

Stochastic Averaging Revisited

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1 Introduction

The extraction of molecular potentials and rates by modeling the dependence of spectra on thermodynamic state is one of the major contributions of magnetic resonance to molecular physics. We argue here that this entire endeavor is conceptually suspect due to the implicit factorization of spin and spatial degrees of freedom in calculating stochastic averages. All such averages have heretofore neglected spin-dependent energies in the potential for nuclear motion and are therefore not results of equilibrium statistical mechanics. We develop an averaging procedure from equilibrium statistical mechanics and find that it predicts large, previously unrecognized contributions to motionally averaged spin Hamiltonians which are directly proportional to *spatial* terms in the energy. We discuss the present state of the experimental evidence for the accepted average, with particular emphasis on indirect scalar couplings averaged by conformer equilibria, and find that the quality of presently available data cannot resolve the issue conclusively. The weakness of the theoretical basis of the accepted theory is also outlined.

2 The Traditional Stochastic Average

For over forty years it has been accepted¹⁻³⁶ that spin states are transported between spatial states with spin-independent rates. This unexamined assumption was clearly stated in the seminal work of Bloembergen, Purcell and Pound:¹ "The atom or molecule is simply a vehicle

by which the nucleus is conveyed from point to point. We thus neglect the reaction of magnetic moments of the nuclei upon the motion." This notion is the basis for all existing formalisms¹⁻³⁶ for calculating the magnetic resonance lineshapes of spin systems undergoing spatial rate processes — most importantly, chemical exchange. A well-known consequence is that the average value of a spin-Hamiltonian parameter (chemical shift, scalar coupling, dipolar coupling, etc.) in the fast-exchange limit is given by

$$\langle X \rangle = \sum_n p_n X_n, \quad (1)$$

where X_n is the value of this parameter in the spin Hamiltonian of the n^{th} spatial manifold and p_n is viewed as the probability of the system being in that manifold, irrespective of spin state. The sum may be over molecular eigenstates or over large groups of them, as when n indexes molecular conformers. The traditional prescription, which neglects spin energies, is to express the molecular partition function q as a sum of parts q_n associated with each indexed manifold. The probability for each manifold is $p_n = q_n/q$, and the ratio of two such probabilities is (in the absence of work terms)

$$p_n/p_{n'} = \exp[-\Delta A_{nn'}/RT] \quad (2a)$$

$$= \exp[(-\Delta U_{nn'} + T\Delta S_{nn'})/RT], \quad (2b)$$

where $\Delta A_{nn'} = -RT \ln(q_n/q_{n'})$ is the difference in the molar Helmholtz free energies of the manifolds. In Eq. 2b, the free energy differences have been divided into

differences in energy $\Delta U_{nn'}$ and entropy $\Delta S_{nn'}$. The connection to molecular energies is $\Delta U_{nn'} = N_A(E_n - E_{n'})$, where E_n is the common spatial contribution to free energy of the n^{th} manifold of spin states and N_A is Avogadro's number.

3 An Alternative Stochastic Average

The actual molecular energies may be written as $E_n^\gamma = E_n + E_\gamma(n)$, where γ indexes a spin eigenstate within the n^{th} manifold. Since spin Hamiltonians are constructed as traceless, the spin-dependent contributions $E_\gamma(n)$ sum to zero in each manifold. Nevertheless, the absence of the spin energy terms in the p_n indicates unambiguously that Eq. 1 is not derivable without approximation from equilibrium statistical mechanics.

We address the following questions. What is the exact equilibrium expression for the stochastically averaged parameters? For which systems will it differ measurably from Eq. 1? Do existing experiments decide the issue conclusively?

To proceed, we specialize to the case that the spin Hamiltonians in all significantly occupied spatial manifolds are mutually commuting. Then the spin eigenbasis $\{|\gamma\rangle\}$ is independent of spatial state and is the basis needed to describe the stochastically averaged spectrum. The spatially-averaged energy of a particular such spin eigenstate $|\gamma\rangle$ is

$$E_{\gamma} = \frac{\sum_n E_n^\gamma \exp(-A_n^\gamma/RT)}{\sum_n \exp(-A_n^\gamma/RT)} \quad (3a)$$

$$= \sum_n p_n^\gamma E_n^\gamma \quad (3b)$$

Note that Eq. 3 uses the complete manifold free energy, $A_n^\gamma = N_A E_n^\gamma - TS_n$, including spin terms, according to the prescription of equilibrium statistical mechanics. Each such summation is restricted to a particular spin state and the distribution among spatial states for each spin state is assumed to be the equilibrium distribution at the lattice temperature. Thus p_n^γ is the conditional probability of

being in the n^{th} spatial manifold, given that the spin state is $|\gamma\rangle$. As in the traditional formulation, no specification of the distribution of population among spin states is needed. Our hypothesis is that the spectral line positions for sufficiently fast exchange between spatial manifolds are the Bohr frequencies, $\nu_{\gamma\gamma'} = (E_\gamma - E_{\gamma'})/h$, corresponding to differences between the average energies of Eq. 3. The corresponding motionally averaged spin-Hamiltonian parameters are those which generate this spectrum.

