to limit the motion to relatively small amplitudes, the effective internal friction must be very great. This could be achieved by imposing large free energy barriers between discrete sites along x, in which case the continuous model would be an approximation to a particular multisite model.

LINEWIDTH AND SPIN-ECHO DECAY FOR THE CONTINUOUS GAUSSIAN MODEL

Because $\delta\omega(x(t)) = \theta\delta x(t)$ is a Gaussian random variable at any time, it is quite simple to evaluate the relevant magnetizations using the trajectory approach in Eqs. [8] and [9]. For simplicity, we set $\delta\omega(\Omega(t)) = \delta\omega(x(t)) = \delta\omega(t)$ in the following. The trajectory average of the phase factor in Eq. [8] is first written as

$$\langle e^{-i\int_0^t dt'\,\delta\omega(t')}\rangle_T = \langle e^{-i\Delta\varphi(t)}\rangle_T, \qquad [30]$$

where

$$\Delta\varphi(t) = \int_0^t dt'\,\delta\omega(t') \qquad [31]$$

is the accumulated phase difference at time t. Since $\Delta\varphi(t)$ is a linear superposition of Gaussian random variables $(\delta\omega(t)dt)$ of zero mean it also is a Gaussian random variable of zero mean with variance

$$\langle\Delta\varphi(t)^2\rangle = \left\langle\int_0^t dt'\,\delta\omega(t')\int_0^t dt''\,\delta\omega(t'')\right\rangle$$
$$= 2\delta^2\tau^2[t/\tau - 1 + e^{-t/\tau}] \qquad [32]$$

which is derived in Appendix B. Consequently, one can write

$$\langle e^{-i\Delta\varphi(t)}\rangle_T = e^{-\langle\Delta\varphi(t)^2\rangle/2} = e^{-\delta^2\tau^2[t/\tau - 1 + e^{-t/\tau}]}. \qquad [33]$$

Upon inserting Eq. [33] into [30] and [30] into [8] (with $\langle\langle M_x(\Omega(0), 0) M_x(\Omega(t), t)\rangle\rangle \equiv \langle\langle M_x(0) M_x(t)\rangle\rangle$) one obtains

$$\langle\langle M_x(0) M_x(t)\rangle\rangle = (\mu^2/8)e^{-(i\omega_o + R_2^o)t}e^{-\delta^2\tau^2[t/\tau - 1 + e^{-t/\tau}]}. \qquad [34]$$

This expression is incorporated into Eq. [5] to obtain the spectrum, which is evaluated numerically. The variance $\langle\Delta\varphi(t)^2\rangle$ is proportional to $(t/\tau)^2$ at small times $t \ll \tau$ and a positive increasing function of the time for all $t > 0$. Consequently, the effect of site exchange is generally to increase the rate of decay of the transverse magnetization above R_2^o and increase the width of the spectrum above $\Delta\nu_{1/2}^o = R_2^o/\pi$. Of course, the spectrum becomes non-Lorentzian as a consequence. Equation [34] describes decay of the free induction signal.

Expressions identical to [32]–[34] were obtained by Abragam (3) for an *ad hoc* scenario, in which $\delta\omega(t)$ was assumed to be a Gaussian random variable of zero mean with an exponentially decaying correlation function. The present study identifies for the first time the physical model that underlies Abragam's *ad hoc* scenario and explicitly derives its relevant properties, namely that $\delta\omega(t)$ is a Gaussian random variable of zero mean with an exponentially decaying correlation function.

The accumulated phase factor in the simple spin-echo decay amplitude is evaluated in a similar fashion by setting

$$\langle e^{+i(\int_0^t dt'\,\delta\omega(t') - \int_t^{2t} dt''\,\delta\omega(t''))}\rangle_T = \langle e^{+i\Delta\epsilon(2t)}\rangle, \qquad [35]$$

where in this case the net accumulated phase is

$$\Delta\epsilon(2t) = \int_0^t dt'\,\delta\omega(t') - \int_0^{2t} dt''\,\delta\omega(t''). \qquad [36]$$

Again, $\Delta\epsilon(2t)$ is a linear superposition of Gaussian random variables of zero mean and is therefore also a Gaussian with zero mean and a variance,

$$\langle\Delta\epsilon(2t)^2\rangle = \left\langle\int_0^t dt'\,\delta\omega(t')\int_0^t dt''\,\delta\omega(t'')\right\rangle$$
$$+ \left\langle\int_t^{2t} dt'\,\delta\omega(t')\int_t^{2t} dt''\,\delta\omega(t'')\right\rangle$$
$$- 2\left\langle\int_0^t dt'\,\delta\omega(t')\int_t^{2t} dt''\,\delta\omega(t'')\right\rangle$$
$$= 2\delta^2\tau^2[+2\tau/t - 3 + 4e^{-t/\tau} - e^{-2t/\tau}]. \qquad [37]$$

This variance is also evaluated in Appendix B. It is proportional to $(t/\tau)^3$ for small $t \ll \tau$, and therefore vanishes in the limit $t/\tau \to 0$, as expected when no transfer between sites is possible. One can now write

$$\langle e^{+i\Delta\epsilon(2t)}\rangle_T = e^{-\langle\Delta\epsilon(2t)^2\rangle/2} = e^{-\delta^2\tau^2[+2t/\tau - 3 + 4e^{-t/\tau} - e^{-2t/\tau}]}. \qquad [38]$$

Upon inserting Eq. [38] into [35] and [35] into [9], the amplitude of the simple spin-echo signal is finally obtained as

$$A(2t) = e^{i\omega_o 2t}\frac{\langle\langle M_+(\Omega(2t), t)\rangle\rangle}{\langle\langle M_+(\Omega(0), 0)\rangle\rangle}$$
$$= e^{-R_2^o 2t}e^{-\delta^2\tau^2[+2t/\tau - 3 + 4e^{-t/\tau} - e^{-2t/\tau}]}. \qquad [39]$$

The multiplication by $e^{i\omega_o 2t}$ in the first line of Eq. [39] simply removes the oscillation at the average Larmor frequency, ω_o. Again, the variance $\langle\Delta\epsilon(2t)^2\rangle$ is a positive,

increasing function of the time for $t > 0$, so the effect of site exchange is generally to increase the rate of decay of the simple spin-echo above R_2^o. That decay also becomes non-exponential.

The accumulated phase factor at the times of the even echoes in a CPMG pulse-sequence is defined in Eqs. [10] and [11]. $\Delta\gamma(0, 4nt)$ is a sum of Gaussian random variables of zero mean, and so is itself a Gaussian random variable of zero mean. Its variance is obtained by a somewhat involved derivation in Appendix B with the result,

$$
\langle\Delta\gamma(0, n4t)^2\rangle
$$

$$
= \delta^2\tau^2\Big\{2n[4t/\tau - 5 + 4e^{-t/\tau} + 4e^{-2t/\tau} - 4e^{-3t/\tau} + e^{-4t/\tau}]
$$

$$
+ (n-1)2\frac{F(t/\tau)}{E(t/\tau)} - 2\frac{F(t/\tau)}{E(t/\tau)^2}(1 - e^{-(n-1)4t/\tau})\Big\},
$$

[40]

where

$$
E(t/\tau) = e^{4t/\tau} - 1 \qquad [41]
$$

and

$$
F(t/\tau) = (1 + e^{-2t/\tau} - 2e^{-t/\tau})e^{t/\tau}
$$

$$
\times (1 - e^{-t/\tau} - e^{-2t/\tau} + e^{-3t/\tau})
$$

$$
\times (1 - e^{t/\tau} - e^{2t/\tau} + e^{3t/\tau}). \qquad [42]
$$

The multiplication by $e^{i\omega_o n4t}$ in the first line of Eq. [43] removes the oscillation at the average Larmor frequency ω_o. In the limit $n4t \ll \tau$, the variance, $\langle\Delta\gamma(0, n4t)^2\rangle$ is proportional to $n(t/\tau)^3$, so vanishes in the limit $t/\tau \to 0$, as expected, when no transfer between sites is possible. As expected, $\langle\Delta\gamma(0, n4t)^2\rangle$ is a positive, increasing function of both t and n for $t > 0$, so the effect of site exchange is generally to increase the rate of decay of the even CPMG spin echoes as a function of either n or t above R_2^o. The decay rate, R_2^{CPMG}, of the CPMG even echoes is here defined by the amplitudes of the echoes observed for $n = 1, 2, 3, 4, \ldots$, at a fixed value of the $4t$ cycle time. In the presence of site exchange, R_2^{CPMG} decreases with decreasing $4t$ cycle time, and approaches R_2^o in the limit $4t/\tau \to 0$.

Equations [34], [39], and [43] provide simple analytical expressions for use in calculating the NMR spectrum and both simple and even CPMG spin-echo decays as a function of the correlation time, τ, for motion in the harmonic well and the equilibrium variance, δ^2, of the chemical shifts. When analyzing experimental data, it is useful to rewrite Eqs. [34], [39], and [43] in terms of the dimensionless quantities,

$$
d \equiv (\delta/R_2^o) \quad \text{and} \quad e \equiv R_2^o\tau \qquad [44]
$$

to obtain

$$
\langle\langle M_x(0) M_x(t)\rangle\rangle = (\mu^2/8)e^{-(i\omega_o + R_2^o)t}e^{-d^2e^2[t/(e/R_2^o) - 1 + e^{-t/(e/R_2^o)}]}
$$

[45]

$$
A(2t) = e^{-R_2^o 2t}e^{-d^2e^2[2t/(e/R_2^o) - 3 + 4e^{-t/(e/R_2^o)} - e^{-2t/(e/R_2^o)}]}
$$

[46]

and

$$
A(n4t)_{CPMG} = \exp[-R_2^o n4t]\exp[-d^2e^2\{n(4t/(e/R_2^o) - 5 + 4e^{-t/(e/R_2^o)} + 4e^{-2t/(e/R_2^o)} - 4e^{-3t/(e/R_2^o)} + e^{-4t/(e/R_2^o)})
$$

$$
+ (n-1)F(t/(e/R_2^o))/E(t/(e/R_2^o)) - F(t/(e/R_2^o))(1 - e^{-(n-1)4t/(e/R_2^o)})/E(t/(e/R_2^o))^2\}]. \qquad [47]
$$

Upon inserting $\langle\exp[-i\Delta\gamma(0, n4t)]\rangle = \exp[-\langle\Delta\gamma(0, n4t)^2\rangle/2]$ into Eq. [10] and making use of [40]–[42], the amplitude of the nth even (or $2n$th) spin-echo of a CPMG sequence is given by

$$
A(n4t)_{CPMG} = e^{i\omega_o n4t}\frac{\langle\langle M_+(\Omega(n4t), n4t)\rangle\rangle}{\langle\langle M_+(\Omega(0), 0)\rangle\rangle}
$$

$$
= e^{-R_2^o n4t}\exp[-\delta^2\tau^2\{n(4t/\tau - 5 + 4e^{-t/\tau}
$$

$$
+ 4e^{-2t/\tau} - 4e^{-3t/\tau} + e^{-4t/\tau})
$$

$$
+ (n-1)F(t/\tau)/E(t/\tau)
$$

$$
- F(t/\tau)(1 - e^{-(n-1)4t/\tau})/E(t/\tau)^2\}].
$$

[43]

In order to estimate τ and δ from experimental spectra and the decay of the CPMG even echoes at a single time delay, one must have an independent estimate of R_2^o. Although one could assume that R_2^o values for the same nuclei at different subunits in the same molecule are similar, whether they do or do not undergo slow site exchange, that presumes that the rapid angular motions responsible for R_2^o are unaffected by any factors associated with the slow conformational mobility. Whether the rms amplitudes of rapid local angular motion are significantly enhanced for nuclei that undergo slow site exchanges (22) is a question of particular interest to us. In order to determine R_2^o, as well as τ and δ, one can either measure the decays of CPMG

even echoes with progressively shorter delay times (t) (*19*), or the $R_{1\rho}$ decay rates in resonant spin-locking fields with progressively larger precession frequencies ω_1 (*19, 22*). The (heuristic) theory for $R_{1\rho}$ is discussed in a subsequent section.

BEHAVIOR OF THE CONTINUOUS GAUSSIAN MODEL IN VARIOUS LIMITS

It can be seen from Eqs. [34], [39], and [43] that the relevant decays (excluding the $e^{-i\omega_o t}$ oscillations) are generally nonexponential, except at very short times and again at very long times, where single-exponential behavior prevails. The arguments are detailed separately for each case below.

Transverse Magnetization in Eq. [34]

In this case the very short time limit is defined by $t \ll \tau$, $t \ll 1/\delta$, and by the requirement that the corresponding site exchange contribution to the exponent, namely $\sim\delta^2 t^2$, be negligibly small compared to $R_2^{o}t$. This limit will be experimentally significant only when $R_2^{o}t \gtrsim 1.0$ for some of the times in this domain, $t \ll \tau$ and $t \ll 1/\delta$, which requires $R_2^{o} \gg 1/\tau$, δ. Only then does significant amplitude decay in this short time limit, and that decay is exponential with rate constant R_2^{o}.

In the long time limit, defined by $t \gg \tau$, the site exchange contribution to the exponent is precisely $\delta^2 \tau t$, and the overall decay is again single exponential, but now with rate constant $R_2^{o} + \delta^2\tau$. This limit will be experimentally significant only when the signal amplitude has not already relaxed at some earlier time. This circumstance occurs only when $\delta\tau \ll 1.0$, and $R_2^{o} \ll 1/\tau$.

Simple Spin Echo in Eq. [39]

In this case the very short time limit is defined by $2t \ll \tau$, $t \ll 1/\delta$, and by the requirement that the corresponding site exchange contribution to the exponent, namely $\sim 2\delta^2 t^3/\tau$, be negligibly small compared to $R_2^{o}2t$. Again this very short time limit is experimentally significant only when $R_2^{o}2t \gtrsim 1.0$ for some of the times in this domain, $2t \ll \tau$ and $t \ll 1/\delta$, which requires $R_2^{o} \gg 1/\tau$, $\delta/2$. In that event, and only then, significant exponential decay occurs in this short time domain with rate constant R_2^{o}.

In the long time limit, defined by $t \gg \tau$, the site exchange contribution in the exponent is precisely $\delta^2\tau 2t$, and the overall decay of the simple spin-echo amplitude is exponential with rate constant $R_2^{o} + \delta^2\tau$. Again, this limit will be experimentally significant only when $\delta\tau \ll 1.0$ and $R_2^{o} \ll 1/\tau$, so the signal has not already relaxed at some earlier time.

CPMG Even Spin-Echoes in Eq. [43]

In this case the very short time limit is defined by $n4t \ll \tau$, $t \ll 1/\delta$, and by the requirement that the corresponding site exchange contribution in the exponent, namely $\sim n\delta^2 t^3/\tau$, be negligibly small compared to $R_2^{o}n4t$. Again, this limit is ex-

perimentally significant only when $R_2^{o}n4t \gtrsim 1.0$ for some of the times in the domain, $n4t \ll \tau$ and $t \ll 1/\delta$, which requires $R_2^{o} \gg 1/\tau$, $\delta/4n$. In that event, and only then, significant exponential decay with increasing n at fixed t occurs in this domain with rate constant R_2^{o}.

In the long time limit, defined by $t \gg \tau$, the site exchange contribution in the exponent is precisely $\delta^2\tau n4t$, and the overall decay of the CPMG even echo train is again exponential with rate constant $R_2^{o} + \delta^2\tau$. Again, this limit will be experimentally significant only when $\delta\tau \ll 1.0$ and $R_2^{o} \ll 1/\tau$, so the signal has not already relaxed at some earlier time.

Particularly simple behavior of all the relevant decays is observed at all times in yet a different limit, namely the fast exchange limit.

