

A Diffusion Equation Approach to Spin Diffusion in Biomolecules

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A theoretical description of ^1H – ^1H dipolar nuclear spin relaxation in a multispin system has been worked out by forming a diffusion equation for a one-dimensional chain of equidistant spins. The spin-diffusion equation is formed from first principles by assuming nearest neighbor interactions for a molecule undergoing isotropic random reorientation. This equation describes diffusion only in the long correlation limit (for $\omega\tau_c > 1.118$) and is solved for driven NOE experiments, for spins in a chain of infinite length ($0 < x < \infty$), or for spins in a chain of finite length ($0 < x < L$). The solutions are obtained using the method of the Laplace transform for specified initial and boundary conditions. The observed selectivity of the NOE transfer in driven NOE experiments on a biomolecule which has a correlation factor $\omega\tau_c \sim 3$ is indeed in conformity with the predictions obtained from the spin-diffusion equation. © 1989 Academic Press, Inc.

The ^1H – ^1H nuclear Overhauser enhancement experiments are powerful methods to determine the spatial proximity of various protons in organic and biomolecules (1–8). This unique method which can determine the three-dimensional structure in solution state has in recent years become of central importance among nuclear magnetic resonance spectroscopists (8–14). The NOE is transmitted by cross relaxation, and this process has a very crucial dependence on the motional process of the molecule (1, 3, 15). The usefulness of the various NOE experiments, such as truncated driven NOE, transient and two-dimensional NOE experiments, therefore strongly depends on the time scale of motional processes (15, 16). This is governed by the parameter “correlation factor,” the product of the Larmor frequency (ω) and the correlation time (τ_c). The extreme narrowing limit, in which $\omega\tau_c \ll 1$, often the prevailing situation in organic and small biomolecules, yields positive proton–proton NOE. But most of the larger molecules are found to be in the region of slow motion, in which $\omega\tau_c \gg 1$, and the NOE is negative (17). In this limit the magnetization migrates over long distances in the molecule, often referred to as spin diffusion. The “spin diffusion” in large molecules causes the NOEs to be nonspecific and can be avoided by experiments with short mixing times, (3, 16) or by performing rotating-frame NOE experiments (18). Most of these experiments have been well used for structural information and for sequential assignment purposes.

The time development of the nuclear Overhauser effect for two dipolar-coupled spins was first treated by Solomon (19). The coupled differential equations, called

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the Solomon equations, were solved by Noggle and Schirmer for different initial conditions for two-spin systems and for higher-order spin systems, by neglecting the cross correlation between different dipolar pairs (1). Even though these generalized equations and their solutions were well known (20, 21), the implications of these solutions under the long correlation-time limit were brought out by Kalk and Berendsen (22), and the importance of this limit was discussed with a special emphasis on proteins. Errors that could have changed the conclusions derived from the experiments without taking care of the multispin effects have been pointed out (22–24). Approaches yielding solutions of generalized Solomon's equations are, in general, appropriate to the multispin NOE problem. Two other approaches to calculations of multispin NOE effects, both based on the methods of normal mode coordinates (25), have been proposed (26), and the kinetics of magnetization diffusion using these approaches was demonstrated (27). The effect of strong J couplings on the NOE experiments has been treated recently (28). On the other hand, conclusions were derived for spin diffusion in the long correlation-time limit by explicit calculations of NOE in three-spin systems (29). Williamson *et al.* recently simulated the NOE effects of a macromolecule of about 200 spins by numerically integrating the generalized Solomon equations (30). The results from the multispin calculations explain well the behavior of cross relaxation among the spins for proteins (31, 32) as well as for nucleic acids (8). This magnetization transport process in biological macromolecules resembles a diffusive process and justifies the name "spin diffusion" (2–18, 21–24, 26–34), but uses no diffusion equation. In this paper we have adopted the approach of forming a diffusion equation to explain the transport of magnetization in biological macromolecules.

Before discussing the formation of the diffusion equation it may be appropriate to distinguish spin diffusion in solids and in macromolecules in solution. In solids the spin diffusion is caused by the energy-conserving flip-flop term of a *time-independent* dipolar interaction. The magnetization thus diffuses over the length of a single crystal or the length of a crystallite in a polycrystalline substance. This process of spatial diffusion of magnetization is well known from the days of its introduction by Bloembergen (35–39). On the other hand, in biological macromolecules in solution, due to rapid tumbling, the dipolar interaction becomes *time dependent*, is averaged to zero in the first order giving rise to a high-resolution NMR spectrum, and contributes in second order to relaxation (39, 40). The flip-flop term in the dipolar *relaxation* then causes transfer of magnetization from one spin to another through the length of the molecule. This transfer of magnetization is monitored in the NOE experiments as spectral diffusion. The flip-flop terms in such cases conserve energy to a large extent, needing only the amount of energy equal to the difference in frequencies of the two spins.