As a simple illustration, consider a spin Hamiltonian with only two distinct eigenvalues, $\pm X_n/2$ (in Hz), for each n . Then the proposed alternative to Eq. (1) is (with $\gamma = \pm$)

$$\langle X \rangle = h^{-1} \sum_n (p_n^+ E_n^+ - p_n^- E_n^-) \quad (4a)$$

$$= (2h)^{-1} \sum_n [(p_n^+ - p_n^-)(E_n^+ + E_n^-) + (p_n^+ + p_n^-)(E_n^+ - E_n^-)] \quad (4b)$$

$$= \sum_n [(p_n^+ - p_n^-)E_n/h + \frac{1}{2}(p_n^+ + p_n^-)X_n] \quad (4c)$$

For the usual high-temperature case where $hX_n \ll kT$, the approximation $p_n \cong \frac{1}{2}(p_n^+ + p_n^-)$ is adequate, and the difference between the formulations of Eqs. 1 and 4 is essentially the sum over n of the first term in brackets of Eq. 4c. This difference vanishes at infinite or zero temperature and at all temperatures if either the E_n or the X_n are all degenerate. Cases without such degeneracy are the ones where $\langle X \rangle$ might provide information on molecular potentials. In these the difference term is of order $X_n E_n/kT$. Thus, it is not in general a small correction and can in fact dominate the temperature dependence over some ranges of the variables (Fig. 1). This new term in the spin Hamiltonian may be viewed as arising from the dependence of average molecular configuration on the spin Hamiltonian, in contrast to the usual analysis which includes only the dependence of the spin Hamiltonian on molecular configuration. Alternatively stated, because the distribution of molecules among the spatial manifolds (eg. conformers)

depends on spin, spatial energy differences between manifolds contribute to the statistically averaged frequencies for spin transitions. The product of a small spin-dependent probability difference multiplied by a large spatial energy difference gives a readily measured contribution to the magnetic resonance line position.

4 Test Systems

In both formulations it is possible ideally to predict the fast exchange observations without adjustable parameters. This would constitute a purely experimental test, the quality of which depends only on the experimental uncertainties. In practice there seems to be no case where NMR spectra of individual molecular eigenstates have been obtained separately and also as a thermal average.

Thus, it seems necessary to look to those situations where n indexes conformers. The experimental concept is simple and well-known. At low temperature, the spin Hamiltonian for each conformer can be determined, since, in the limit of negligible chemical exchange between them, separate spectra are seen for each. The relative areas of these spectra at each slow-exchange temperature provide the relative populations and thus the free-energy difference between conformers. A linear fit to the temperature dependence of this free-energy difference allows it to be decomposed into two terms, which can be viewed as an energy difference and an entropy difference if one additionally assumes that the temperature dependence of these is negligible over the experimental range.

Since a conformer is a set of molecular eigenstates, additional dependence on thermodynamic state (eg. temperature dependence) is possible due to averaging within this set. Theoretically, one has precisely the same problem in deciding how to take this average as for the averaging over conformers. However, if one can measure any such temperature dependence within the slow-exchange regime and extrapolate to fast-exchange, then the stochastic theory need not enter at this level.

Thus, we arrive at a set of criteria which need to be met for a compelling, fully experimental test of any theory relating

slow-exchange and fast-exchange spectra:

i) The system must have state-dependent rates such that measurements in both the slow- and fast-exchange regimes are possible. For fluids this typically requires barriers between conformers on the order of 10 kcal/mole.

ii) The state dependence of the conformer spin Hamiltonians and the free-energy differences must be measured in the slow-exchange region to allow extrapolation through the fast-exchange region. This is often the major source of uncertainty because of the small temperature range corresponding to slow-exchange. The difference in thermodynamic state between these regimes ideally is small or even zero, so as to minimize the propagation of errors due to phenomenological extrapolation. Using different NMR transitions or field conditions to measure the same spin Hamiltonian parameter can help in this regard; since the criterion for motional collapse varies with the transition observed, there is no minimum