The Fast Exchange Limit

In the fast exchange limit, defined by $\delta\tau \ll 1.0$, the relevant decays all become single exponential. The site exchange contribution to transverse magnetization relaxes negligibly until $t \gg \tau$, in which case Eq. [34] can be accurately approximated by

$$\langle\langle M_x(0)\, M_x(t)\rangle\rangle = (\mu^2/8)e^{-(i\omega_o+R_2^{o})t}e^{-\delta^2\tau t}. \qquad [48]$$

Likewise, when $\delta\tau \ll 1.0$, the simple spin-echo amplitude relaxes negligibly until $2t \gg \tau$, in which case Eq. [39] can be accurately approximated by

$$A(2t) = e^{-R_2^{o}2t}e^{-\delta^2\tau 2t}. \qquad [49]$$

Similarly, when $\delta\tau \ll 1.0$, the CPMG even echoes relax negligibly until $n4t \gg \tau$, in which case [43] can be accurately approximated by

$$A(n4t)_{\text{CPMG}} = e^{-R_2^{o}n4t}e^{-\delta^2\tau f(t/\tau)n4t}, \qquad [50]$$

where

$$f(t/\tau) \equiv 1 + (-5 + 4e^{-t/\tau} + 4e^{-2t/\tau} - 4e^{-3t/\tau}$$
$$+ e^{-4t/\tau})/(4t/\tau) + F(t/\tau)/(E(t/\tau)(4t/\tau)). \qquad [51]$$

The decay of the CPMG even echoes is exponential with increasing n, though not with increasing t. At any fixed t, the time is incremented by adding another CPMG cycle ($4t$) to the sequence, which increases n by 1. Because a total time $n4t$ is associated with the nth echo amplitude, the decay rate constant is $R_2^{o} + \delta^2\tau f(t/\tau)$. In the limit $t \ll \tau$, $f(t/\tau) \sim (t/\tau)^2 \ll 1.0$, so $\delta^2\tau f(t/\tau)$ must fall below R_2^{o} for some sufficiently small t/τ. In that case, the rate constant for the CPMG decay approaches R_2^{o}. In the opposite limit $t \gg \tau$, $f(t/\tau) \cong 1.0$, and the rate constant for the CPMG decay approaches $R_2^{o} + \delta^2\tau$. Thus, by decreasing the CPMG cycle time, it is possible to map out the dispersion of $\delta^2\tau f(t/\tau)$, as it descends monotonically from $\delta^2\tau$

for $t/\tau \gg 1.0$ to 0 for sufficiently small t/τ. In this way one can determine (i) the relaxation time τ from the position (midpoint time) of the dispersion, (ii) the standard deviation of the Larmor frequency δ from the magnitude of the dispersion and knowledge of τ, and (iii) also the intrinsic R_2° from the residual rate constant at small times, provided that only a single site exchange process occurs. The predicted behavior, when two different site exchange processes take place concurrently on different time scales, both in their fast exchange limits, is discussed subsequently.

The effect of site exchange on the decay of the transverse magnetization in Eq. [34] and the simple echo in Eq. [39] is maximal for times such that the site exchange exponent is ~ 1.0 and is negligible at either much shorter times where that exponent is $\ll 1.0$ or much longer times after the transverse magnetization or spin-echo amplitude has already decayed away. In the fast exchange limit, the site exchange exponent reaches 1.0 only at some long time $t \gg \tau$, and that is the time for which the site exchange contribution is mainly sampled by the decay of the transverse magnetization and simple spin-echo. In contrast, the decay of the CPMG even echoes in Eq. [43] with increasing n can probe the site exchange contribution even at much shorter times by using a small cycle time $(4t)$, but also a very large n to obtain significant decay. With sufficiently short cycle times, the dephasing due to variations in Larmor frequency are reversed and refocused by the CPMG pulse sequence before site exchange leads to irreversible loss of coherence, but with longer cycle times such irreversible coherence loss is not prevented and the rate constant for the relaxation increases, as indicated by Eqs. [50] and [51].

RELATION OF THE CONTINUOUS GAUSSIAN MODEL TO DISCRETE JUMP MODELS

Our Eq. [50] is directly analogous to Eq. [31a] of Davis *et al.* (*19*) for the decay of the CPMG even echoes of a two-site jump model in the fast exchange limit. For the particular case of a symmetrical two-site jump model, in which the populations and intrinsic R_2° rates for both sites are identical, the fast exchange CPMG results for the two-site model are identical to those for the continuous Gaussian model in both the short and the long time limits, provided δ is identified with $\Delta\omega/2$, where $\Delta\omega$ is the difference in Larmor frequency between the two sites and τ is identified with the relaxation time, $1/2k$, of a two-site model with transition rate constants k for hopping in either direction. The spectrum and simple spin-echo decay are likewise identical for the two models in this fast exchange limit. This equivalence can be understood by the following arguments. (1) In the fast exchange limit, significant decay due to site exchange occurs only at long times, specifically at $t \gg \tau$ for the transverse magnetization in Eq. [34], at $2t \gg \tau$ for the simple spin-echo decay in Eq. [39], and at $n4t \gg \tau$ for the CPMG decay in Eq. [43]. (2) Even though the fluctuating Larmor frequency of a discrete multisite model is not a Gauss-

ian random variable, the accumulated phase (relative to its own mean) becomes a Gaussian random variable of zero mean and variance $2\delta^2\tau t$, where δ^2 is the variance of the Larmor frequency and τ is the time integral of the normalized autocorrelation function of the fluctuations in Larmor frequency, whenever the phase accumulation period t greatly exceeds the relaxation time τ. This result is proved in Appendix E, where it is also generalized to arbitrary discrete multisite models. Thus, any discrete multisite model with the same intrinsic R_2° for all sites must yield the same results as a continuous Gaussian model with the same δ^2 and τ, whenever $t \gg \tau$. For such a discrete multisite model in the fast exchange limit, significant decay of either the transverse magnetization in Eq. [34] or the simple spin-echo in Eq. [39] occurs only for $t \gg \tau$, and that model behaves exactly like a continuous Gaussian model. Moreover, when $t \gg \tau$, the decay of the CPMG even echoes must also follow the behavior of a continuous Gaussian model. When $t \lesssim \tau$, the accumulated phase of such a discrete model is no longer a Gaussian random variable. Nevertheless, at very short times, $t \ll \tau$ and $t \ll 1/\delta$, it is expected on physical grounds that site exchange will make no significant contribution to the decay, so that such a discrete model in its very short time limit will exhibit exponential decay with rate constant R_2°. Thus, any discrete model with a uniform R_2° for all sites is expected to behave in precisely the same fashion as the continuous Gaussian model in both the very short time ($t \ll \tau$, $t \ll 1/\delta$) and the long time ($t \gg \tau$) limits, neither of which is necessarily experimentally significant. In the particular case of such a discrete model with uniform R_2° in the fast exchange limit, where the decay of the CPMG even echoes is exponential for all times t, the rate constant for that decay will be identical to that for the continuous Gaussian model at both very short ($t \ll \tau$) and long ($t \gg \tau$) limits, as is found to be the case for the two-state model. In this limit, the results are probably not very different even at intermediate times. Of course, results for these two models will be very different in other limits. For example, in the slow exchange limit, defined by $\delta\tau \gg 1.0$, when also $R_2^{\circ} \ll \delta$, the site exchange contribution to the decay is maximal at a short (but not very short) time, $t \sim 1/\delta \ll \tau$. In this case, the site exchange exponent in Eq. [34] is $\delta^2 t^2/2$ for the continuous Gaussian model, which yields a Gaussian spectrum, whereas a discrete m-site model with uniform R_2° yields a multiline spectrum containing m peaks.

$R_{1\rho}$ FOR THE CONTINUOUS GAUSSIAN MODEL

A quantity called $R_{1\rho} = T_{1\rho}^{-1}$ is commonly measured to investigate slow site exchange. In this method an initial $\pi/2$ pulse rotates the equilibrium magnetization into the transverse plane, where its orientation defines the z' axis in the rotating frame (x', y', z'). Then a spin-locking RF pulse is applied along z' in the rotating frame for a time duration t, after which it is cut off and the subsequent free-induction decay measured. The initial amplitude of the free induction decay is recorded as

a function of the duration t of the spin-locking pulse and is typically found to decay exponentially.

Relevant theory for the contribution of heteronuclear dipole–dipole interactions to $R_{1\rho}$ was formulated by Peng *et al.* (*6*) and Peng and Wagner (*5*), and their result is presented in Appendix C. Additional theory to treat the contributions of both homonuclear dipole–dipole interactions (between nuclei with slightly different resonance frequencies) and chemical shift anisotropy to $R_{1\rho}$ for the particular case of resonant RF power is also presented in Appendix C. We assume again that the relevant molecular motions can be divided into those rotations that take place on a time-scale equal to or less than the longest uniform rotational relaxation time and much slower transitions between conformations that give rise to site exchange. It is shown in Appendix C that the contribution of the rapid rotational motions to $R_{1\rho}$, which is here designated by $R_{1\rho}^{o}$, is practically identical to the corresponding contribution of those same rapid rotations to the spin-echo decay, namely R_2^o. That is, $R_{1\rho}^o \cong R_2^o$ to very high accuracy. Thus, under the assumed conditions, the difference between $R_{1\rho}$ and the simple spin-echo decay rate arises entirely from the contributions of slow site exchange. Qualitatively, the effect of the spin-locking pulse is to rotate the magnetization around the z' axis in the rotating frame, so it can be regarded as a train of contiguous, π pulses, if it is not actually so in practice. Thus, the inversion of the accumulated phase takes place continuously, and the effects of site exchange to diminish the amplitude of the signal are correspondingly reduced in $R_{1\rho}$ compared to the simple spin-echo decay, where the time delays between π pulses are normally much greater.

An approximate theory of the contribution of site exchange in the continuous Gaussian model to $R_{1\rho}$ is presented in Appendix D. After a spin-lock time t, the transverse magnetization is given by

$$\frac{\langle\langle(M_+(\Omega(t),\,t))\rangle\rangle}{\langle\langle(M_+(\Omega(0),\,0))\rangle\rangle} = e^{-(i\omega_o + R_2^o)t}e^{-\langle\Delta\gamma(t)^2\rangle/2}, \qquad [52]$$

where under the conditions discussed in Appendix D,

$$\langle\Delta\gamma(t)^2\rangle/2 = R_{1\rho}^{se}t + D \qquad [53]$$

$$R_{1\rho}^{se} = \delta^2\tau/(4(1 + \omega_1^2\tau^2)), \qquad [54]$$

where ω_1 is the angular precession frequency of the spin vector around the spin-locking field in the rotating frame, and D is a constant (independent of t) given in Eq. [D12]. A more general expression for $\langle\Delta\gamma(t)^2\rangle/2$ is given in Eq. [D9]. It contains oscillatory terms that will vanish whenever the spin-lock consists of an even number of π pulses and will probably vanish in any case for times sufficiently long that $\omega_1 t \gg 1.0$, for reasons discussed in Appendix D. The expression for $R_{1\rho}^{se}$ is similar in form to that presented previously for a 2-site jump

model in the fast exchange limit (*17–21*), but its domain of validity is not restricted to the fast exchange limit $\delta\tau \ll 1.0$, but instead to $\omega_1 \gg \delta$, which could in principle be satisfied even when $\delta\tau \gtrsim 1.0$. The total rate of exponential decay of the transverse magnetization during the spin-lock is

$$R_{1\rho} = R_2^o + R_{1\rho}^{se}. \qquad [55]$$

In terms of the dimensionless variables of Eq. [44]

$$R_{1\rho} = R_2^o + d^2 e R_2^o/(4(1 + \omega_1^2(e/R_2^o)^2)). \qquad [56]$$

The requirement, $\omega_1 \gg \delta$, for validity of the $R_{1\rho}^{se}$ formula [54] may confine ω_1 to relatively large values in order to obtain interpretable data. In that case, $R_{1\rho}$ becomes very insensitive to any very slow site exchange processes, for which $\omega_1\tau \gg 1.0$ and $R_{1\rho}^{se}$ is very small.

This continuous Gaussian model is the only site exchange model for which simple and accurate analytical formulas for the lineshape, decays of both simple and CPMG spin-echoes, and $R_{1\rho}$ are available valid outside the fast-exchange limit, $\delta\tau \ll 1.0$. In fact, Eqs. [34] and [45] (in conjunction with Eq. [5]) for the lineshape, [39] and [46] for the simple spin-echo decay, and [43] and [47] for the CPMG spin-echo decay are valid for all values of the standard deviation, δ, of the Larmor frequency and relaxation time, τ, of the Gaussian site exchange process and Eqs. [52]–[56] for the decay of the transverse magnetization in a resonant spin-locking field are valid whenever $\omega_1 \gg \delta$, even outside the fast exchange limit.

APPLICATION OF THE CONTINUOUS GAUSSIAN MODEL TO ANALYZE EXPERIMENTAL DATA

Estimates of R_2^o, τ, and δ can be obtained when $R_{1\rho}$ is measured as a function of increasing spin-lock frequency ω_1 and found to bottom out at its minimum value, R_2^o. This circumstance prevailed in a study of the $^{13}C1'$ nucleus of the A4 deoxyribose in the duplex sequence 5′-GCGAAATT-TCGC-3′ (*22*). Fits of $R_{1\rho}$ to an equation of the form of Eq. [56] yielded values for R_2^o, τ, and δ. However, in the absence of CPMG spin-echo decay and linewidth data, one cannot be certain that there exist no additional much slower site exchange processes. As illustrated below, when the ω_1 values examined are all sufficiently large, it is possible for much slower site exchange processes to contribute significantly to the linewidth and decay of the even CPMG spin-echoes, but to make virtually no contribution to $R_{1\rho}$.

In a ^1H NMR study of the duplex sequence 5′-CGAGGTT-TAAACCTCG-3′, considerable evidence was obtained for a site exchange process involving A9 (*25*). For the A9-H2 proton at 31°C, (1) the reported linewidth (after correction for 3 Hz instrumental broadening due mainly to field inhomogeneity (M. A. Kennedy, personal communication) was $\Delta\nu_{1/2} = 10$ Hz

(FWHM), or equivalently $(1/2)\Delta\omega_{1/2} = 31.4$ rad s^{-1} (HWHM); (2) the reported decay rate of the CPMG even echoes in a sequence with a cycle time of $4t = 4$ ms (M. A. Kennedy, personal communication) was $R_2^{\text{CPMG}} = 26.3$ s^{-1}; and (3) the reported decay rate of the transverse magnetization in a resonant spin-locking field with $\omega_1 = 13800 \times 2\pi = 8.67 \times 10^4$ rad s^{-1} was $R_{1\rho} = 6.25$ s^{-1} (25). In the absence of site exchange, these values of $(1/2)\Delta\omega_{1/2}$, R_2^{CPMG}, and $R_{1\rho}$ must all be identical and equal to R_2°. Hence, the presence of one or more site exchange processes can be immediately inferred.