In order to study spin diffusion in biomolecules, we form a diffusion equation for a dipolar-relaxation-coupled one-dimensional chain of equidistant spins. This spin-diffusion equation is solved for driven NOE experiments yielding analytical solutions for the infinite or finite length of the chain. These solutions explain well the observed results.

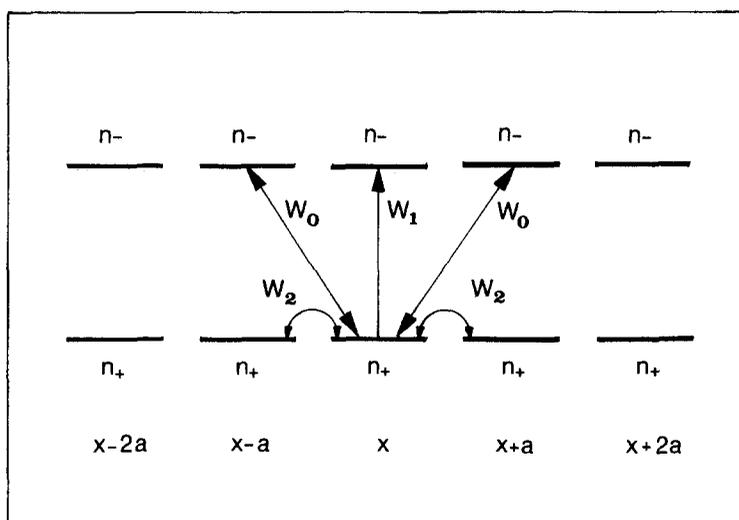


FIG. 1. Schematic energy level description of spins (each spin- $\frac{1}{2}$) in a one-dimensional chain. W_0 represents the mutual flip-flop term in which, for example, the spin at x goes up and the spin at $x+a$ comes down or vice versa, and thus is multiplied by the deviation of populations $n_+(x)$ and $n_-(x+a)$. W_2 represents simultaneous upward (or downward) flip of the pairs of spins, for example, at x and $x+a$, and thus is multiplied by the deviation of populations $n_+(x)$ and $n_+(x+a)$. W_1 represents the transition probability for a single spin transition and should be counted twice for each pair of spins. Equation [1] has been derived from detailed balance of a three-spin energy level diagram but can as well be written using the above arguments.

SPIN-DIFFUSION EQUATION

We consider a one-dimensional chain of spin- $\frac{1}{2}$ nuclei separated by an interval a , and dipolar-relaxation coupled among themselves. A single sequential chain of protons is assumed such that each proton interacts with its nearest neighbors and negligibly with remote protons. Furthermore the cross correlation between various dipolar interactions, which has been shown to have negligible influence on NOE in biomolecules (41, 42), is neglected. The spatial coordinates for these spins along one dimension have positions $\dots x-a, x, x+a, \dots$. The rate of change of deviation of populations from equilibrium $n_+(x, t)$ of lower energy level of the spin at coordinate x at any time t (Fig. 1) can be written as (19, 39, 40)

$$\begin{aligned} \frac{\partial n_+(x, t)}{\partial t} = & -2n_+(x, t)W_1 + 2n_-(x, t)W_1 - n_+(x, t)n_-(x+a, t)W_0 \\ & + n_-(x, t)n_+(x+a, t)W_0 - n_+(x, t)n_-(x-a, t)W_0 \\ & + n_-(x, t)n_+(x-a, t)W_0 - n_+(x, t)n_+(x+a, t)W_2 \\ & + n_-(x, t)n_-(x+a, t)W_2 - n_+(x, t)n_+(x-a, t)W_2 + n_-(x, t)n_-(x-a, t)W_2, \end{aligned} \quad [1]$$

where W_0 , W_1 , and W_2 are, respectively, the transition probabilities of zero-, single,

and double-quantum transitions for a two-spin- $\frac{1}{2}$ system which for the dipole-dipole interaction with isotropic rotational correlation time (τ_c) are obtained as (39, 40)

$$\begin{aligned} W_0 &= \frac{1}{10} \frac{\gamma^4 \hbar^2}{a^6} \left\{ \frac{\tau_c}{1 + (\omega_x - \omega_{x+a})^2 \tau_c^2} \right\} \\ W_1 &= \frac{3}{20} \frac{\gamma^4 \hbar^2}{a^6} \left\{ \frac{\tau_c}{1 + (\omega_x)^2 \tau_c^2} \right\} \\ W_2 &= \frac{3}{5} \frac{\gamma^4 \hbar^2}{a^6} \left\{ \frac{\tau_c}{1 + (\omega_x + \omega_{x+a})^2 \tau_c^2} \right\}. \end{aligned} \quad [2]$$

For homonuclear spin systems $W_0 = W_0(x, x+a) \cong W_0(x, x-a)$, and $W_2 = W_2(x, x+a) \cong W_2(x, x-a)$.