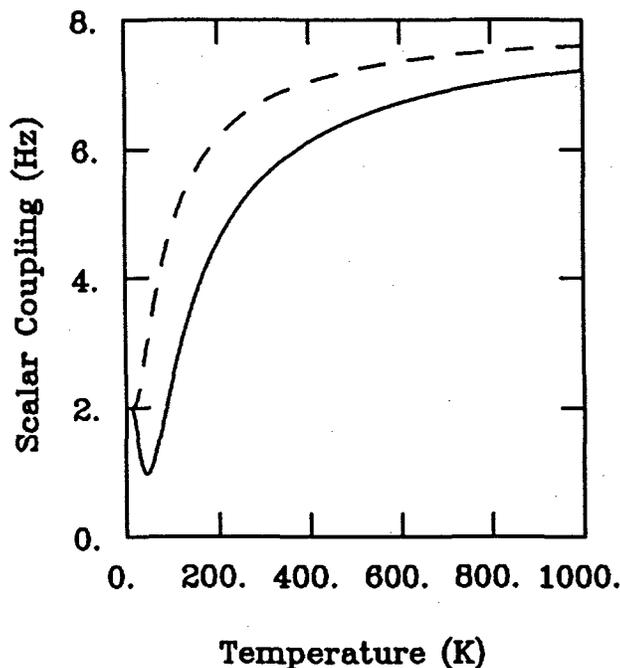


Figure 1. Traditional (dashed) and alternative (solid) stochastic averages for a simple two-conformer, two-spin system. Simulations have the general features of some substituted ethanes: a gauche coupling of 2.0 Hz, a trans coupling of 20.0 Hz, the trans conformer with a free energy 200 cal/mol greater than the doubly-degenerate gauche conformer.

difference in thermodynamic state between fast and slow exchange.

iii) Some or all of the fast-exchange data should fall outside the error bars on the predictions of one of the theories, thereby disproving it. The accepted and alternative theories embodied in Eqs. 1 and 3, respectively, have identical predictions for mutual exchange and whenever the occupied conformers are degenerate in spatial energy or in spin Hamiltonians. For two-site problems, the theories will typically differ measurably when the conformer free energies differ by $> 10^2$ cal/mole. When this difference exceeds 10^3 cal/mole, sensitivity will usually preclude observing the slow-exchange spectrum of the minor conformer. Figure 1 is a numerical comparison of the two theories for the simple case of two conformers and a two-spin system. It demonstrates that the predictions of the theories are different by a magnitude that should be measurable. There is also a qualitative difference: the sign of the temperature dependence of the fast-exchange spin Hamiltonian parameter is opposite to that of the accepted theory over part of the temperature range. This behavior is inconsistent with Eq. 1 regardless of how the p_n are calculated.

The above conditions are not extremely restrictive; a substantial fraction of the molecules whose conformer equilibria have been studied by solution-state NMR fall into this range of free-energy differences. Since the accepted theory has been in increasing use for four decades, it might be expected that it would have substantial and diverse experimental support. While it is difficult to have confidence in the completeness of a search through such a large literature, we are as yet unaware of any data set that meets the criteria above. Thus, no theory has presently been evaluated by this seemingly reasonable standard.

The only theories ever considered previously are of the form of Eq. 1. Numerous authors have noted failures in its application,¹⁹⁻²¹ but these have usually been plausibly attributed to inadequacies in the data, most commonly uncertainties of conformer assignment or unmeasured temperature dependence of a conformer spin Hamiltonian.

5 Substituted Ethanes

Substituted ethanes in solution¹⁴⁻²⁴ are the most studied systems and include cases which nearly meet the criteria of the previous section. Figure 2 illustrates, with the example of 1-fluoro-1,1,2,2-tetrachloroethane, the trans and gauche rotational isomers which interconvert at convenient rates. Since the two gauche conformers are mirror-images, there are only two magnetically distinct conformers, one with the H and F atoms trans to one another and the other a degenerate pair of gauche rotamers at the other two staggered positions of the dihedral angle of rotation about the carbon-carbon single bond. Increasing temperature carries the system from the slow-exchange limit to the fast-exchange limit without a change in composition or phase. The fast-exchange, three-bond vicinal coupling $\langle J_{HF} \rangle$ is known to be temperature dependent and this has been attributed to the averaging, according to Eqs. 1 and 2, between distinct values J_t and J_g in the trans and gauche conformers, respectively.¹⁵⁻¹⁶ Unlike chemical shifts, scalar couplings do not require a nominally temperature-independent reference resonance to compensate for the usual uncontrolled shifts of internal field with temperature. Also, scalar couplings are generally believed to be less sensitive to intermolecular interactions which could provide a confounding mechanism of temperature dependence.