If only a single site exchange process occurs, then these three experimental values in conjunction with Eqs. [45] (in [5]), [47], and [56] in principle allow a determination of R_2°, τ, and δ. For any given choice of R_2°, τ, and δ, or equivalently, of R_2°, $d = (\delta/R_2^\circ)$ and $e = (R_2^\circ\tau)$, the spectrum can be calculated via Eqs. [45] and [5] and its half-width measured directly. Similarly, the decay of the even CPMG spin-echoes can be calculated via Eq. [47] and least-squares fitted to a single exponential function in the same manner as the experimental data to obtain the CPMG echo decay rate, R_2^{CPMG}. A general strategy is to select trial values of $R_2^\circ(\leq R_{1\rho})$, and for each of those to compute the curve of e vs d that satisfies the experimental linewidth constraint, $\Delta\nu_{1/2} = 10$ Hz, and another curve of e vs d that satisfies the CPMG even echo constraint, $R_2^{\text{CPMG}} = 26.3$ s^{-1}. The region where these curves cross locates the area of the e–d plane that is to be grid searched. Beginning with the central cross point, trial pairs of e and d values are used to calculate $R_{1\rho}$ as well as $\Delta\nu_{1/2}$ and R_2^{CPMG}, and from those is calculated a chi-squared,

$$\chi^2 = ((\Delta\nu_{1/2})^{\text{th}} - (\Delta\nu)_{1/2}^{\text{ex}})^2/\sigma_{\text{LW}}^2$$
$$+ ((R_2^{\text{CPMG}})^{\text{th}} - (R_2^{\text{CPMG}})^{\text{ex}})^2/\sigma_{\text{CPMG}}^2$$
$$+ ((R_{1\rho})^{\text{th}} - (R_{1\rho})^{\text{ex}})^2/\sigma_{\text{SL}}^2, \qquad [57]$$

where the superscripts th and ex denote theoretical and experimental values, respectively, and σ_{LW}, σ_{CPMG}, and σ_{SL} are the estimated errors in the experimental linewidth, CPMG even echo decay rate, and $R_{1\rho}$ rate, respectively. The grid search in the d–e plane should yield the d and e pair that minimizes χ^2 for any given choice of R_2° and may even reduce χ^2 completely to zero for the correct choice of R_2°. By sampling several values of R_2°, the choice of all three parameters defining the global minimum in χ^2 can presumably be found.

In the present case, it was not necessary to iterate R_2°, since the initial choice, $R_2^\circ = R_{1\rho} = 6.25$ s^{-1}, proved to be self-consistent. The e vs d curves that satisfy the linewidth and CPMG even spin-echo constraints for $R_2^\circ = 6.25$ s^{-1} are shown in Fig. 1. The central crossing point, $e = 1.25 \times 10^{-3}$, $d = 56.8$, satisfies those two constraints accurately. When those values of e and d together with $R_2^\circ = 6.25$ s^{-1} are used in Eq. [52], one calculates $R_{1\rho} = 6.25 + 2.1 \times 10^{-2} \cong 6.27$ s^{-1}, which is experimentally indistinguishable from the measured
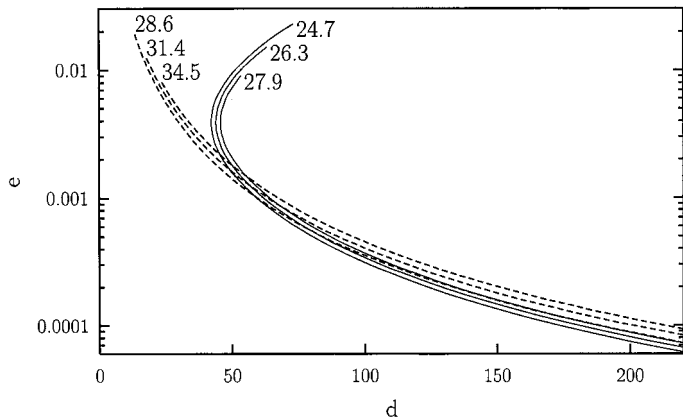

FIG. 1. Curves of e versus d that yield the linewidths (HWHM) $(1/2)\Delta\omega_{1/2}$ = 28.6, 31.4, or 34.5 rad s^{-1} (dashed lines as indicated) and the CPMG spin-echo decay rates R_2^{CPMG} = 24.7, 26.3, and 27.9 s^{-1} (solid lines as indicated). The middle curves in each case apply to the reported experimental values, $(1/2)\Delta\omega_{1/2} = 31.4$ rad s^{-1} and $R_2^{\text{CPMG}} = 26.3$ s^{-1}, whereas the outer curves apply for the experimental values plus or minus one standard deviation. The curves that yield the three $(1/2)\Delta\omega_{1/2}$ values are generated in the following way. The target value of $(1/2)\Delta\omega_{1/2}$ (e.g., 31.4 rad s^{-1}) is selected. A particular value of d is then chosen and entered into Eq. [45] along with a trial value of e. The correlation function in Eq. [45] is then computed for a range of time points and Fourier transformed to compute the spectrum. The full width of the spectrum at half-height is then determined and compared with the target value. The value of e is adjusted and the process is iterated until the computed $(1/2)\Delta\omega_{1/2}$ matches the target value. Then a new value of d is selected and the process repeated until again the same target value is matched, but now for a different (d, e) pair. In this way the curve of e versus d that yields the target linewidth is mapped out. The curves that yield the three R_2^{CPMG} values are generated in a similar fashion. Again, the target value (e.g., 26.3 s^{-1}) is selected. A particular value of d is then chosen and entered into Eq. [47] along with a trial value of e. The amplitude in Eq. [47] is computed for a range of time points and fitted to a single exponential decay (as were the experimental data). The best-fit decay constant, R_2^{CPMG}, is then determined and compared with the target value. The value of e is adjusted and the process is iterated until the computed best-fit R_2^{CPMG} matches the target value. The points where the dashed and solid curves cross define the (d, e) pair that simultaneously yields both the target $(1/2)\Delta\omega_{1/2}$ and R_2^{CPMG} values. The crosspoint for the curves that yield $(1/2)\Delta\omega_{1/2} = 31.4$ rad s^{-1} and $R_2^{\text{CPMG}} = 26.3$ s^{-1} is $d = 56.8$ and $e = 1.25 \times 10^{-3}$. Given the value $R_2^\circ = 6.25$ s^{-1}, these values correspond to $\tau = 2 \times 10^{-4}$ s and $\delta = 355$ rad s^{-1}.

value. Consequently, the initial choice, $R_2^\circ = 6.25$ s^{-1} and the central crossing point of the e vs d curves give $\chi^2 \cong 0$ and provide a satisfactory solution in that regard. Curves of d vs e were also calculated for each constraint value (i.e., $\delta\nu_{1/2}$ or R_2^{CPMG}) plus or minus one standard deviation, and these are also displayed in Fig. 1. The overlap region is seen to span a wide range of both e and d values. However, as d increases within the overlap region, the contribution of this site exchange process to $R_{1\rho}^{\text{se}}$ also increases sufficiently that $R_{1\rho}$ significantly exceeds the experimental value (by $\geq 5\%$) for $d \geq 100$. Hence, the acceptable range of d values is probably limited to 50 to 100, and the corresponding range of e values is limited to 1.2×10^{-3} to 3.5×10^{-4}. The implied values of τ and δ from the optimum e, d at the central crossing point and $R_2^\circ =$

6.25 s^{-1} are $\tau = 2.00 \times 10^{-4}$ s $\simeq 0.2$ ms, and $\delta = 355$ rad s^{-1}. The implied rate of this conformational exchange process is considerably slower than that estimated by Kennedy *et al.* (*25*). However, this is not the only solution consistent with the $\Delta\nu_{1/2}$, R_2^{se}, and $R_{1\rho}$ data from the A9-H2 proton and is almost certainly not the whole picture, as detailed below.

Kennedy *et al.* presented evidence that the magnetization transfer rates from A10-H2 and A11-H2 to their neighboring protons actually exceed those of A9-H2, despite their much smaller linewidths. Because both the magnetization transfer rates and the R_2^o rates arise from the same dipolar interactions, and depend on similar spectral densities of the same correlation function, this finding suggests that R_2^o for A9-H2 should be less than or equal to R_2^o for A10-H2 and A11-H2. In view of Eq. [55], this would imply that R_2^o for A9-H2 should also be less than or equal to $R_{1\rho}$ for A10-H2 and A11-H2. However, at 31°C, the reported $R_{1\rho}$ values for A9-H2, A10-H2, and A11-H2 are, respectively, 6.25, 3.15, and 2.6 s^{-1}. Thus, if R_2^o for A9-H2 were equal to its $R_{1\rho}$, then it would exceed $R_{1\rho}$ for A10-H2 and A11-H2 by at least 2-fold, contrary to expectation. This suggests that $R_{1\rho}$ for A9-H2 has a substantial contribution from site exchange, $R_{1\rho}^{se} \geq 3.1$ s^{-1}, so that its R_2^o contribution does not exceed 3.15 s^{-1} and may be even smaller. However, we found that no single site exchange process with $R_2^o = 3.15$ s^{-1} can simultaneously fit the experimental $\Delta\nu_{1/2}$ and R_2^{CPMG} data for A9-H2 and still yield so large a value of $R_{1\rho}^{se} \geq 3.1$ s^{-1}.

We now suppose that there occur two concurrent site exchange processes, a faster one responsible for the substantial contribution to $R_{1\rho}^{se} \geq 3.1$ s^{-1} and a much slower process that makes a negligible contribution to $R_{1\rho}^{se}$. For purposes of illustration, we suppose that $R_2^o = 3.10$ s^{-1} and $R_{1\rho}^{se} = 3.15$ s^{-1} for A9-H2. A rather large standard deviation δ of the Larmor frequency is required to produce so large a value of $R_{1\rho}^{se}$. Plots of $R_{1\rho}^{se}$ vs τ for two assumed standard deviations, $\delta = 250$ π and 500 π, are presented in Fig. 2. Additional calculations (not shown) demonstrate that a value $\delta \geq 471$ π rad s^{-1} is required to achieve $R_{1\rho}^{se} = 3.15$ s^{-1} for any value of τ. The value $\delta = 500$ π rad s^{-1} corresponds to a standard deviation of 0.5 ppm at 500 MHz, so the span of chemical shift from $-\delta$ to $+\delta$ is 1 ppm. In fact, δ cannot be much larger than this, because the maximum change in chemical shift of an H2 proton of one adenine in the ring current of a neighboring adenine is about 1.33 ppm (*25*). If we assume that $\delta \cong 500$ π, then either of two τ-values, namely $\tau_1 \cong 7$ μs or $\tau_{1'} \cong 19$ μs, yields the target value, $R_{1\rho}^{se} = 3.15$ s. However, only the former value is consistent with the observed $R_2^{CPMG} = 26.3$ s^{-1} and $(1/2)\Delta\omega_{1/2} = \pi \cdot \Delta\nu_{1/2} = 31.4$ rad s^{-1}. If only this single site exchange process is considered, the choice $R_2^o = 3.1$ s^{-1}, $\delta = 500$ π rad s^{-1} and $\tau_1 = 7$ μs, yields $R_2^{CPMG} = 20.3$ s^{-1} and $(1/2)\Delta\omega_{1/2} = 20.3$ rad s^{-1}, which are both smaller than the corresponding experimental values, 26.3 s^{-1} and 31.4 rad s^{-1}, respectively. However, the choice, $\tau_{1'} = 19$ μs, with the same choices of R_2^o and δ yields $R_2^{CPMG} = 50.2$ s^{-1} and $(1/2)\Delta\omega_{1/2} = 50.3$ rad s^{-1}, both of which exceed their experimental values. In the former case, agreement with
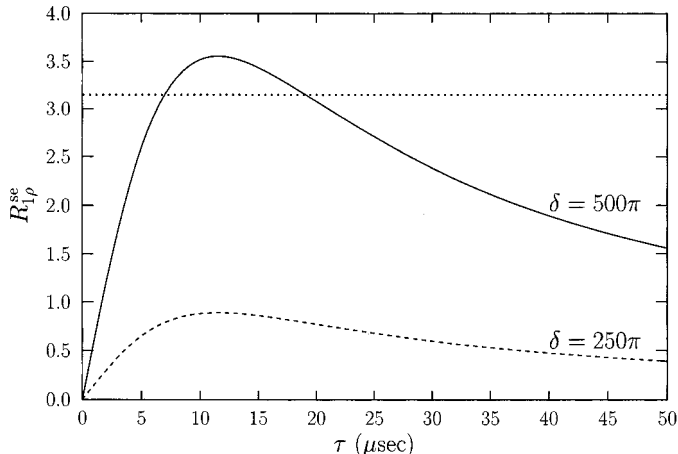
FIG. 2. Curves of $R_{1\rho}^{se}$ vs τ for $\delta = 500$ π and $\delta = 250$ π. $R_{1\rho}^{se}$ is computed according to the second term on the right hand side of Eq. [56] using $\omega_1 = 13800$ (2π) rad s^{-1}.

experiment can still be achieved by including a second much slower site exchange process which acts to increase both the calculated R_2^{CPMG} and $(1/2)\Delta\omega_{1/2}$ values, but in the latter case that would only increase the discrepancy between calculated and experimental values. By this criterion, the choice $\tau_{1'} = 19$ μs is effectively ruled out.

We now consider how to treat two concurrent site exchange processes for A9-H2. The faster process is assumed to be characterized by $R_2^o = 3.1$ s^{-1}, $\delta_1 = 500$ π rad s^{-1}, and $\tau_1 = 7$ μs, for reasons discussed above. Although these values are not a unique solution for the faster process, it is expected that any satisfactory solution will have parameters that do not differ from these by more than about 2-fold. A second slower site exchange process with standard deviation δ_2 and relaxation time τ_2 is superposed on the faster process in the following way. In Eqs. [32] and [40], it is assumed that

$$\langle\Delta\varphi(t)^2\rangle = \langle\Delta\varphi_1(t)^2\rangle + \langle\Delta\varphi_2(t)^2\rangle \qquad [58]$$

and

$$\langle\Delta\gamma(0, n4t)^2\rangle = \langle\Delta\gamma_1(0, n4t)^2\rangle + \langle\Delta\gamma_2(0, n4t)^2\rangle \qquad [59]$$

are superpositions of the variances of two independent Gaussian random processes, $\Delta\varphi_1(t)$ and $\Delta\gamma_1(t)$, corresponding to the faster site exchange process, and $\Delta\varphi_2(t)$ and $\Delta\gamma_2(t)$, corresponding to the slower site exchange process. Consequently, Eqs. [45] and [47] will each contain two exponential site exchange factors like the last factor shown in each case, one containing d_1 and e_1 and the other containing d_2 and e_2. Also, Eq. [56] will contain two site exchange terms like the second term shown, one containing d_1 and e_1 and the other containing d_2 and e_2. By using these augmented equations with the assumed $R_2^o = 3.1$ s^{-1}, $d_1 = 500$ $\pi/R_2^o = 507$, and
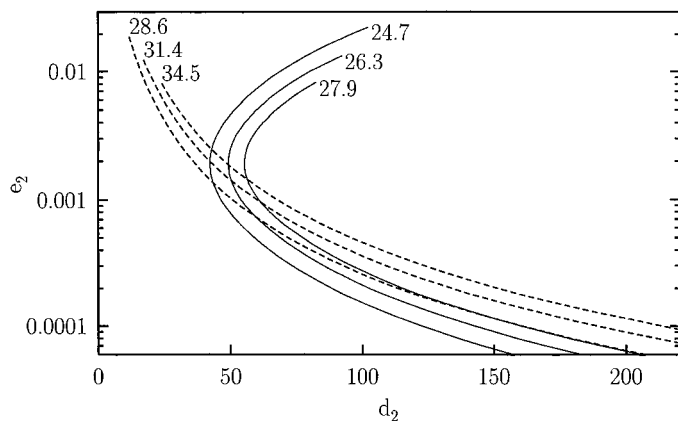
FIG. 3. Curves of e_2 versus d_2 for the slower of two concurrent site exchange processes that yield the linewidths (HWHM) $(1/2)\Delta\omega_{1/2} = 28.6$, 31.4, or 34.5 rad s^{-1} (dashed lines as indicated) and the CPMG spin-echo decay rates $R_2^{CPMG} = 24.7$, 26.3, and 27.9 s^{-1} (solid lines as indicated). The middle curves in each case apply to the reported experimental values, $(1/2)\Delta\omega_{1/2} = 31.4$ rad s^{-1} and $R_2^{se} = 26.3$ s^{-1}, whereas the outer curves apply for the experimental values plus or minus one standard deviation. The curves that yield the three $(1/2)\Delta\omega_{1/2}$ values are generated in the following way. The target value of $(1/2)\Delta\omega_{1/2}$ (e.g., 31.4 rad s^{-1}) is selected. Then the exponent in the last factor in Eq. [45] is calculated using parameters appropriate for the faster site exchange process, namely $R_2^o = 3.1$ s^{-1}, $d_1 = (500\ \pi)/R_2^o = 507$, and $e_1 = \tau_1 R_2^o = (7 \times 10^{-6})(3.1) = 2.16 \times 10^{-5}$. To that is added a second exponent of identical form, as indicated in Eq. [58], but evaluated with $R_2^o = 3.1$ s^{-1}, a particular choice of d_2 and a trial value of e_2. The resulting "augmented" correlation function in Eq. [45] is then computed for a range of time points and Fourier transformed to compute the spectrum. The full width of the spectrum at half-height is then determined and compared with the target value. The value of e_2 is adjusted and the process is iterated until the computed $(1/2)\Delta\omega_{1/2}$ matches the target value. Then a new value of d_2 is selected and the process repeated until again the same target value is matched, but now for a different (d_2, e_2) pair. In this way the curve of e_2 vs d_2 that yields the target linewidth is mapped out. The curves that yield the three R_2^{CPMG} values are generated in a similar fashion. Again, the target value (e.g., 26.3 s^{-1}) is selected. Then the exponent in the last factor in Eq. [47] is calculated using parameters appropriate for the faster site exchange process, namely $R_2^o = 3.1$ s^{-1}, $d_1 = (500\ \pi)/R_2^o = 507$, and $e_1 = \tau_1 R_2^o = (7 \times 10^{-6})(3.1) = 2.15 \times 10^{-5}$. To that is added a second exponent of identical form, as indicated in Eq. [59], but evaluated with $R_2^o = 3.1$ s^{-1}, a particular choice of d_2 and a trial value of e_2. The amplitude of the resulting "augmented" correlation function in Eq. [47] is computed for a range of time points and fitted to a single exponential decay (as were the experimental data). The best-fit decay constant, R_2^{CPMG}, is then determined and compared with the target value. The value of e_2 is adjusted and the process is iterated until the computed best-fit R_2^{CPMG} matches the target value. The points where the dashed and solid curves cross define the (d_2, e_2) pair that simultaneously yields both the target $(1/2)\Delta\omega_{1/2}$ and R_2^{CPMG} values. The crosspoint for the curves that yield $(1/2)\Delta\omega_{1/2} = 31.4$ rad s^{-1} and $R_2^{CPMG} = 26.3$ s^{-1} is $d_2 = 50.3$ and $e = 1.42 \times 10^{-3}$. Given the value, $R_2^o = 3.1$ s^{-1}, these values correspond to $\tau = 4.6 \times 10^{-4}$ s and $\delta = 156$ rad s^{-1}.