Writing similar equations for $n_-(x, t)$ and taking the difference, the deviation of magnetization from equilibrium at time t of the spin at coordinate x can be written, neglecting quadratic terms, as,

$$\frac{\partial}{\partial t} \chi(x, t) = -2\rho[\chi(x, t)] - \sigma[\chi(x-a, t)] - \sigma[\chi(x+a, t)], \quad [3]$$

where $\chi(x, t) = [n_+(x, t) - n_-(x, t)]$ and ρ and σ are given by

$$\rho = W_0 + 2W_1 + W_2 \quad \text{and} \quad \sigma = W_2 - W_0. \quad [4]$$

Equation [3] is also obtained from the generalized Solomon equations (1, 22) by substitution of the relaxation parameters appropriate for the above model. Expanding $\chi(x+a, t)$ and $\chi(x-a, t)$ about x in Taylor series yields

$$\begin{aligned} \chi(x+a, t) &= \chi(x, t) + \frac{a}{1!} \frac{\partial}{\partial x} \chi(x, t) + \frac{a^2}{2!} \frac{\partial^2}{\partial x^2} \chi(x, t) + \dots, \\ \chi(x-a, t) &= \chi(x, t) - \frac{a}{1!} \frac{\partial}{\partial x} \chi(x, t) + \frac{a^2}{2!} \frac{\partial^2}{\partial x^2} \chi(x, t) - \dots. \end{aligned} \quad [5]$$

When Eqs. [5] are substituted in Eq. [3], the odd derivatives of $\chi(x, t)$ cancel. Truncating the Taylor expansions to second derivatives yields for Eq. [3]

$$\frac{\partial}{\partial t} \chi(x, t) = -2\rho[\chi(x, t)] - \sigma \left(2\chi(x, t) + \frac{2a^2}{2!} \frac{\partial^2}{\partial x^2} \chi(x, t) \right), \quad [6]$$

$$\frac{\partial}{\partial t} \chi(x, t) = -2(\rho + \sigma)\chi(x, t) + D \frac{\partial^2}{\partial x^2} \chi(x, t), \quad [7]$$

where $D = -\sigma a^2$.

Equation [7] has the well-known form of a homogeneous one-dimensional diffusion equation with D as the diffusion coefficient. The first term on the right hand side represents dissipation of magnetization and describes the self-relaxation of the spin at x . This equation describes diffusion only for positive values of D , which is obtained for negative values of σ . The cross-relaxation coefficient σ is a function of $\omega\tau_c$ and varies from a positive value of $0.5(\gamma^4 \hbar^2 \tau_c / a^6)$ for $\omega\tau_c \ll 1$ to a negative value of

$-0.1(\gamma^4 \hbar^2 \tau_c / a^6)$ for $\omega \tau_c \gg 1$, crossing zero at $\omega \tau_c = 1.118$. Thus, as is well known, spin diffusion in biomolecules can be described only in the slow motion limit, for $\omega \tau_c > 1.118$.

In order to obtain a solution of Eq. [7], the exponential time dependence arising from the damping term is removed by the substitution

$$\chi(x, t) = u(x, t)e^{-2(\rho+\sigma)t}. \quad [8]$$

Equation [7] reduces to

$$\frac{\partial}{\partial t} u(x, t) = D \frac{\partial^2}{\partial x^2} u(x, t). \quad [9]$$

This is the general form of the diffusion equation and its solutions are discussed in the following section.

DRIVEN NUCLEAR OVERHAUSER EFFECTS

Driven NOE experiments are often used for structural and conformational aspects of proteins and nucleic acids (1, 3). In driven NOE experiments, a particular spin is saturated by selective irradiation and the NOE is monitored as a function of the irradiation time τ , during which a steady state is reached between the irradiation and the relaxation. Truncated driven NOE experiments (TOE) which utilize a limited irradiation time τ are often used for controlled spin diffusion (29). This section deals with solution of the spin-diffusion equation (Eq. [7]) for such experiments. Let the spin at coordinate $x = 0$ be irradiated and the NOE buildup on the other spins be monitored as a function of the irradiation time τ . The solution of Eq. [9] in this case has been obtained using the method of the Laplace transform (44, 45). In all the experiments discussed in this section the common initial condition will be

$$\chi(x, t) = 0, \quad x > 0, \quad t = 0, \quad [10]$$

since all spins except the perturbed spin at $x = 0$ will be assumed to be in equilibrium at $t = 0$. If L is the length of the one-dimensional chain, the boundary conditions, in general, can be stated as

$$\begin{aligned} \chi(x, t) &= \psi_0(t), & x = 0, & \quad t > 0, \\ \chi(x, t) &= \psi_L(t), & x = L, & \quad t > 0. \end{aligned} \quad [11]$$

The substitution (Eq. [8]) leaves the initial condition unchanged, that is,

$$u = \chi(x, t)e^{2(\rho+\sigma)t} = 0, \quad x > 0, \quad t = 0, \quad [12]$$

and the boundary conditions (Eq. [11]) become

$$u(x, t) = \psi_0(t)e^{2(\rho+\sigma)t} = \phi_0(t), \quad x = 0, \quad t > 0, \quad [13]a$$

$$u(x, t) = \psi_L(t)e^{2(\rho+\sigma)t} = \phi_L(t), \quad x = L, \quad t > 0. \quad [13]b$$

Taking the Laplace transform of Eq. [9], by multiplying both sides by e^{-pt} , integrating from 0 to ∞ , and using the initial condition (Eq. [12]), one obtains

$$\int_0^{\infty} u(x, t) e^{-pt} (p) dt = D \frac{\partial^2}{\partial x^2} \int_0^{\infty} u(x, t) e^{-pt} dt. \quad [14]$$

With the notation

$$\bar{u} = \int_0^{\infty} u(x, t) e^{-pt} dt, \quad [15]$$

Eq. [14] becomes

$$p\bar{u}(x) = D \frac{\partial^2}{\partial x^2} \bar{u}(x). \quad [16]$$

The boundary conditions (Eq. [13]) in the Laplace domain become

$$\begin{aligned} \bar{u}(x) &= \bar{\phi}_0, & x &= 0, \\ \bar{u}(x) &= \bar{\phi}_L, & x &= L, \end{aligned} \quad [17]$$

where $\bar{\phi}_0$ and $\bar{\phi}_L$ are the Laplace transforms of $\phi_0(t)$ and $\phi_L(t)$, respectively. Equation [16] can be rewritten as

$$\frac{\partial^2}{\partial x^2} \bar{u}(x) - q^2 \bar{u}(x) = 0, \quad [18]$$

where $q^2 = p/D$. Equation [18] has the general solution

$$\bar{u}(x) = k_1 e^{qx} + k_2 e^{-qx}, \quad [19]$$

where k_1 and k_2 are the constants to be determined from the boundary conditions. The quantity $\bar{u}(x)$ is converted into $u(x, t)$ by taking the inverse Laplace transform, which in turn will give the deviation of magnetization $\chi(x, t)$ and describes the manner in which a nonequilibrium magnetization will propagate along the chain and can be used for interpretation of various types of difference NOE experiments.

Infinite chain of spins. In driven NOE experiments, although not strictly valid, it is often assumed that the irradiated spin is instantaneously saturated leading to the boundary condition for the spin at $x = 0$ as

$$\chi(x, t) = \psi_0 = -I_z^0, \quad x = 0, \quad t > 0,$$

or

$$\bar{u}(x) = \bar{\phi}_0, \quad x = 0, \quad [20]$$

where $\bar{\phi}_0$ is the Laplace transform of $\psi_0 \exp[2(\rho + \sigma)t]$. Since u and \bar{u} should be bounded as x tends to ∞ , Eq. [19] retains only one term, namely

$$\bar{u}(x) = k_2 e^{-qx}. \quad [21]$$

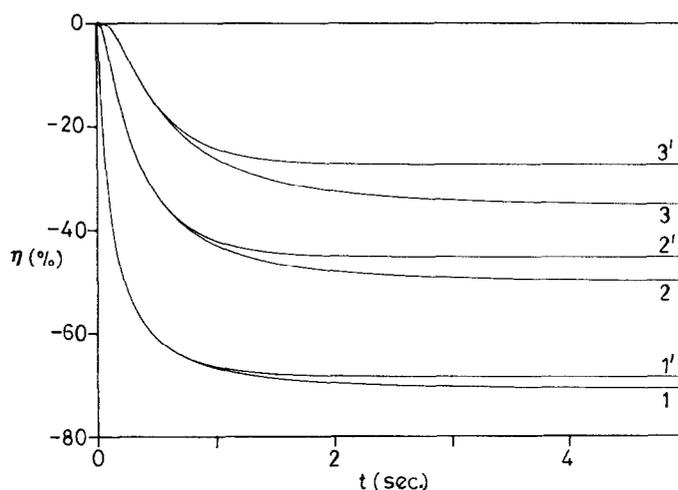


FIG. 2. The plot of NOE (η) in driven NOE experiments for the spins at $x = a, 2a,$ and $3a$, in the infinite ($n = 1, 2,$ and 3) and the finite ($n = 1', 2',$ and $3'$) cases as a function of the irradiation time when the spin at $x = 0$ is saturated. The parameters used are $a = 2 \text{ \AA}$, $\omega = 270 \text{ MHz}$, and $\omega\tau_c = 10$ and the length of the chain in the finite case, $L = 5a$, with the end spin held at thermal equilibrium.