$e_1 = \tau_1 R_2^o = 2.16 \times 10^{-5}$, curves of e_2 vs d_2 that satisfy the total spin-echo constraint, $R_2^{CPMG} = 26.3$ s^{-1}, and total linewidth constraint, $\Delta\nu_{1/2} = 10$ Hz, can be calculated. The results are shown in Fig. 3. The central cross point, $e_2 = 1.42 \times 10^{-3}$, $d_2 = 50.3$ corresponds to $\tau_2 = 4.6 \times 10^{-4}$ s $= 0.46$ ms, and $\delta_2 = 156$ rad s^{-1}. This slower site exchange process makes a negligible contribution, 1.76×10^{-3} s^{-1}, to $R_{1\rho}^{se}$ (when $\omega_1 =$

8.67×10^4 rad s^{-1}), so $R_{1\rho} = 6.25$ s^{-1} is determined almost exclusively by $R_2^o = 3.1$ s^{-1} and $R_{1\rho}^{se} = 3.15$ s^{-1} from the fast process. An essential point is that the same linewidth ($\Delta\nu_{1/2} = 10$ Hz), spin-echo decay ($R_2^{CPMG} = 26.3$ s^{-1}), and $R_{1\rho} = 6.25$ s^{-1} data for the A9-H2 proton can be fitted by either a single site-exchange process or two concurrent site exchange processes, one about 65-fold faster than the other. The model of two concurrent site exchange processes allows R_2^o for A9-H2 to be decreased into or below the range of $R_{1\rho}$ values measured for A10-H2 and A11-H2, and in that regard is more consistent with other data. For the fast process, the time constant $\tau_1 = 7$ μs is near the lower end of the range of τ_L values, $\tau_L = 10$ to 160 μs, suggested by Kennedy et al. from somewhat different considerations, and $\delta_1 = 500\ \pi$ (equivalent to 0.5 ppm) lies within the range, 0.2 to 1.2 ppm, suggested by those same authors (13). It is notable that such a fast process fits the $R_{1\rho}$ datum, but not R_2^{CPMG} or $\Delta\nu_{1/2}$. Kennedy et al. noted that the range of correlation times required to fit $\Delta\nu_{1/2}$ was up to 50 times longer than the slowest correlation time consistent with the $R_{1\rho}$ data and attributed that discrepancy to uncertainties in ω_1 and in estimates of the ring current shifts. We suggest here that a second much slower site exchange process is a more likely explanation of the discrepancy.

It is interesting to compare τ_2 and δ_2 for this second slow process with the corresponding values obtained by fitting $\Delta\nu_{1/2}$, R_2^{se}, and $R_{1\rho}$ under the assumption of a single site exchange process. In brief, $\tau_2 = 0.46$ ms exceeds $\tau = 0.20$ ms for the single site exchange process by 2.3-fold, and $\delta_2 = 156$ rad s^{-1} is less than $\delta = 355$ rad s^{-1} for the single site exchange process by 2.3-fold. Evidently, the fit of a single site exchange process to the data yields τ and δ values that are not so far from those obtained for the slower of two concurrent site exchange processes. Hence, the fit of a single site exchange process to $\Delta\nu_{1/2}$, R_2^{CPMG} and $R_{1\rho} = R_2^o$ may be used to identify the presence of the slower site exchange process and indicate roughly the values of τ_2 and δ_2 for that.

Finally, the evidence for two site exchange processes with very different relaxation times, as found for A9-H2, suggests that a broad spectrum of site exchange processes might actually be occurring. However, in the absence of additional information, those could not be uniquely determined. In principle, additional data for either R_2^{CPMG} vs $4t$ or $R_{1\rho}$ vs ω_1 would allow much more complete characterization.

PROTOCOLS FOR CHARACTERIZING TWO CONCURRENT SITE-EXCHANGE PROCESSES

Accurate characterization of site exchange processes and determination of R_2^o may be accomplished by measuring $R_{1\rho}$ as a function of ω_1 over a wide range (19, 22). An example of results expected for the two concurrent site exchange processes discussed above is indicated in Fig. 4, where the two dispersions are clearly evident. A potential problem with this approach is that the theory embodied in Eq. [56], or in its
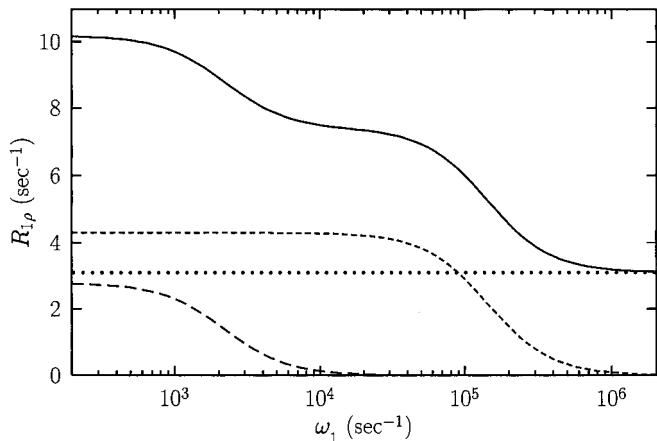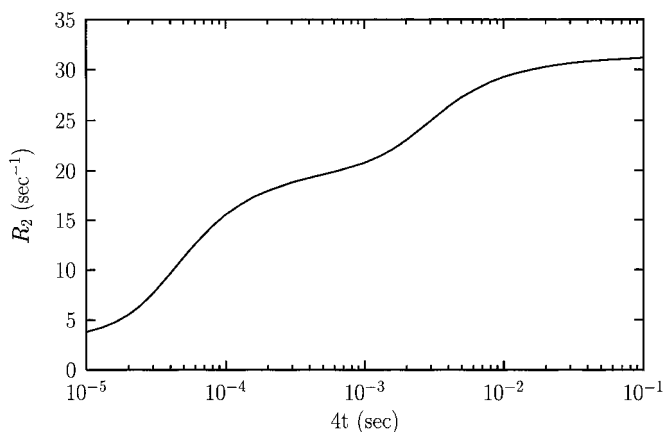
FIG. 4. $R_{1\rho}$ vs ω_1 for a continuous Gaussian model with two concurrent site exchange processes. The relevant parameters are those estimated for the A9-H2 proton of the sequence discussed in the text, namely $R_2^\circ = 3.1$ s^{-1}, $d_1 = 500$ $\pi/R_2^\circ = 507$, $e_1 = \tau_1 R_2^\circ = 2.16 \times 10^{-5}$, $d_2 = 50.3$, and $e_2 = 1.42 \times 10^{-3}$. These are employed in Eq. [56], which is augmented to include a second site exchange factor, as described in the text. The solid line is the full $R_{1\rho}$. The short (upper) dashed line is $R_{1\rho}^{se}$ for the faster process, and the long (lower) dashed line is $R_{1\rho}^{se}$ for the slower process. The dotted line is R_2°. Note that $R_{1\rho}^{se}$ for the slower process is significant for small ω_1, but practically vanishes at the angular frequency $\omega_1 = 8.67 \times 10^4$ rad s^{-1}, where the single measurement of Kennedy *et al.* (*25*) was made.

augmented counterpart that includes a second site-exchange process, is valid only when $\omega_1 \gg \delta_1$, δ_2, or when any site exchange process for which that condition does not hold is in the fast exchange limit, namely $\delta_1 \tau_1 \ll 1.0$, or $\delta_2 \tau_2 \ll 1.0$. Although these conditions are both met in the present example, that will not always be the case. A theoretically more robust procedure is to measure R_2^{CPMG} as a function of cycle time $4t$ down to very small times (*19*). There are no restrictions on the validity of the theory in that case (given the adequacy of the underlying model). An example of results expected for the two concurrent site exchange processes discussed above is presented in Fig. 5, where the two dispersions are clearly evident. In cases where it is not possible to attain sufficiently high ω_1 that $R_{1\rho}$ bottoms out, or sufficiently short $4t$ cycle times that R_2^{CPMG} bottoms out, it will be necessary to make use of $R_{1\rho}$, R_2^{CPMG}, $\Delta\nu_{1/2}$, and NOESY data not only for the nucleus in question, but also for the corresponding nuclei in other base-pairs, as done by Kennedy *et al.* (*25*), in order to identify and approximately characterize the site exchange process(es). In such a case, R_2° probably cannot be precisely estimated.

A question that may arise, when $R_{1\rho}$ vs ω_1 is observed to bottom out with increasing ω_1 over a limited range of ω_1 values or when R_2^{CPMG} vs $4t$ is observed to bottom out with decreasing t over a limited range of $4t$ values, is whether an additional site exchange process remains undetected at either smaller ω_1 or larger $4t$. This can readily be ascertained by adopting the apparent bottom value of either $R_{1\rho}$ or R_2^{CPMG} as the trial value of R_2°, which would be valid if no other site exchange process occurs. Then by using the parameters τ, δ inferred for that

single process by fitting either Eq. [56] to the $R_{1\rho}$ vs ω_1 data or Eq. [47] to the R_2^{CPMG} vs $4t$ data, the expected values of $R_{1\rho}$, R_2^{CPMG}, and $\Delta\omega_{1/2}$ can all be calculated and compared with the experimental values. Although good agreement presumably prevails for the quantity that was initially fitted, some disagreement in the case of the other two quantities is expected whenever a second site exchange process makes a significant contribution. When the presence of a second site exchange process is detected in this manner, and when δ_1, τ_1 for the first process are known (e.g., from fitting the limited $R_{1\rho}$ vs ω_1 or R_2^{CPMG} vs $4t$ data) it might be possible to estimate R_2°, δ_2, and τ_2 from the same data plus the linewidth and a single measurement of the third property whose dispersion was not measured (i.e., $R_{1\rho}$ at fixed ω or R_2^{CPMG} at fixed $4t$) by selecting trial values of R_2°, computing the curves of d_2 vs e_2 that satisfy the total linewidth and third property constraints, performing a grid search around the cross point in the d_2, e_2 plane for the minimum in the χ^2 reckoned for all three measured properties for that choice of R_2°, and then identifying the particular choice of R_2° for which that minimum χ^2 takes the lowest value.

An essential point of the present work is that measurements of $R_{1\rho}$ over a limited range of $\omega_1 \gg \delta$ or of R_2^{CPMG} over a limited range of $4t$ may in favorable cases (*19, 22*) enable quantitative estimates of δ and τ for a single fast site exchange process, as well as of R_2°, but provide little or no information about any much slower concurrent site exchange processes that may nevertheless be manifested in the lineshape and in the third property ($R_{1\rho}$ or R_2^{CPMG}) whose dispersion was not measured. In general, all three kinds of information are required to glean as much information as possible about both fast and slow site exchanges.

FIG. 5. R_2^{CPMG} vs $4t$ for a continuous Gaussian model with two concurrent site exchange processes. The relevant parameters are those estimated for the A9-H2 proton of the sequence discussed in the text, namely $R_2^\circ = 3.1$ s^{-1}, $d_1 = 500$ $\pi/R_2^\circ = 507$, $e_1 = \tau_1 R_2^\circ = 2.16 \times 10^{-5}$, $d_2 = 50.3$ and $e_2 = 1.42 \times 10^{-3}$. These are employed in Eq. [47], which is augmented to include a second site-exchange factor, as described in the text. Note that unless $4t$ is decreased below 3×10^{-4} s, the dispersion due to the faster relaxation process will not be resolved. The single R_2^{CPMG} experiment reported by Kennedy *et al.* (*25*) was performed at $4t = 10^{-3}$ s.