Using the above boundary condition (Eq. [20]) one obtains $k_2 = \bar{\phi}_0$ and $\bar{u}(x)$ as

$$\bar{u}(x) = \frac{-I_z^0}{[p - 2(\rho + \sigma)]} e^{-qx}. \quad [22]$$

Taking the inverse Laplace transform (44-46) of Eq. [22] and using Eq. [8] the solution $\chi(x, t)$ is given by

$$\chi(x, t) = -\frac{1}{2} I_z^0 \left[\exp \left\{ -x \left(\frac{2(\rho + \sigma)}{D} \right)^{1/2} \right\} \text{Erfc} \left\{ \frac{x}{2(Dt)^{1/2}} - [2(\rho + \sigma)t]^{1/2} \right\} \right. \\ \left. + \exp \left\{ x \left(\frac{2(\rho + \sigma)}{D} \right)^{1/2} \right\} \text{Erfc} \left\{ \frac{x}{2(Dt)^{1/2}} + [2(\rho + \sigma)t]^{1/2} \right\} \right], \quad [23]$$

where Erfc is the error-function complement. (The definition and some properties of the error function and the error-function complement are given for ready reference in the Appendix.) Equation [23] describes the NOE at time t at any point x in the chain of infinite length. For t tending to ∞ and for finite values of x (since $\text{Erfc}(\infty) = 0$ and $\text{Erfc}(-\infty) = 2$), Eq. [23] yields a steady-state value given by

$$\chi(x, t)|_{t \rightarrow \infty} = -I_z^0 \exp(-x[2(\rho + \sigma)/D]^{1/2}). \quad [24]$$

For small values of t , on the other hand, the first term in the error-function argument dominates and yields

$$\chi(x, t)|_{t \rightarrow 0} = -I_z^0 \text{Cosh}(x[2(\rho + \sigma)/D]^{1/2}) \text{Erf}\{x/2(Dt)^{1/2}\}. \quad [25]$$

This equation describes the initial build-up rate of magnetization as a function of x . Both the steady-state value and the initial rate depend on $x, a, \omega,$ and $\omega\tau_c$. Figure 2 shows the transfer of magnetization ($\chi(x, t)$ from Eq. [23]) to the spins at positions

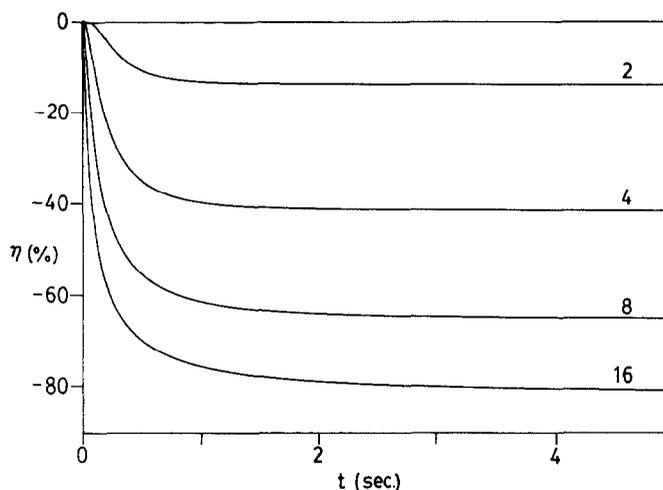


FIG. 3. The time development of η (Eq. [23]) in the TOE experiment for the spin at $x = a$ ($n = 1$) in the infinite length chain model for various correlation factors ($\omega\tau_c = 2, 4, 8,$ and 16) with $a = 2 \text{ \AA}$ and $\omega = 270 \text{ MHz}$.

$a, 2a,$ and $3a$ ($n = 1, 2,$ and 3) from the irradiated spin as a function of the irradiation time t , for $\omega = 270 \text{ MHz}$ and $\omega\tau_c = 10$. The variation of NOE (η) with different values of $\omega\tau_c$, for $x = a$, is shown in Fig. 3. These results show that the magnetization diffuses to distant spins slowly and that the final magnetization is a function of the distance from the irradiated spin, ω and $\omega\tau_c$. The steady-state values of NOE (η_{ss}) for the spins at $x = a, 2a,$ and $3a$ ($n = 1, 2,$ and 3) ($\chi(x, t)$ from Eq. [24]) as a function of $\omega\tau_c$ are given in Fig. 4. The results conform to the general expected behavior of NOE build-up and steady-state values.