APPENDIX A

Equivalence of Trajectory and Stochastic Operator Approaches

The exponential in the trajectory average in Eq. [8] is factored by dividing the time interval 0 to t into an extremely large number N of subintervals t/N. As $N \to \infty$, the duration of these intervals becomes sufficiently short that $\delta\omega(\Omega(t))$ is practically constant over each interval. Then, one can write

$$
\begin{aligned}
\langle e^{-i \int_0^t dt' \delta\omega(\Omega(t'))} \rangle_T = \sum_\alpha \sum_\beta \cdots \sum_\eta \sum_\zeta \\
\times e^{-i\delta\omega(\alpha)t/N} G_{\alpha\beta}(t - t/N, t/N) \\
\times e^{-i\delta\omega(\beta)t/N} G_{\beta\gamma}(t - 2t/N, t/N) \ldots \\
\times e^{-i\delta\omega(\eta)t/N} G_{\eta\zeta}(0, t/N) e^{-i\delta\omega(\zeta)t/N} f^o(\zeta),
\end{aligned}
$$

[A1]

where $f^o(\zeta) = \langle f(\zeta, 0) \rangle_{ens}$ arises from averaging over the initial distribution, and $G_{\alpha\beta}(t, t/N)$ is the probability that in the time interval t to $t + t/N$ a transition from site β to site α has occurred. The vector $\mathbf{F}(t) = (f(\alpha, t), f(\beta, t), \ldots, f(\eta, t), f(\zeta, t))$ of fractions of the spins in the different sites evolves according to

$$
\frac{d\mathbf{F}(t)}{dt} = \Gamma(t)\mathbf{F}(t) \qquad [A2]
$$

for which the formal solution is

$$
\mathbf{F}(t + \tau) = T e^{\int_t^{t+\tau} dt' \Gamma(t')} \mathbf{F}(t), \qquad [A3]
$$

where T is the time-ordering operator. Let $\langle\alpha| = |00\ldots010\ldots0|$ be a row vector with a 1 in the α-position and zeros everywhere else and $|\beta\rangle$ be a column vector with a 1 in the β position and zeros everywhere else. Then by definition, $G_{\alpha\beta}(t, \tau)$ is the α-element of $\mathbf{F}(t + \tau)$ when $\mathbf{F}(t) = |\beta\rangle$, that is

$$
G_{\alpha\beta}(t, \tau) = (\mathbf{F}(t + \tau))_\alpha = \langle\alpha| T e^{\int_t^{t+\tau} dt' \Gamma(t')} |\beta\rangle. \quad [A4]
$$

In the limit $N \to \infty$, one has $t/N \to 0$, and $G_{\alpha\beta}(t, t/N) = \langle\alpha|\mathbf{1} + \Gamma(t)t/N|\beta\rangle$. Also,

$$
\begin{aligned}
e^{-i\delta\omega(\alpha)t/N} G_{\alpha\beta}(t, t/N) \\
= (1 - i\delta\omega(\alpha)t/N)(\delta_{\alpha\beta} + \Gamma(\alpha, \beta, t)t/N) \\
= \delta_{\alpha\beta} + (-i\delta\omega(\alpha)\delta_{\alpha\beta} + \Gamma(\alpha, \beta, t))t/N \\
= \delta_{\alpha\beta} + (\mathbf{Q}(t))_{\alpha\beta} t/N = \langle\alpha|\mathbf{1} + \mathbf{Q}(t)t/N|\beta\rangle, \quad [A5]
\end{aligned}
$$

where

$$
(\mathbf{Q}(t))_{\alpha\beta} \equiv -i\delta\omega(\alpha)\delta_{\alpha\beta} + \Gamma(\alpha, \beta, t). \qquad [A6]
$$

Now, we note that $(\mathbf{1} + \mathbf{Q}(t)t/N) = ((\mathbf{1} + \mathbf{Q}(t)t/N)^{N/t})^{t/N}$ and that $((\mathbf{1} + \mathbf{Q}(t)t/N)^{N/t})$ has the same power series for $\mathbf{Q}(t)$ as $(1 + xt/N)^{N/t}$ has for x. Since $(1 + xt/N)^{N/t} = ((1 + xt/N)^{N/tx})^x = e^x$ as $N \to \infty$, it must then hold that $(\mathbf{1} + \mathbf{Q}(t)t/N)^{N/t} = e^{\mathbf{Q}(t)}$ and also that $((\mathbf{1} + \mathbf{Q}(t)t/N)^{N/t})^{t/N} = (e^{\mathbf{Q}(t)})^{t/N} = e^{\mathbf{Q}(t)t/N}$, as $N \to \infty$.

Using this result in Eq. [A5] gives

$$
e^{-i\delta\omega(\alpha)t/N} G_{\alpha\beta}(t, t/N) = \langle\alpha|e^{\mathbf{Q}(t)t/N}|\beta\rangle. \qquad [A7]
$$

Inserting this result into Eq. [A1] gives

$$
\begin{aligned}
\langle e^{-i \int_0^t dt' \delta\omega(\Omega(t'))} \rangle_T \\
= \sum_\alpha \sum_\beta \cdots \sum_\eta \sum_\zeta \langle\alpha|e^{\mathbf{Q}(t-t/N)t/N}|\beta\rangle \\
\times \langle\beta|^{\mathbf{Q}(t-2t/N)t/N}|\gamma\rangle\langle\gamma|\ldots\langle\eta|e^{\mathbf{Q}(0)t/N}|\zeta\rangle e^{-i\delta\omega(\zeta)t/N} f^o(\zeta) \\
= \sum_\alpha \sum_\zeta \langle\alpha|e^{\mathbf{Q}(t-t/N)t/N} e^{\mathbf{Q}(t-2t/N)t/N} \ldots e^{\mathbf{Q}(0)t/N}|\zeta\rangle f^o(\zeta).
\end{aligned}
$$

[A8]

If $t > t'$, then by definition of the time-ordering operator one can write

$$
e^{\mathbf{Q}(t)t/N} e^{\mathbf{Q}(t')t/N} = T e^{(\mathbf{Q}(t) + \mathbf{Q}(t'))t/N} \qquad [A9]
$$

and

$$
\begin{aligned}
\langle e^{-i \int_0^t dt' \delta\omega(\Omega(t'))} \rangle_T = \sum_\alpha \sum_\zeta \langle\alpha|T e^{\sum_{j=0}^{N-1} \mathbf{Q}(t-jt/N)t/N}|\zeta\rangle f^o_\zeta \\
= \sum_\alpha \sum_\zeta \langle\alpha|T e^{\int_0^t dt' \mathbf{Q}(t')}|\zeta\rangle f^o_\zeta \\
= \sum_\alpha \sum_\zeta (T e^{\int_0^t dt' \mathbf{Q}(t')})_{\alpha\zeta} f^o_\zeta. \qquad [A10]
\end{aligned}
$$

Use of Eq. [A10] in Eq. [8] gives Eq. [20] identically.

Essentially identical arguments can be used to show that

$$
\begin{aligned}
\langle e^{-i \int_0^\tau dt' \delta\omega(t')} e^{+i \int_\tau^{2\tau} dt'' \delta\omega(t'')} \rangle_T \\
= \sum_\alpha \sum_\zeta (T e^{\int_\tau^{2\tau} dt' \mathbf{Q}^*(t')} T e^{\int_0^\tau dt'' \mathbf{Q}(t'')})_{\alpha\beta} f^o_\zeta, \qquad [A11]
\end{aligned}
$$

where $\mathbf{Q}^*(t)$ is the complex conjugate (not the Hermitian adjoint) of $\mathbf{Q}(t)$. Use of Eq. [A11] in Eq. [9] provides an alternative expression for the spin-echo amplitude in terms of

the stochastic evolution matrix, $\Gamma(\alpha, \beta, t)$ and the site-dependent frequency shifts, $\delta\omega(\alpha)$. $\mathbf{Q}^*(t)$ does not generally commute with $\mathbf{Q}(t)$.

Similar arguments also yield

$$\langle e^{-i\Delta\gamma(0,n4t)}\rangle = \sum_\alpha \sum_\zeta (Te^{\int_{((n-1)4+3)t}^{n4t} dt'\mathbf{Q}(t')} \cdot Te^{\int_{((n-1)4+1)t}^{((n-1)4+3)t} dt''\mathbf{Q}^*(t'')}$$

$$\times\ Te^{\int_{(n-1)4t}^{((n-1)4+1)t} dt'''\mathbf{Q}(t''')} \cdots\cdots Te^{\int_{3t}^{4t} d\tilde{t}'\mathbf{Q}(\tilde{t}')}$$

$$\times\ Te^{\int_t^{3t} d\tilde{t}''\mathbf{Q}^*(\tilde{t}'')} \cdot Te^{\int_0^t d\tilde{t}'''\mathbf{Q}(\tilde{t}''')})_{\alpha\zeta} f_\zeta^o$$

$$= \sum_\alpha \sum_\zeta [(Te^{\int_{3t}^{4t} dt'\mathbf{Q}(t')}$$

$$\times\ Te^{\int_t^{3t} dt''\mathbf{Q}^*(t'')} Te^{\int_0^t dt'''\mathbf{Q}(t''')})^n]_{\alpha\zeta} f_\zeta^o \qquad [A12]$$

APPENDIX B

Evaluation of the Correlation Functions for the Linewidth, Simple Spin-Echo Decay, and Decay of the CPMG Even Spin-Echoes in the Gaussian Exchange Model

The relevant quantity for the linewidth is the variance

$$\langle\Delta\varphi(t)^2\rangle = \left\langle \int_0^t dt'\,\delta\omega(t') \int_0^t dt''\,\delta\omega(t'') \right\rangle$$

$$= \int_0^t dt' \int_0^t dt'' \langle\delta\omega(t')\delta\omega(t'')\rangle$$

$$= \int_0^t dt' \int_0^t dt''\,\delta^2 e^{-|t'-t''|/\tau}$$

$$= 2\delta^2 \int_0^t dt' \int_0^t dt''\,e^{-(t'-t'')/\tau}$$

$$= 2\delta^2 \int_0^t dt'\,e^{-t'/\tau}\tau(e^{t'/\tau}-1)$$

$$= 2\delta^2\tau \int_0^t dt'(1-e^{-t'/\tau})$$

$$= 2\delta^2\tau(t-(-\tau)(e^{-t/\tau}-1))$$

$$= 2\delta^2\tau^2[t/\tau - 1 + e^{-t/\tau}]. \qquad [B1]$$

The relevant quantity for the spin-echo decay is the variance

$$\langle\Delta\epsilon(2t)^2\rangle = \left\langle \int_0^t dt'\,\delta\omega(t') \int_0^t dt''\,\delta\omega(t'') \right\rangle$$

$$+ \left\langle \int_t^{2t} dt'\,\delta\omega(t') \int_t^{2t} dt''\,\delta\omega(t'') \right\rangle$$

$$- 2\left\langle \int_0^t dt'\,\delta\omega(t') \int_t^{2t} dt''\,\delta\omega(t'') \right\rangle.$$

The first term is just that in Eq. [B1]. Shifting the origin of time from 0 to t in the second term reduces it to the first term, which is then also given by [B1]. It remains to evaluate the crossterm

$$-2\left\langle \int_0^t dt'\,\delta\omega(t') \int_t^{2t} dt''\,\delta\omega(t'') \right\rangle$$

$$= 2 \int_0^t dt' \int_t^{2t} dt''\,\delta^2 e^{-(t''-t')/\tau}$$

$$= -2\delta^2[(\tau)(e^{t/\tau}-1)(-\tau)(e^{-2t/\tau}-e^{-t/\tau})]$$

$$= -2\delta^2\tau^2(1+e^{-2t/\tau}-2e^{-t/\tau}). \qquad [B2]$$

Combining this result with those for the first two terms gives

$$\langle\Delta\epsilon(2t)^2\rangle = 2\delta^2\tau^2[2t/\tau - 3 + 4e^{-t/\tau} - e^{-2t/\tau}]. \quad [B3]$$

When Eq. [B3] is expanded for small times up to order t^2, it vanishes, and the first nonvanishing term is of order $(t/\tau)^3$. Thus, when $t \ll \tau$, the variance of the net accumulated phase vanishes, as expected, because in this limit the spins remain in their sites without transfer between sites. For each site in which a spin remains fixed, the net accumulated phase is expected to vanish at the echo, so $\Delta\epsilon(2t) = 0$ for every spin in this limit.

The derivation of $\langle\Delta\gamma(0, n4t)^2\rangle$ proceeds in several steps. The total elapsed time from 0 to $n4t$ is subdivided into n equal intervals of $4t$, each corresponding to a full cycle of the CPMG echo sequence ($t–\pi–t–t–\pi–t$) subsequent to the initial $\pi/2$ pulse. During the first and last quarters (of duration t) of each cycle, the deviation in Larmor frequency $\delta\omega(t)$ is entered with a positive sign and during the second and third quarters it is entered with a negative sign. The derivation proceeds in several steps.

First, we calculate $\langle\Delta\gamma(0, 4t)^2\rangle$ for the first full cycle alone, wherein

$$\Delta\gamma(0, 4t) \equiv \int_0^t dt' \, \delta\omega(t') - \int_t^{2t} dt'' \delta\omega(t'')$$

$$- \int_{2t}^{3t} dt''' \delta\omega(t''') + \int_{3t}^{4t} dt'''' \delta\omega(t'''').\quad [B4]$$

Then

$$\langle \Delta\gamma(0, 4t)^2 \rangle = S(0, t) + S(t, 2t)$$
$$+ S(2t, 3t) + S(3t, 4t)$$
$$- 2C(0, t; t, 2t) - 2C(0, t; 2t, 3t)$$
$$+ 2C(0, t; 3t, 4t) + 2C(t, 2t; 2t, 3t)$$
$$- 2C(t, 2t; 3t, 4t) - 2C(2t, 3t; 3t, 4t)$$
$$[B5]$$

wherein the self-terms are given by

$$S(mt, (m+1)t) \equiv \left\langle \int_{mt}^{(m+1)t} dt' \, \delta\omega(t') \int_{mt}^{(m+1)t} dt'' \delta\omega(t'') \right\rangle$$

and the crossterms by

$$C(mt, (m+1)t; qt, (q+1)t)$$
$$\equiv \left\langle \int_{mt}^{(m+1)t} dt' \, \delta\omega(t') \int_{qt}^{(q+1)t} dt'' \delta\omega(t'') \right\rangle.$$

Upon invoking the stationarity of the random process (with respect to a shift in the origin of time) and Eq. [B1], it is found that

$$S(mt, (m+1)t) \equiv 2\delta^2\tau^2[t/\tau - 1 + e^{-t/\tau}] \quad \text{for all } m \geq 0.$$
$$[B7]$$

By using the relation (for $t_3 \geq t_2$),

$$\left\langle \int_{t_1}^{t_2} dt' \, \delta\omega(t') \int_{t_3}^{t_4} dt'' \delta\omega(t'') \right\rangle$$

$$= \delta^2 \int_{t_1}^{t_2} dt' \int_{t_3}^{t_4} dt'' e^{-(t''-t')/\tau}$$

$$= -\delta^2\tau^2[e^{-(t_4-t_2)/\tau} - e^{-(t_3-t_2)/\tau} - e^{-(t_4-t_1)/\tau} + e^{-(t_3-t_1)/\tau}]$$
$$[B8]$$

and also the stationarity condition, one finds

$$C(0, t; t, 2t) = \delta^2\tau^2(1 + e^{-2t/\tau} - 2e^{-t/\tau}) \quad [B9a]$$

$$C(0, t; 2t, 3t) = \delta^2\tau^2 e^{-t/\tau}(1 + e^{-2t/\tau} - 2e^{-t/\tau}) \quad [B9b]$$

$$C(0, t; 3t, 4t) = \delta^2\tau^2 e^{-2t/\tau}(1 + e^{-2t/\tau} - 2e^{-t/\tau}) \quad [B9c]$$

$$C(t, 2t; 2t, 3t) = \delta^2\tau^2(1 + e^{-2t/\tau} - 2e^{-t/\tau}) \quad [B9d]$$

$$C(t, 2t; 3t, 4t) = \delta^2\tau^2 e^{-t/\tau}(1 + e^{-2t/\tau} - 2e^{-t/\tau}) \quad [B9e]$$

$$C(2t, 3t; 3t, 4t) = \delta^2\tau^2(1 + e^{-2t/\tau} - 2e^{-t/\tau}). \quad [B9f]$$

Finally, after collecting terms,

$$\langle \Delta\gamma(0, 4t)^2 \rangle = 2\delta^2\tau^2[4t/\tau - 5 + 4e^{-t/\tau}$$
$$+ 4e^{-2t/\tau} - 4e^{-3t/\tau} + e^{-4t/\tau}]. \quad [B10]$$

In the next step, we write

$$\Delta\gamma(0, (n+1)4t) = \Delta\gamma(0, n4t) + \Delta\gamma(n4t, (n+1)4t)$$
$$[B12]$$
$$\langle \Delta\gamma(0, (n+1)4t)^2 \rangle = \langle \Delta\gamma(0, n4t)^2 \rangle$$
$$+ \langle \Delta\gamma(n4t, (n+1)4t)^2 \rangle$$
$$+ 2\langle \Delta\gamma(0, n4t)\Delta\gamma(n4t, (n+1)4t) \rangle. \quad [B13]$$

Due to stationarity of the Gaussian random process,

$$\langle \Delta\gamma(n4t, (n+1)4t)^2 \rangle = \langle \Delta\gamma(0, 4t)^2 \rangle \quad [B14]$$

which is given in [B10]. The other two terms in [B13] are as yet unknown. Our strategy is first to evaluate the crossterm in Eq. [B13] and then to evaluate $\langle \Delta\gamma(0, n4t)^2 \rangle$ by a stepwise induction process.

The crossterm in [B13] can be written as a sum of n terms, in each of which $\Delta\gamma(n4t, (n+1)4t)$ is crosscorrelated with the accumulated phase, $\Delta\gamma(m4t, (m+1)4t)$, over one particular cycle in the interval, 0 to $n4t$. That is,

$$\langle \Delta\gamma(0, n4t)\Delta\gamma(n4t, (n+1)4t) \rangle = \sum_{m=0}^{n-1} T_{nm}, \quad [B15]$$

where (for $m < n$)

$$T_{nm} = \left\langle \left[\int_{m4t}^{(m4+1)t} dt' \, \delta\omega(t') - \int_{(m4+1)t}^{(m4+2)t} dt'' \delta\omega(t'') \right. \right.$$

$$\left. - \int_{(m4+2)t}^{(m4+3)t} dt''' \delta\omega(t''') + \int_{(m4+3)t}^{(m+1)4t} dt'''' \delta\omega(t'''') \right]$$

$$\times \left[\int_{n4t}^{(n4+1)t} dT' \delta\omega(T') - \int_{(n4+1)t}^{(n4+2)t} dT'' \delta\omega(T'') \right.$$

$$\left. - \int_{(n4+2)t}^{(n4+3)t} dT''' \delta\omega(T''') + \int_{(n4+3)t}^{(n+1)4t} dT'''' \delta\omega(T'''') \right] \Bigg\rangle$$

$$= [f(4m, 4n) - f(4m, 4n + 1) - f(4m, 4n + 2)$$

$$+ f(4m, 4n + 3)] + [-f(4m + 1, 4n)$$

$$+ f(4m + 1, 4n + 1) + f(4m + 1, 4n + 2)$$

$$- f(4m + 1, 4n + 3)]$$

$$+ [-f(4m + 2, 4n) + f(4m + 2, 4n + 1)$$

$$+ f(4m + 2, 4n + 2) - f(4m + 2, 4n + 3)]$$

$$+ [f(4m + 3, 4n) - f(4m + 3, 4n + 1)$$

$$- f(4m + 3, 4n + 2) + f(4m + 3, 4n + 3)],$$

$$[B16]$$

where for $(k > j)$,

$$f(j, k) \equiv \left\langle \int_{jt}^{(j+1)t} dt' \delta\omega(t') \int_{kt}^{(k+1)t} dt'' \delta\omega(t'') \right\rangle$$

$$= -\delta^2 \tau^2 (e^{-(k-j)t/\tau} - e^{-(k-j-1)t/\tau}$$

$$- e^{-(k+1-j)t/\tau} + e^{-(k-j)t/\tau})$$

$$= e^{-(k-j)t/\tau} e^{t/\tau} g(t, \tau), \qquad [B17]$$

where

$$g(t, \tau) \equiv \delta^2 \tau^2 (1 + e^{-2t/\tau} - 2e^{-t/\tau}). \qquad [B18]$$

Making use of [B17] and [B18] in [B16] and collecting terms with common factors yields

$$T_{nm} = g(t, \tau)e^{t/\tau} e^{-(n-m)4t} (1 - e^{t/\tau} - e^{2t/\tau} + e^{3t/\tau})$$

$$\times (1 - e^{-t/\tau} - e^{-2t/\tau} + e^{-3t/\tau})$$

$$= G(t, \tau)e^{-(n-m)4t/\tau}, \qquad [B19]$$

where

$$G(t, \tau) \equiv \delta^2 \tau^2 (1 + e^{-2t/\tau} - 2e^{-t/\tau})$$

$$\times e^{t/\tau} \cdot (1 - e^{-t/\tau} - e^{-2t/\tau} + e^{-3t/\tau})$$

$$\times (1 - e^{t/\tau} - e^{2t/\tau} + e^{3t/\tau}). \qquad [B20]$$

Upon substituting [B19] into [B15] and performing the sum-

mation, using $\sum_{m=0}^{n-1} x^m = (1 - x^n)/(1 - x)$, there results finally

$$\langle \Delta\gamma(0, n4t)\Delta\gamma(n4t, (n + 1)4t)\rangle$$

$$= (G(t, \tau)/(e^{4t/\tau} - 1))(1 - e^{-n4t/\tau}). \qquad [B21]$$

In order to obtain the total variance, $\langle \Delta\gamma(0, (n + 1)4t)^2 \rangle$, we proceed stepwise using [B13], [B14], and [B21] for $n = 1$, $2, \ldots$. For simplicity, the quantity $H(t, \tau) \equiv G(t, \tau)/(e^{4t/\tau} - 1)$ is employed.

$n = 1$:

$$\langle \Delta\gamma(0, 2 \cdot 4t)^2 \rangle = 2\langle \Delta\gamma(0, 4t)^2 \rangle + 2H(t, \tau)(1 - e^{-4t/\tau})$$

$n = 2$:

$$\langle \Delta\gamma(0, 3 \cdot 4t)^2 \rangle = 3\langle \Delta\gamma(0, 4t)^2 \rangle + 2H(t, \tau)(1 - e^{-4t/\tau})$$

$$+ 2H(t, \tau)(1 - e^{-2 \cdot 4t/\tau})$$

$\vdots$

$n = k$:

$$\langle \Delta\gamma(0, (k + 1)4t)^2 \rangle$$

$$= (k + 1)\langle \Delta\gamma(0, 4t)^2 \rangle + \sum_{m=1}^{k} 2H(t, \tau)(1 - e^{-m4t/\tau})$$

$$= (k + 1)\langle \Delta\gamma(0, 4t)^2 \rangle + k \cdot 2 \cdot H(t, \tau) - 2H(t, \tau)$$

$$\times \left[\frac{(1 - e^{-(k+1)4t/\tau})}{(1 - e^{-4t/\tau})} - 1 \right]$$

$$= (k + 1)\langle \Delta\gamma(0, 4t)^2 \rangle + k \cdot 2 \cdot \frac{G(t, \tau)}{e^{4t/\tau} - 1}$$

$$- \frac{2 \cdot G(t, \tau)}{(e^{4t/\tau} - 1)^2}(1 - e^{-k4t/\tau}). \qquad [B22]$$

Equation [B22] in conjunction with [B10] for $\langle \Delta\gamma(0, 4t)^2 \rangle$ and [B20] for $G(t, \tau)$ gives the variance of the accumulated phase from 0 to $n4t$ during a CPMG pulse sequence. The final result is presented in Eq. [40] in the main text. The even spin-echoes of the CPMG pulse sequence are observed at $n4t$, $n = 1, 2, \ldots$.

APPENDIX C

Contribution of Rapid Rotational Motions to $R_{1\rho}$

The Case when Dipole–Dipole Relaxation Predominates

Peng *et al.* (5, 6) derived an expression for the rate of relaxation of the rotating *xy* component of the magnetization of a nucleus (I) due to dipolar interactions with a neighboring

nucleus S in the presence of a spin-locking field (i.e., circularly polarized RF power in the xy plane.) The frequency (ω) of the RF power was assumed to be near the Larmor frequency (ω_I^o) of the I nucleus in the main magnetic field ($\mathbf{H}_0 = H_0\hat{\mathbf{z}}$), but very far from that (ω_S^o) of the S nucleus, which is of a different kind. In the limit where the RF power is on resonance with ω_I^o, and the magnitude of the rotating magnetic field ($|\mathbf{B}_1|$) of the RF field is small, so that the precession frequency (ω_1) of the I nucleus about $\mathbf{H}_1$ is very small compared to ω_I^o, the result of Peng $et\ al.$ (5, 6) can be approximated by

$$R_{1\rho}^o = \frac{\gamma_I^2\gamma_S^2}{40r^6}\hbar^2\{4J_0(\omega_1) + J_0(\omega_I^o - \omega_S^o) + 3J_1(\omega_I^o)$$

$$+ 6J_1(\omega_S^o) + 6J_2(\omega_I^o - \omega_S^o)\}, \qquad [C1]$$

where

$$J_n(\omega) = 2\ \mathrm{Re}\int_0^\infty d\tau \mathrm{e}^{i\omega\tau}4\pi\langle Y_{2n}^*(\Omega(0))Y_{2n}(\Omega(t))\rangle, \quad [C2]$$

and $\Omega(t) = (\theta(t), \phi(t))$ is the solid angle of the I–S internuclear vector in the lab frame. For solutions with an isotropic equilibrium state, $4\pi\langle Y_{2n}^*(\Omega(0))Y_{2n}(\Omega(t))\rangle$ is independent of n (1, 2, 34); hence $J_n(\omega)$ is also independent of n. Equation [C1] differs from the usual expression for R_2^o relaxation in the absence of a spin-locking field only by the presence of ω_1 instead of 0 in the first term.

For isotropic solutions wherein the reorienting motions are all very rapid, the correlation function $4\pi\langle Y_{2n}^*(\Omega(0))Y_{2n}(\Omega(t))\rangle$ decays to zero via one or more processes with time constants less than or equal to the slowest rotational relaxation time (τ_L), which is still sufficiently short that $\omega_1\tau_L \ll 1.0$. In this limit, $J_0(\omega_1) \cong J_0(0)$, and the corresponding $R_{1\rho}^o$ is practically identical to R_2^o in this same limit.

We consider next the case wherein the S spin and the I spin are of the same kind, but experience different environments, so their Larmor frequencies are slightly different. In this case, the RF power is necessarily nearly resonant with both nuclei, so the interaction between the S nucleus and the RF power cannot be ignored, as it was in the example treated by Peng $et\ al.$ (5, 6). A brief description of the derivation for this case follows. This derivation applies when both I and S nuclei have spin $\frac{1}{2}$.

The Hamiltonian (divided by $\hbar$) is given by

$$H(t) = H_0 + H_1(t) + H_p(t), \qquad [C3]$$

where

$$H_0 = -\omega_I^o I_z - \omega_S^o S_z, \qquad [C4a]$$

$$H_1 = -\omega_1^I(I_x\cos\ \omega t - I_y\sin\ \omega t)$$

$$- \omega_1^S(S_x\cos\ \omega t - S_y\sin\ \omega t), \qquad [C4b]$$

where ω is the frequency of circularly polarized RF power, and the perturbation Hamiltonian is given generally by

$$H_p = \sum_q (-1)^q A^{(q)}F^{(-q)}(t). \qquad [C4c]$$

For the particular case of dipolar interactions (3),

$$A^{(0)} = \alpha\left\{-\frac{2}{3}I_zS_z + \frac{1}{6}(I_+S_- + I_-S_+)\right\} \qquad [C5a]$$

$$A^{(\pm1)} = \mp\alpha\{I_zS_\pm + I_\pm S_z\} \qquad [C5b]$$

$$A^{(\pm2)} = \frac{\alpha}{2}I_\pm S_\pm \qquad [C5c]$$

$$F^{(0)}(t) = \left(\frac{16\pi}{5}\right)^{1/2}\frac{Y_{20}(\Omega(t))}{r(t)^3} = \frac{1 - 3\cos^2\theta(t)}{r(t)^3} \qquad [C6a]$$

$$F^{(\pm1)}(t) = -\left(\frac{8\pi}{15}\right)^{1/2}\frac{Y_{2,\pm1}(\Omega(t))}{r(t)^3} = \frac{\pm\sin\theta\cos\theta\ \mathrm{e}^{\pm i\phi(t)}}{r(t)^3} \qquad [C6b]$$

$$F^{(\pm2)}(t) = \left(\frac{32\pi}{15}\right)^{1/2}\frac{Y_{2,\pm2}(\Omega(t))}{r(t)^3} = \frac{\sin^2\theta(t)\mathrm{e}^{\pm 2i\phi(t)}}{r(t)^3}, \qquad [C6c]$$

where $\alpha \equiv -(3/2)\gamma_I\gamma_S\hbar$, $\Omega(t) = (\theta(t), \phi(t))$ is the solid angle of the $\mathbf{r}_I$–$\mathbf{r}_S$ internuclear vector in the lab frame, and $r(t) = |\mathbf{r}_I(t) - \mathbf{r}_S(t)|$. In keeping with the usual precedent, it will be assumed in the following that $r(t) \cong r$ remains essentially constant.

The density matrix expression

$$i\frac{\partial\rho}{\partial t} = [H(t), \rho(t)] \qquad [C7]$$

is transformed to the first interaction representation by operating with e^{iH_0t} on the left and e^{-iH_0t} on the right to obtain

$$i\frac{\partial\rho^{(R)}}{\partial t} = [H_1(t)^{(R)} + H_p(t)^{(R)}, \rho^{(R)}] \qquad [C8]$$

wherein $\rho^{(R)} \equiv \mathrm{e}^{iH_0t}\rho\mathrm{e}^{-iH_0t}$. Use is made of the definitions, $I_j = \sigma_j/2$, $j = x, y, z$, where the σ_j are the normalized Pauli matrices, and the relations $\sigma_x\sigma_y = i\sigma_z$, $\sigma_y\sigma_z = i\sigma_x$, $\sigma_z\sigma_x =$

$i\sigma_y$, $\sigma_z\sigma_\pm = \sigma_z(\sigma_x \pm i\sigma_y) = \pm\sigma_\pm$, $\sigma_\pm\sigma_z = \mp\sigma_\pm$, and $e^{-i(\omega_0/2)t\sigma_z}\sigma_\pm e^{i(\omega_0 t/2)\sigma_z} = \sigma_\pm e^{-i\omega_0 t}$, to obtain

$$(H^1(t))^{(R)} = e^{iH_0 t}H_1(t)e^{-iH_0 t}$$

$$= -\omega_1^I(I_x\cos\Delta\omega_I t + I_y\sin\Delta\omega_I t)$$

$$- \omega_1^S(S_x\cos\Delta\omega_S t + S_y\sin\Delta\omega_S t), \quad [C9]$$

where $\Delta\omega_I \equiv \omega_I^\circ - \omega$ and $\Delta\omega_S \equiv \omega_S^\circ - \omega$. A useful simplification results from the following considerations. Because the reorientational dynamics of the molecules is very rapid, and $\Delta\omega_I = \omega_I^\circ - \omega$ is rather small, one has $\Delta\omega_I\tau_L \ll 1.0$, where τ_L is the slowest relaxation time among the rotational motions. Since the time-dependent coefficients of the spin operators appear in integrals over a particular orientation correlation function ($4\pi\langle Y_{20}^*(\Omega(0))Y_{20}(\Omega(t))\rangle$), which vanishes for $t \gtrsim \tau_L$, it is permissible to assume that $\Delta\omega_I t \ll 1.0$ for all times of practical interest, and to set $\cos(\Delta\omega_I t) \cong 1.0$ and $\sin(\Delta\omega_I t) \cong 0$ in Eq. [C9]. If S is a nucleus of the same kind, then also $\Delta\omega_S\tau_L \ll 1.0$, and one may similarly set $\cos\Delta\omega_S t \cong 1.0$ and $\sin(\Delta\omega_S t) \cong 0$ in Eq. [C9]. Alternatively, if S is a different kind of nucleus, then $\Delta\omega_S \gg \omega_1^S$, so $\cos\Delta\omega_S t$ undergoes many oscillations in a time $t < (\omega_1^S)^{-1}$. Consequently, the precession "frequency" of the S nucleus about the spin-lock field, namely $\omega_1^S\cos\Delta\omega_S t$, is effectively averaged to zero before $\omega_S t$ is comparable to 1.0. In that case, the S_x and S_y terms in Eq. [C9] can be ignored, which corresponds to the circumstance treated by Peng *et al.* (5, 6). However, such terms must be retained in the present treatment, so

$$(H_1(t))^{(R)} \cong -\omega_1^I I_x - \omega_1^S S_x. \quad [C10]$$

It is also found that

$$(A^{(0)})^{(R)} = \alpha\left\{-\frac{2}{3}I_zS_z + \frac{1}{6}(I_+S_-e^{-i(\omega_I^\circ - \omega_S^\circ)t}\right.$$

$$\left. + I_-S_+e^{i(\omega_I^\circ - \omega_S^\circ)t})\right\} \quad [C11a]$$

$$(A^{(\pm1)})^{(R)} = \mp\alpha\{I_zS_\pm e^{\mp i\omega_S^\circ t} + I_\pm S_z e^{\mp i\omega_I^\circ t}\} \quad [C11b]$$

$$(A^{(\pm2)})^{(R)} = \frac{\alpha}{2}I_\pm S_\pm e^{\mp i(\omega_I^\circ + \omega_S^\circ)t}. \quad [C11c]$$