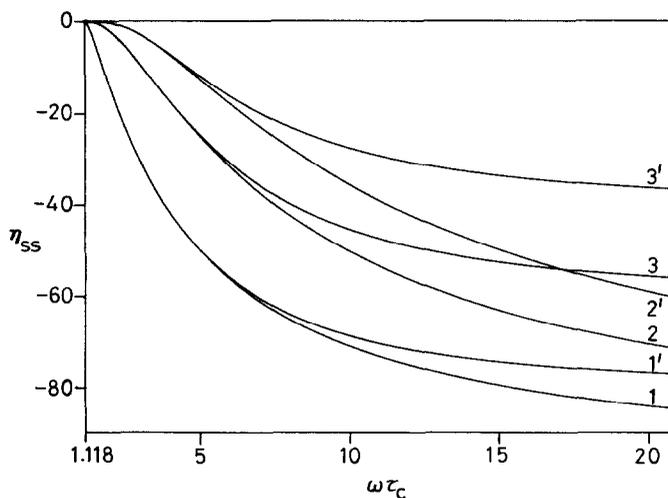


FIG. 4. The variation of the steady-state value of η (η_{ss}) in TOE experiments as a function of $\omega\tau_c$ (Eq. [30]) for the spins at $x = a, 2a,$ and $3a$, for infinite chain ($n = 1, 2,$ and 3) and finite chain ($n = 1', 2',$ and $3'$) models. The remaining parameters for this figure are the same as those in Fig. 2.

Finite chain of spins. We consider a one-dimensional chain of finite length L with an interspin distance a . The solution of the spin-diffusion equation (Eq. [18]) follows a procedure similar to that for the infinite chain except for the fact that the solution here depends also on the boundary condition at $x = L$. Using the boundary condition of Eq. [17], and the expansion

$$[1 - e^{-2qL}] = \sum_{n=0}^{\infty} e^{-2nqL},$$

the general solution of Eq. [18], for the finite case, is obtained as

$$\bar{u}(x) = [\bar{\phi}_L e^{-qL} - \bar{\phi}_0 e^{-2qL}] \sum_{n=0}^{\infty} e^{-2nqL} e^{qx} + [\bar{\phi}_0 - \bar{\phi}_L e^{-qL}] \sum_{n=0}^{\infty} e^{-2nqL} e^{-qx}. \quad [26]$$

In the limit of L tending to ∞ , the above solution reduces to Eqs. [22] of the infinite case.

Specific boundary condition at $x = L$. Further solution requires a specific condition for the spin at $x = L$. If it is assumed that the spin at $x = L$ is partially saturated through transfer of NOE and attains a finite deviation of magnetization $-\zeta_L$ exponentially at a rate λ given by

$$\chi(L, t) = \psi_L(t) = -\zeta_L [1 - e^{-\lambda t}], \quad t > 0, \quad [27]$$

the solution for the finite case is obtained as

$$\begin{aligned} \bar{u}(x) = & -\left(\frac{I_z^0}{p - \alpha}\right) \sum_{n=0}^{\infty} (e^{-qz_1} - e^{-qz_2}) + \left(\frac{\zeta_L}{p - (\alpha - \lambda)}\right) \sum_{n=0}^{\infty} (e^{-qz_3} - e^{-qz_4}) \\ & - \left(\frac{\zeta_L}{p - \alpha}\right) \sum_{n=0}^{\infty} (e^{-qz_3} - e^{-qz_4}), \quad [28] \end{aligned}$$

where $\alpha = 2(\rho + \sigma)$; $z_1 = 2nL + x$; $z_2 = 2(n + 1)L - x$; $z_3 = (2n + 1)L - x$; and $z_4 = (2n + 1)L + x$.

The Laplace transform of Eq. [28] yields the general solution for the finite case (47). A particular solution assuming that the end spin remains at thermal equilibrium ($\zeta_L = 0$) is obtained as

$$\begin{aligned} \chi(x, t) = & -\frac{I_z^0}{2} \sum_{n=0}^{\infty} \left[\exp[-z_1(\alpha/D)^{1/2}] \operatorname{Erfc}\left\{\frac{z_1}{2(Dt)^{1/2}} - (\alpha t)^{1/2}\right\} \right. \\ & + \exp[z_1(\alpha/D)^{1/2}] \operatorname{Erfc}\left\{\frac{z_1}{2(Dt)^{1/2}} + (\alpha t)^{1/2}\right\} \\ & - \exp[-z_2(\alpha/D)^{1/2}] \operatorname{Erfc}\left\{\frac{z_2}{2(Dt)^{1/2}} - (\alpha t)^{1/2}\right\} \\ & \left. - \exp[z_2(\alpha/D)^{1/2}] \operatorname{Erfc}\left\{\frac{z_2}{2(Dt)^{1/2}} + (\alpha t)^{1/2}\right\} \right]. \quad [29] \end{aligned}$$