The density matrix expression in Eq. [C8] is further transformed to the second interaction representation by operating with $U^\dagger(t) = e^{-i\omega_1^I tI_x}e^{-i\omega_1^S tS_x}$ on the left and $U(t) = e^{i\omega_1^I tI_x}e^{i\omega_1^S tS_x}$ on the right to obtain

$$i\frac{\partial\rho^{(r)}}{\partial t} = [H_p(t)^{(r)}, \rho^{(r)}], \quad [C12]$$

where $\rho^{(r)} \equiv U^\dagger(t)\rho^{(R)}U(t)$ is the density matrix in the second interaction frame. It is also found that

$$U^\dagger(t)I_\pm U(t) = I_x \pm i(I_yC_a(t) + I_zS_a(t)) \quad [C13a]$$

$$U^\dagger(t)S_\pm U(t) = S_x \pm i(S_yC_b(t) + S_zS_b(t)) \quad [C13b]$$

$$U^\dagger(t)(I_y \pm iI_z)U(t) = (I_y \pm iI_z)e^{\mp i\omega_1^I t} \quad [C14a]$$

$$U^\dagger(t)(S_y \pm iS_z)U(t) = (S_y \pm iS_z)e^{\mp i\omega_1^S t} \quad [C14b]$$

$$U^\dagger(t)I_zU(t) = I_zC_a(t) - I_yS_a(t) \quad [C15a]$$

$$U^\dagger(t)S_zU(t) = S_zC_b(t) - S_yS_b(t) \quad [C15b]$$

$$U^\dagger(t)(I_zS_z)U(t) = I_zS_zC_a(t)C_b(t) + I_yS_yS_a(t)S_b(t)$$

$$- I_yS_zS_a(t)C_b(t) - I_zS_yC_a(t)S_b(t) \quad [C16a]$$

$$U^\dagger(t)(I_\pm S_\mp e^{-i(\omega_I^\circ - \omega_S^\circ)t})U(t) = \{I_xS_x + I_yS_yC_a(t)C_b(t)$$

$$+ I_zS_zS_a(t)S_b(t) + I_yS_zC_a(t)S_b(t) + I_zS_yS_a(t)C_b(t)$$

$$\pm i(I_yS_xC_a(t) + I_zS_xS_a(t) - I_xS_yC_b(t)$$

$$- I_xS_zS_b(t))\}e^{\mp i(\omega_I^\circ - \omega_S^\circ)t} \quad [16b]$$

$$U^\dagger(t)(I_zS_\pm e^{\mp i\omega_S^\circ t})U(t) = [I_zS_xC_a(t) - I_yS_xS_a(t)$$

$$\pm i(I_zS_yC_a(t)C_b(t) + I_zS_zC_a(t)S_b(t)$$

$$- I_yS_yS_a(t)C_b(t) - I_yS_zS_a(t)S_b(t))]e^{\mp i\omega_S^\circ t} \quad [C17a]$$

$$U^\dagger(t)(I_\pm S_z e^{\mp i\omega_I^\circ t})U(t) = [I_xS_zC_b(t) - I_xS_yS_b(t)$$

$$\pm i(I_yS_zC_a(t)C_b(t) + I_zS_zS_a(t)C_b(t)$$

$$- I_yS_yC_a(t)S_b(t) - I_zS_yS_a(t)S_b(t))]e^{\mp i\omega_I^\circ t} \quad [C17b]$$

$$U^\dagger(t)(I_\pm S_\pm e^{\mp i(\omega_I^\circ - \omega_S^\circ)t})U(t) = [I_xS_x - I_yS_yC_a(t)C_b(t)$$

$$- I_yS_zC_a(t)S_b(t) - I_zS_yS_a(t)C_b(t) - I_zS_zS_a(t)S_b(t)$$

$$\pm i(I_yS_xC_a(t) + I_zS_xS_a(t)$$

$$+ I_xS_yC_b(t) + I_xS_zS_b(t))]e^{\mp i(\omega_I^\circ - \omega_S^\circ)t}, \quad [C18]$$

where $C_a(t) = \cos\omega_1^I t$, $C_b(t) = \cos\omega_1^S t$, $S_a(t) = \sin\omega_1^I t$, and $S_b(t) = \sin\omega_1^S t$.

Following Abragam, the solution of Eq. [C12] is approximated to second order by

$$\overline{\frac{\partial\rho^{(r)}}{\partial t}} = -\int_0^t d\tau\overline{[h(t)^{(r)}, [h(t-\tau)^{(r)}, \rho^{(r)}(t-\tau)]]},$$

$$[C19]$$

where $h(t)^{(r)} \equiv U^\dagger(t)\{\sum_q (-1)^q A^{(q)(R)}F^{(-q)}(t)\}U(t)$. We assume that the integral converges in a time $T_c \lesssim 10\tau_L$, where τ_L is again the slowest relaxation time of the rotational mo-

tions. We further assume that, owing to the smallness of the perturbation, $\rho(t)^{(r)}$ is practically unchanged from $\rho(0)^{(r)}$ at all times from $t = 0$ up to T_c. That is, because the rate of relaxation of $\rho(t)^{(r)}$ is very slow, it is permissible to set $\rho(t - \tau) \cong \rho(0)$ for all $t - \tau \leq T_c$. Then, the initial rate of change of the density matrix can be written as

$$\overline{\frac{\partial \rho^{(r)}}{\partial t}}\bigg|_{t=0} = -\int_0^{T_c} d\tau \overline{[h(0)^{(r)}, [h(0 - \tau)^{(r)}, \rho_R(0)]]}.$$

[C20]

Since the integrand in Eq. [20] vanishes for all $\tau \geq T_c$, the upper limit can be extended to ∞ without error. Use of Eq. [C20] facilitates the evaluation of various terms, since all of the $S_a(0)$ and $S_b(0)$ factors vanish. Following Abragam, the expectation value of I_x "in the second interaction frame" in this early time regime is found to obey the relation:

$$\frac{d\langle I_x \rangle}{dt}\bigg|_0 = tr\left\{-\int_0^\infty d\tau \overline{[h(0 - \tau)^{(r)}, [h(0)^{(r)}, I_x]]\rho_R(0)}\right\}.$$

[C21]

Determination of the coefficients of $\langle I_x \rangle$ in [C24] requires the evaluation of numerous double commutators using Eqs. [16]–[18]. Terms with residual oscillations at frequencies ω_I^o, ω_S^o, and $\omega_I^o + \omega_S^o$ are ignored, but all terms oscillating at ω_I^I, ω_I^S, $\omega_I^o - \omega_S^o$, and their sums and differences were retained. All final terms containing the factor i, except when part of a time-dependent phase factor, cancel. The terms that did not survive either vanished directly or coupled with others to sum to zero, within the approximation that the rotational motions are very fast compared to ω_I^I, ω_I^S, $\omega_I^I + \omega_I^S$, and $\omega_I^I - \omega_I^S$, so $\omega_I^I \tau_L \ll 1.0, \ldots$ etc. The final result for the coefficient of $\langle I_x \rangle|_0$ on the right-hand side of Eq. [C21] is

$$R_{1\rho}^{dd} = \frac{1}{40} \frac{\gamma_I^2 \gamma_S^2 \hbar^2}{r^6} \left\{ 2[J_0(\Sigma_1) + J_0(\Delta_1)] \right.$$

$$+ \frac{1}{8}[J_0(\omega_I^o - \omega_S^o + \Sigma_1) + J_0(\omega_I^o - \omega_S^o - \Sigma_1)$$

$$+ J_0(\omega_I^o - \omega_S^o + \Delta_1) + J_0(\omega_I^o - \omega_S^o - \Delta_1)]$$

$$+ \frac{1}{2} J_0(\omega_I^o - \omega_S^o + \omega_I^I) + \frac{3}{2}[J_1(\omega_S^o + \omega_I^I)$$

$$+ J_1(\omega_S^o - \omega_I^I)] + \frac{3}{4}[J_1(\omega_S^o + \Sigma_1)$$

$$+ J_1(\omega_S^o - \Sigma_1) + J_1(\omega_S^o + \Delta_1) + J_1(\omega_S^o - \Delta_1)]$$

$$+ \frac{3}{4}[J_1(\omega_I^o + \Sigma_1) + J_1(\omega_I^o - \Sigma_1)$$

$$+ J_1(\omega_I^o + \Delta_1) + J_1(\omega_I^o - \Delta_1)]$$

$$+ \frac{3}{4}[J_2(\omega_I^o + \omega_S^o + \Sigma_1) + J_2(\omega_I^o + \omega_S^o - \Sigma_1)$$

$$+ J_2(\omega_I^o + \omega_S^o + \Delta_1) + J_2(\omega_I^o + \omega_S^o - \Delta_1)]$$

$$+ \frac{3}{2}[J_2(\omega_I^o + \omega_S^o + \omega_I^I)$$

$$+ \left. J_2(\omega_I^o + \omega_S^o - \omega_I^I)] \right\},$$

[C22]

where $\Sigma_1 \equiv \omega_I^I + \omega_I^S$ and $\Delta_1 \equiv \omega_I^I - \omega_I^S$. If the S nucleus is of a different kind, so it is greatly off resonance, then ω_I^S should be replaced by $\omega_I^S \cos(\omega_S^o - \omega)t \cong 0$ (see discussion following [C9]).

In the anticipated limit that ω_I^I, ω_I^S, Σ_1, and Δ_1 are much smaller than ω_I^o and ω_S^o, they can be neglected against those quantities, but not against $\omega_I^o - \omega_S^o$, to obtain

$$R_{1\rho}^{dd} = \frac{1}{40} \frac{\gamma_I^2 \gamma_S^2 \hbar^2}{r^6} \{2[J_0(\Sigma_1) + J_0(\Delta_1)]$$

$$+ (1/8)[J_0(\omega_I^o - \omega_S^o + \Sigma_1)$$

$$+ J_0(\omega_I^o - \omega_S^o - \Sigma_1) + J_0(\omega_I^o - \omega_S^o + \Delta_1)$$

$$+ J_0(\omega_I^o - \omega_S^o - \Delta_1)]$$

$$+ (1/2)J_0(\omega_I^o - \omega_S^o + \omega_I^I)$$

$$+ 3J_1(\omega_I^o) + 6J_1(\omega_S^o) + 6J_2(\omega_I^o + \omega_S^o)\}. \quad [C23]$$

Equation [C23] reduces to Eq. [C1] when the S nucleus is of a different kind, so $\omega_I^S = 0$, and $\omega_I^I \ll \omega_I^o$. In the anticipated limit, where $\omega_I^I \tau_L \ll 1.0$, $\Sigma_1 \tau_L \ll 1.0$, $\Delta_1 \tau_L \ll 1.0$, and $(\omega_I^o - \omega_S^o)\tau_L \ll 1.0$, all of the J_0 spectral densities can be replaced by $J_0(0)$ to obtain

$$(R_{1\rho}^{dd})^o = \frac{1}{40} \frac{\gamma_I^2 \gamma_S^2 \hbar^2}{r^6} \{5J_0(0) + 3J_1(\omega_I^o)$$

$$+ 6J_1(\omega_S^o) + 6J_2(\omega_I^o + \omega_S^o)\} \quad [C24]$$

which is practically identical to $(R_2^{dd})^o$ in the same limit.

Explicit expressions were presented previously for the pertinent correlation functions (which are independent of m), namely $4\pi\langle Y_{20}(\Omega(0))Y_{20}(\Omega(t))\rangle$, and the spectral densities (also independent of n), namely $J_0(\omega)$, for molecules that exhibit mean local cylindrical symmetry and undergo both collective twisting and bending deformations and also various local angular motions (1, 2). These correlation functions always vanish at long times, and their slowest relaxation time is invariably the slowest uniform global rotational relaxation time (τ_L) of the molecule.

The Case when Chemical Shift Anisotropy
Relaxation Predominates

We consider next the case of relaxation by the chemical shift anisotropy. In this case,

$$H_p(t)/\hbar = (-\omega_1^o \delta_{z'}/2)[f^{(0)}a^{(0)} + (-1)f^{(-1)}(t)a^{(-1)} \\ + (-1)f^{(1)}(t)a^{(-1)}], \qquad [\text{C25}]$$

where $\omega_1^o = \gamma_I H_z$, and δ_z' is the largest component of the traceless part of the CSA tensor in its principal axis frame. Elements of the CSA tensor are here defined according to the convention of Abragam (*2, 3, 34*). The various quantities in Eq. [C25] are

$$a^{(0)} = 2I_z$$

$$a^{(1)} = \mp \frac{\sqrt{6}}{2} I_\pm \qquad [\text{C26}]$$

$$f^{(0)} = \left\{ \mathscr{D}_{00}^2(\Phi^{-1}) + \frac{\eta}{\sqrt{6}} [\mathscr{D}_{02}^2(\Phi^{-1}) + \mathscr{D}_{0-2}^2(\Phi^{-1})] \right\}$$
$$[\text{C27}]$$

$$f^{(\pm 1)} = \left\{ \mathscr{D}_{\pm 10}^2(\Phi^{-1}) + \frac{\eta}{\sqrt{6}} [\mathscr{D}_{\pm 12}^2(\Phi^{-1}) + \mathscr{D}_{\pm 1-2}^2(\Phi^{-1})] \right\}$$
$$[\text{C28}]$$

wherein η is the asymmetry of the traceless part of the CSA tensor, and $\Phi = (\alpha\beta\gamma)$ is the Euler rotation that carries a coordinate frame from coincidence with the laboratory frame to coincidence with the principal axis frame of the CSA tensor. The rotation functions in Eqs. [C29] and [C30], namely

$$\mathscr{D}_{mn}^2(\Phi) = e^{-im\alpha} \hat{d}_{mn}^2(\beta) e^{-in\gamma}, \qquad [\text{C29}]$$

are taken in the convention of Rose (*35*) and Tinkham (*36*), and the $\hat{d}_{mn}^2(\beta)$ are given by Eq. [C2] of Spiess (*4*). The pertinent correlation functions have been evaluated previously (*2*) for rotation functions ($D_{mn}^\ell(\Phi)$) in the convention of Wigner (*37*) and Edmonds (*38*), which are related to those of Rose (*35*) and Tinkham (*36*) by

$$\mathscr{D}_{mn}^\ell(\Phi^{-1}) = D_{nm}^{\ell*}(\Phi^{-1}) = D_{mn}^\ell(\Phi). \qquad [\text{C30}]$$

As before, H_0 and $H_1(t)$ are given by Eqs. [C3] and [C4]. Again the system is doubly transformed to the second interaction representation where H_0 and $H_1(t)$ no longer appear and where

$$U^\dagger(t)(a^{(0)})^{(R)}U(t) = 2I_z \qquad [\text{C31a}]$$

$$U^\dagger(t)(a^{(\pm 1)})^{(R)}U(t) = \mp (I_x \pm i(I_y C_a(t) \\ + I_z S_a(t)))e^{-i\omega_1^o t}. \qquad [\text{C31b}]$$

Equation [C21] must be evaluated using

$$h(t)^{(r)} = U^\dagger(t)\{f^{(0)}(a^{(0)})^{(R)} + (-1)f^{(-1)}(t)(a^{(1)})^{(R)} \\ + (-1)f^{(1)}(t)(a^{(-1)})^{(R)}\}U(t). \qquad [\text{C31c}]$$

The final result is

$$R_{1\rho}^{\text{CSA}} = (1/2)\omega_p^2 \delta_z^2 [j_0(\omega_1^I) + (3/8)(j_1(\omega_1^o + \omega_1^I) \\ + j_1(\omega_1^o - \omega_1^I))], \qquad [\text{C32}]$$

where

$$j_m(\omega) = 2 \text{ Re} \int_0^\infty d\tau e^{-i\omega\tau} j_m^C(t) \qquad [\text{C33}]$$

and

$$j_m^C(\tau) = (-1)^m \langle f^{(m)}(0) f^{(-m)}(\tau) \rangle. \qquad [\text{C34}]$$

For a solution that exhibits an isotropic equilibrium state, it was shown previously that $j_m^C(t) = j_0^C(t)$ is independent of m. Explicit expressions were obtained for molecules that exhibit mean local cylindrical symmetry and undergo both collective twisting and bending deformations and also various local angular motions (*2*). We note that Eq. [C13c] of Ref. (*2*) contains an error in the last term, where η should be replaced by η^2. These correlation functions all vanish at long times and their slowest relaxation time is invariably the slowest uniform global rotational relaxation time (τ_L) of the molecule.

Because typically $\omega_1^I \ll \omega_1^o$, the ω_1^I can be ignored in the $j_1(\omega_1^o \pm \omega_1^I)$ spectral densities. In the anticipated limit, $\omega_1^I \tau_L \ll 1.0$, the $j_0(\omega_1^I)$ spectral density can be replaced by $j_0(0)$ to obtain finally

$$(R_{1\rho}^{\text{CSA}})^o = (1/2)\omega_p^2 \delta_z^2 [j_0(0) + (3/4)j_1(\omega_1^o)] \qquad [\text{C37}]$$

which is identical to $(R_2^{\text{CSA}})^o$.

APPENDIX D

Evaluation of the Gaussian Exchange Model Contribution to $R_{1\rho}$

The following classical derivation is considerably more heuristic than rigorous. At the start of the experiment prior to the $\pi/2$ pulse, the spins exhibit a cylindrically symmetric distribu-

tion around the lab z_L axis. Immediately after the $\pi/2$ pulse, the distribution of spins is cylindrically symmetric around the z' axis of the rotating frame $(x'y'z')$, and the average spin defines the z' axis, which rotates at the mean Larmor frequency, ω_0, in the laboratory frame. y' is taken to be the lab-z_L axis, and x' is taken perpendicular to y' and z' so as to form a right-handed coordinate system. The polar coordinates μ, ν define the orientation of a spin vector in the rotating frame (x', y', z'). The polar angle μ is the angle between the spin vector and the z' axis. The distribution of initial ν_o values is uniform over the interval 0 to 2π. The probability of observing an initial μ_o value in the interval $d\mu_o$, namely $P(\mu_o)\sin \mu_o d\mu_o$, is assumed to exhibit a maximum at small, but nonvanishing, values of μ_o.

As a consequence of being instantaneously off resonance the spin vector will rotate with angular velocity $\delta\omega(t)$ about y' (i.e., z_L) in the rotating frame. At the same time, the spin-locking field will cause the spin vector to rotate with angular frequency ω_1 around z' in the rotating frame. It is assumed that $\omega_1 \gg |\delta\omega(t)|$, so the rapid rotation by ω_1 around z' limits μ to small values, such that $\mu \ll 1.0$. It is imagined that the spin points along the z_s axis of a coordinate frame (x_s, y_s, z_s) attached to the spin. The Euler rotation that carries a coordinate frame from coincidence with x', y', z' to coincidence with x_s, y_s, z_s is $\Phi = (\nu\mu\eta)$, and the inverse Euler rotation that orients the rotating frame in the spin-frame is $\Phi^{-1} = (-\eta -\mu -\nu)$. When viewed from the spin-frame, the rotating frame appears to be rotating with angular velocity $dRy'/dt = -\delta\omega(t)$ around its y' axis, $dRz'/dt = -\omega_1$ around its z' axis, and $dRx'/dt = 0$ around its x' axis. The canonical relations between cartesian and Eulerian angular velocities give, $d(-\mu)/dt = \cos(-\nu)(-\delta\omega(t))$, hence

$$\frac{d\mu(t)}{dt} = \delta\omega(t)\cos \nu(t) \qquad [D1]$$

and $d(-\nu)/dt = (-)\sin(-\nu)(\cos(-\mu)/\sin(-\mu))(-\delta\omega(t)) - \omega_1$, hence

$$\frac{d\nu(t)}{dt} = \omega_1 - \delta\omega(t)\cot \mu(t)\sin \nu(t). \qquad [D2]$$

The second term in Eq. [D2] is neglected on the basis that ω_1 is much greater than $\delta\omega(t)$. Then,

$$\nu(t) \cong \nu_o + \omega_1 t \qquad [D3]$$

and

$$\mu(t) = \mu_o + \int_0^t dt' \delta\omega(t')\cos(\omega_1 t + \nu_o). \qquad [D4]$$

The effect of the second term in Eq. [D2], which is neglected in [D3] and [D4], is to cause both periodic and random dithering of the effective frequency about ω_1. The consequences of this dithering of ω_1 will be considered subsequently. The instantaneous phase of the spin relative to the x' axis (or $x'z'$ plane) in the rotating frame is

$$\Delta\gamma(t) = \arctan(m_{x'}/m_{z'}) = \arctan\left(\frac{\sin \mu \cos \nu}{\cos \mu}\right), \qquad [D5]$$

where $m_{x'}$ and $m_{z'}$ are the projections of the spins onto the x' and z' axes, respectively. Because μ is small, $\sin \mu \cos \nu/\cos \mu \cong \mu \cos \nu$, and the arctan function can be expanded in a Taylor series to lowest order to give

$$\Delta\gamma(t) = \mu(t)\cos \nu(t) = \cos(\omega_1 t + \nu_o)$$

$$\times \left(\mu_o + \int_0^t dt' \delta\omega(t')\cos(\omega_1 t' + \nu_o)\right). \qquad [D6]$$

Equations [D3], [D4], and [D6] are predicated on the assumption that $\mu(t) \ll 1.0$, but at the same time $\omega_1 \gg \delta\omega(t)\cot(\mu(t))$. Thus, $\mu(t)$ needs to be small enough to satisfy the former inequality, but not so small as to violate the latter inequality, which is required for validity of Eqs. [D3], [D4], and [D6]. The term in [D6] containing $\delta\omega(t')$ is a sum of Gaussian random variables of zero mean, so it too is a Gaussian random variable of zero mean. μ_o can also be regarded as a Gaussian random variable near the peak of its distribution, but its mean does not vanish. However, when averaged over ν_o this $\mu_o\cos(\omega_1 t + \nu_o)$ term actually does vanish. Hence, relatively little error should be incurred by assuming that $\mu_o\cos(\omega_1 t + \nu_o)$ is also a Gaussian random variable of zero mean. Then, $\Delta\gamma(t)$ is likewise a Gaussian random variable of zero mean.

The normalized magnetization at the end of a spin-lock interval of duration t is obtained from Eq. [4] as

$$\frac{\langle\langle M_+(\Omega(t), t)\rangle\rangle}{\langle\langle M_+(\Omega(0), 0)\rangle\rangle} = e^{-(i\omega_o + R_2^o)t}\langle e^{i\Delta\gamma(t)}\rangle_T$$

$$= e^{-(i\omega_o + R_2^o)t}e^{-\langle\Delta\gamma(t)^2\rangle_T/2}, \qquad [D7]$$

where the symbol T denotes an average over the initial polar angles, μ_o, ν_o, as well as a trajectory average.

$$\langle \Delta \gamma(t)^2 \rangle_T = \overline{\mu_o^2 \cos^2(\omega_1 t + \nu_o) + \cos^2(\omega_1 t + \nu_o) \left\langle \int_0^t dt' \, \delta\omega(t') \cos(\omega_1 t' + \nu_o) \int_0^t dt'' \delta\omega(t'') \cos(\omega_1 t'' + \nu_o) \right\rangle}$$

$$= C + 2 \, \cos^2(\omega_1 t + \nu_o) \int_0^t dt' \int_0^t dt'' \cos(\omega_1 t' + \nu_o)\cos(\omega_1 t'' + \nu_o)\langle \delta\omega(t')\delta\omega(t'')\rangle, \qquad [\text{D8}]$$

where the overbar denotes an average over the initial distributions of μ_o and ν_o, and $C = \overline{\mu_o^2}/2$. After substituting $\langle \delta\omega(t')\delta\omega(t'')\rangle = \delta^2 \exp[-(t' - t'')/\tau]$, the integrals can be performed and averages taken over the initial conditions. After considerable tedious algebra, the final result is obtained:

$$\langle \Delta \gamma(t)^2 \rangle / 2 = \frac{\delta^2 \tau^2}{1 + \omega_1^2 \tau^2} \left\{ \frac{t}{4\tau} - \frac{1}{16} - \frac{1}{4}\left(\frac{1 - \omega_1^2 \tau^2}{1 + \omega_1^2 \tau^2} \right) \right.$$

$$+ \frac{1}{8}\left(\frac{1 - \omega_1^2 \tau^2}{1 + \omega_1^2 \tau^2} \right) \cos \, \omega_1 t e^{-t/\tau}$$

$$- \frac{1}{8} \cos 2\omega_1 t - \frac{1}{2} \sin \, \omega_1 t e^{-t/\tau}$$

$$\left. \times \left(\frac{\omega_1 \tau}{1 + \omega_1^2 \tau^2} \right) \right\} + \overline{\mu_o^2}/4. \qquad [\text{D9}]$$

The oscillatory terms are not as coherent as they appear, due to the random dithering of the effective ω_1 that would result from retention of the second term in Eq. [D2]. Indeed, it is likely that averaging the final result over the dithered ω_1 would cause the oscillatory terms to vanish for times sufficiently large that $\omega_1 t \gg 1.0$. In any case the oscillatory terms are expected to vanish completely, whenever the spin-lock consists of an even number of contiguous π pulses, as in the studies of Peng and Wagner (5), Peng *et al.* (6), and Gaudin *et al.* (22). We assume in the following that the oscillatory terms can be neglected for one reason or another. Then, Eq. [D7] can be rewritten as

$$\frac{\langle\langle M_+(\Omega(t), t)\rangle\rangle}{\langle\langle M_+(\Omega(0), 0)\rangle\rangle} = e^{-(i\omega_o + R_2^o)t} e^{-R_{1\rho}^{se} t} e^{+D}, \qquad [\text{D10}]$$

where

$$R_{1\rho}^{se} \equiv \delta^2 \tau / (4(1 + \omega^2 \tau^2)) \qquad [\text{D11}]$$

and

$$D = (\delta^2 \tau^2 / (1 + \omega^2 \tau^2))$$

$$\times [1/16 + (1 - \omega^2 \tau^2)/(4(1 + \omega^2 \tau^2))] + \overline{\mu_o^2}/4.$$
$$[\text{D12}]$$

D is a constant independent of the time duration of the spin lock. Under conditions when equation [D10] is valid, the total rate of exponential decay of the amplitude of the transverse magnetization during the spin lock is

$$R_{1\rho} = R_2^o + R_{1\rho}^{se}. \qquad [\text{D13}]$$

Under conditions where Eq. [D10] is not valid, one might use Eq. [D9] in [D7] to predict the decay in transverse magnetization during the spin lock.

APPENDIX E

Gaussian Behavior of Discrete Multi-Site Jump Models at Long Times

We consider a discrete multisite jump model in which all sites ($\Omega = 1, 2, \ldots$) exhibit the same intrinsic R_2^o rate. The mean Larmor frequency is given by Eq. [1] and the variance is defined by

$$\delta^2 = \langle \omega(\Omega)^2 \rangle - \omega_o^2 = \sum_\Omega f_\Omega^o (\omega(\Omega)^2 - \omega_o^2). \qquad [\text{E1}]$$

For such a model, the variation of the Larmor frequency along a trajectory is a non-Gaussian stationary random process of zero mean with autocorrelation function,

$$\langle \delta\omega(0)\delta\omega(t)\rangle = \delta^2 g(t), \qquad [\text{E2}]$$

where $g(t)$ is the normalized autocorrelation function, so $g(0) = 1.0$. For any multisite jump process that obeys the stochastic rules of kinetics, $g(t)$ will decay monotonically from 1.0 at $t = 0$ to 0 at $t = \infty$. Moreover, $g(t)$ will consist of a sum of exponentially decaying functions, whose decay constants are the nonvanishing eigenvalues of the stochastic matrix Γ in Eqs. [12], [13], [20], and [A2]–[A6]. The accumulated phase along a trajectory is given by Eq. [31], $\Delta\phi(t) = \int_0^t \delta\omega(t')dt'$, and the variance of the accumulated phase in this case is given by

$$\langle \Delta \phi(t)^2 \rangle = \left\langle \int_0^t dt' \, \delta\omega(t') \int_0^t dt'' \delta\omega(t'') \right\rangle$$

$$= \int_0^t dt' \int_0^t dt'' \langle \delta\omega(t')\delta\omega(t'') \rangle$$

$$= \int_0^t dt' \int_0^t dt'' \langle \delta\omega(0)\delta\omega(|t' - t''|) \rangle$$

$$= 2\delta^2 \int_0^t dt' \int_0^{t'} dt'' g(|t' - t''|)$$

$$= 2\delta^2 \int_0^t dt' \int_0^{t'} dT g(T)$$

$$= 2\delta^2 \left(\int_0^t dt' \int_0^t dT g(T) \right.$$

$$\left. - \int_0^t dt' \int_{t'}^t dT g(T) \right). \quad \text{[E3]}$$

Now, when $T = n\tau_1$, where τ_1 is the longest relaxation time in $g(T)$ and n is a suitably large fixed integer, $g(T)$ effectively vanishes. Hence, the upper limits of the dT integrals in [E3] can be replaced by $n\tau_1$. This restricts the upper limit of the dt' integral in the second term in [E3] also to $n\tau_1$, but does not affect that of the dt' integral in the first term. After defining the effective relaxation time

$$\tau \equiv \int_0^{n\tau_1} dT g(T) = \int_0^\infty dT g(T), \quad \text{[E4]}$$

[E3] can be rewritten as

$$\langle \Delta\phi(t)^2 \rangle = 2\delta^2 \left(t\tau - \int_0^{n\tau_1} dt' t' g(t') \right). \quad \text{[E5]}$$

Because t can increase without bound, whereas $n\tau_1$ remains fixed, at some sufficiently long time ($t \gg \tau$) the second term becomes negligible compared to the first, and the variance of the accumulated phase becomes proportional to t. In this limit, the accumulated phase exhibits diffusive behavior and obeys a diffusion equation with diffusion coefficient $D_{\text{eff}} = \langle \Delta\phi(t)^2 \rangle / 2t = \delta^2\tau$. Hence, the distribution of the phase accumulated over a sufficiently long time ($t \gg \tau$) is given by

$$P(\Delta\phi(t))d\Delta\phi(t) = \frac{e^{-\Delta\phi(t)^2/2(2D_{\text{eff}}t)}}{(2\pi 2 D_{\text{eff}}t)^{1/2}} d\Delta\phi(t), \quad \text{[E6]}$$

which is manifestly Gaussian. The same qualitative conclu-

sion could also have been reached by noting that even though the distribution of accumulated phase over a much shorter time interval is non-Gaussian, under the central limit theorem the distribution of the sum of accumulated phases over a very large number of such intervals, or equivalently of a single integral over a much longer interval, must approach Gaussian behavior. The variance of the accumulated phase of the discrete multisite model in the long time limit, namely $2\delta^2\tau t$, will match that of the continuous Gaussian model in the same limit, namely $2\delta^2\tau t$ (cf. Eq. [B1]), provided the δ^2 and τ values of the latter are chosen to match the corresponding values of the former.

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