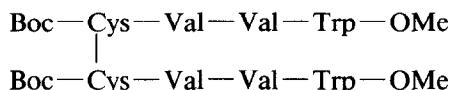
The steady-state value of NOE for the spin at x (from Eq. (29)) is obtained as

$$\chi(x, t)|_{t \rightarrow \infty} = -I_z^0 \sum_{n=0}^{\infty} (\exp(-z_3(\alpha/D)^{1/2}) - \exp(-z_1(\alpha/D)^{1/2})). \quad [30]$$

Figure 2 also shows the transfer of magnetization for the spins at $x = a, 2a$, and $3a$ ($n = 1', 2'$, and $3'$) in the finite case for $L = 5a$ with the other parameters the same as those for the infinite case. The spin at $x = a$ behaves almost identically for finite and infinite cases, while the effect on the farther spins, at $x = 2a, 3a, \dots$ is progressively altered because of the finite dimension of the chain. The spins near the boundary have reduced NOE because of specific boundary condition of thermal equilibrium at $L = 5a$. For the infinite chain, the spin at $5a$ has a finite NOE. Figure 4 also shows the plot of the variation of η_{ss} for the finite case (curves with the numbers primed). The difference between the finite and the infinite case is enhanced, along with the magnitude of the NOE, for larger values of $\omega\tau_c$.

EXPERIMENTAL

Truncated driven NOE experiments have been carried out at 270 MHz on the peptide



(where Boc is *t*-butyloxycarbonyl and OMe is methyl ester). This peptide has been shown to be entirely in antiparallel β -sheet conformation under the solvent condition used in the experiments described here (48). Data corresponding to the irradiation of the Val(3) NH with the NOE monitored on the Val(2) C $^{\alpha}$ H, Val(3) C $^{\alpha}$ H, and Val(3) C $^{\beta}$ H protons is given in Fig. 5. Since this molecule is in extended structure with the NH $_i$ -C $^{\beta}_{i-1}$ H distance about 2.2 Å (49), the NOE has been calculated using the interspin distance $a = 2.2$ Å. The magnetization in addition to traveling along the main chain also migrates to side chains and to other relaxation processes. These have been included here as an ad hoc leakage term l added to ρ . Similar leakage terms have been added in the analysis of NOE data by other methods (1, 43). The calculated NOE using $a = 2.2$ Å and $\omega\tau_c = 2.5$ is also plotted in Fig. 5. While the calculated curves fit the experimental behavior quite well, it may be mentioned that this fit is not unique and should be taken as qualitative.

CONCLUSIONS

Starting from first principles we have shown that spin diffusion in a biomolecule can indeed be described by a diffusion equation for $\omega\tau_c > 1.118$ for a one-dimensional chain of spins having interspin distance a and retaining only the nearest neighbor interactions. Solutions of the spin-diffusion equation have been obtained for the driven NOE experiments by considering appropriate initial and boundary conditions. The solutions describe the known experimental features in a systematic manner.

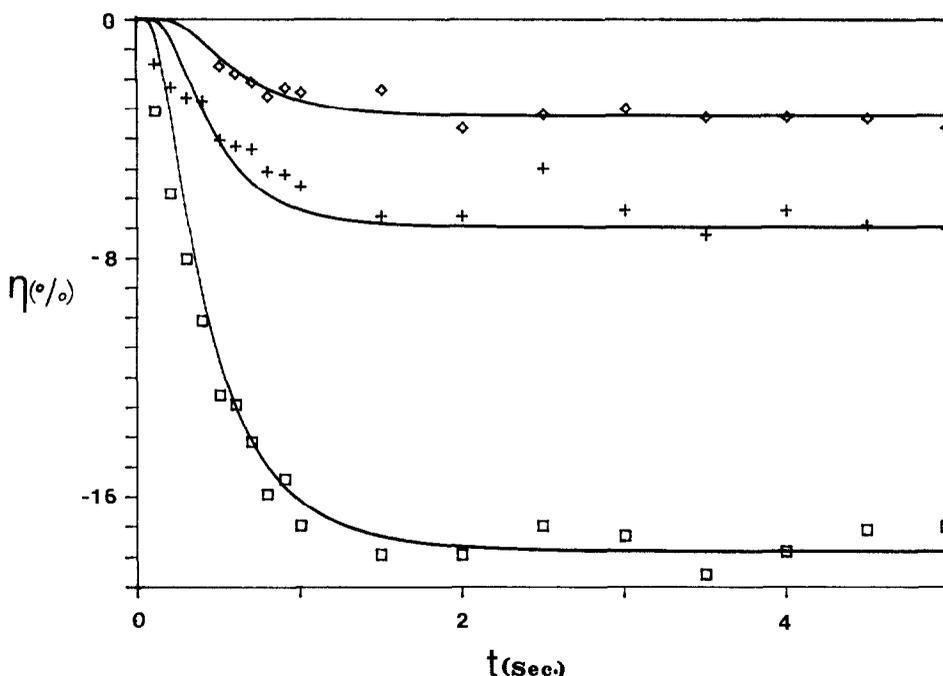


FIG. 5. Experimental and theoretical fit of the TOE experiment on an oligopeptide (Boc-Cys-Val-Val-Trp-OMe)₂ which has a correlation factor $\omega\tau_c \sim 3$, in 270 MHz. The transfer of NOE at these correlation factors is selective (Figs. 3 and 4). The Val(3) NH is irradiated and NOEs corresponding to antiparallel β -sheet conformation of the molecule are observed. The infinite chain model is utilized for the theoretical fit with $a = 2.2 \text{ \AA}$ (characteristic $\text{NH}_i\text{-C}_{i-1}^\alpha\text{H}$ distance in antiparallel β -sheet conformation). (\square) NOE on Val(2) C^αH , $x = 2.2 \text{ \AA}$ and $l = 0.2$, (+) NOE on Val(3) C^αH , $x = 2.8 \text{ \AA}$ and $l = 0.6$, (\diamond) NOE on Val(3) C^βH , $x = 3.6 \text{ \AA}$ and $l = 0.6$, where l is the leakage relaxation factor and $\omega\tau_c = 2.5$.

The assumption of a one-dimensional chain of equidistant spins to describe spin diffusion in a biomolecule is not as unreasonable as it may appear at first. Most often in a polypeptide the magnetization does go from one spin to the next in the backbone, which is more or less a transfer along a one-dimensional chain. For example, in a helical structure the shortest distance between adjacent NH protons ($\text{NH}_i\text{-NH}_{i+1}$) is between 2.5 and 2.8 \AA (49). Once the NH proton is disturbed, the dominant path for the migration of the magnetization is along the NH-NH chain in the helices. On the other hand, in extended structures the $\text{NH}_i\text{-C}_{i-1}^\alpha\text{H}$ distance is of the order of 2.2 \AA while the $\text{NH}_i\text{-C}_i^\alpha\text{H}$ distance is about 2.8 \AA . Here although the magnetization basically travels along a one-dimensional chain the interspin distance is not constant. Some amount of the magnetization also diffuses out to side chains where it finds either a blocked end or a sink such as a methyl group. These effects have not been included in this analysis explicitly and have been added in an ad hoc manner as a leakage term. As a next step, we propose to solve the spin-diffusion equation for the transient NOE case, to generalize it to a stochastic variation of interspin distance a , and to extend the equation to two or three dimensions.

APPENDIX. DEFINITIONS AND PROPERTIES OF ERROR FUNCTION (44-46)

The error function and its complement are defined as

$$\begin{aligned}\text{Erf}(z) &= (2/\pi^{1/2}) \int_0^z e^{-y^2} dy \\ \text{Erfc}(z) &= (2/\pi^{1/2}) \int_z^\infty e^{-y^2} dy = 1 - \text{Erf}(z).\end{aligned}\quad [\text{A1}]$$

For negative arguments, one obtains

$$\text{Erf}(-z) = -\text{Erf}(z)$$

and

$$\text{Erfc}(-z) = 1 + \text{Erf}(z).\quad [\text{A2}]$$

The limiting values of the Erf and Erfc are

$$\begin{aligned}\text{Erf}(0) &= 0, & \text{Erfc}(0) &= 1 \\ \text{Erf}(\infty) &= 1, & \text{Erfc}(\infty) &= 0 \\ \text{Erf}(-\infty) &= -1, & \text{Erfc}(-\infty) &= 2.\end{aligned}\quad [\text{A3}]$$

The error function under rational approximation (for $0 \leq z < \infty$) is given by

$$\text{Erf}(z) = 1 - (a_1\nu + a_2\nu^2 + a_3\nu^3 + a_4\nu^4 + a_5\nu^5)e^{-z^2} + \epsilon(z)$$

with

$$\begin{aligned}\nu &= 1/(1 + \mu z), & |\epsilon(z)| &\leq 1.5 \times 10^{-7} \\ \mu &= 0.3275911, & a_1 &= 0.254829592 \\ a_2 &= -0.284496736, & a_3 &= 1.421413741 \\ a_4 &= -1.453152027, & a_5 &= 1.061405429.\end{aligned}\quad [\text{A4}]$$

Expression [A4] has been used for calculating the numerical values of Erf(z) and Erfc(z) in the solutions described in the text.

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