For the particular case of 1-fluoro-1,1,2,2-tetrachloroethane, a test as

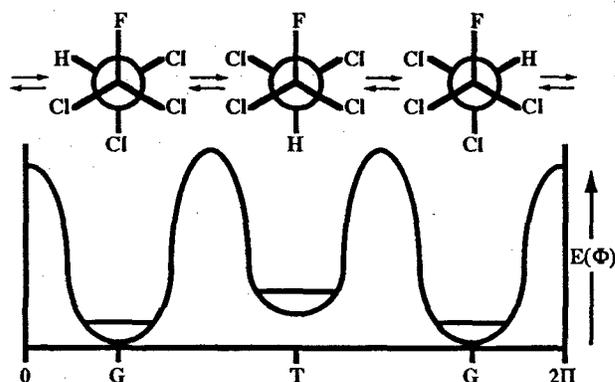


Figure 2. Potential energy versus dihedral angle (ϕ) for the conformers of 1-fluoro-1,1,2,2-tetrachloroethane.

described of the stochastic averaging theories is prevented by the failure to resolve the coupling J_g .³⁷ This quantity has an experimental upper bound of 2 Hz. If it is assumed that J_g is independent of temperature, then the data are consistent with the accepted theory.¹⁶ However a temperature dependence of 0.005–0.01 Hz/K between 150 K, where slow-exchange observations have been made on the ^{19}F resonances, and 300 K, where the ^1H spectrum is motionally averaged, would allow our alternative stochastic average in the form

$$\langle J_{\text{HF}} \rangle = h^{-1}(E_{\alpha\alpha} - E_{\beta\alpha} - E_{\alpha\beta} + E_{\beta\beta}) \quad (5)$$

to fit the data as well or better.

Reason to suspect such a temperature dependence can be found from a close reading of the literature on the related system 1-fluoro-1,1,2,2-tetrabromoethane.²² A value of $J_g = 2.4 \pm 0.3$ Hz in dimethylether at 188 K can be measured from published data,³⁹ but has been reported as 1.7 Hz at 180 K in the same solvent.²³ In CFCl_3 this coupling has been tabulated as 1.15 Hz from 171 to 178 K,²² but our recent fits of the spectrum (at 171 K only) in reference 23 indicate $J_g = 1.5 \pm 0.3$ Hz. Thus the reported absence of temperature dependence to three significant figures is dubious and further experimental work is needed.

6 Discussion

The present conformer model is by no means the most refined version of Eq. 3 possible, but has the advantage of employing only quantities that are experimentally measured on the same sample. Continuous classical-mechanical forms of the present theory are readily written down and the differences from the accepted theory persist. Alternatively, the quantum partition functions could be modeled. Such modifications would introduce unmeasured parameters. Such extensions might be warranted after improvements in the experimental data base.

It is of interest to note that the same theoretical prediction for $\langle J_{\text{HF}} \rangle$ obtained by use of Eqs. 3 and 5 also results if the same conformer model is evaluated using Eq. 4

with $X_n = J_n$ and + and - indicating, respectively, triplet and singlet zero-field eigenstates. Thus, no measurable field dependence of $\langle J_{\text{HF}} \rangle$ is predicted by the alternative theory, which is not obvious because of the entanglement of different spin Hamiltonian parameters in the spin energies.

The theoretical justification for Eq. 1 and related propositions is also weaker than has been appreciated. Such an average follows from dynamic models¹⁻³⁶ based on the assumption that spin states in superposition are transported between different spatial states in perfect concert. Any such model exists in a truncated Liouville space that excludes superpositions of states that differ in both their spin and spatial factors. Whether such a truncated space suffices to describe magnetic resonance lineshapes is an open question. What is clear is that such a space cannot describe the approach to equilibrium of the total system, since this requires spin-dependent rates between spatial manifolds. Thus a full dynamic solution is needed in this complete Liouville space. One result of such a full solution will be the equilibrium average spin energies of Eq. 3. Less clear is under what dynamic assumptions either these energies or those that follow from Eq. 1 will describe the fast-exchange spectrum. In any case the problem is richer than has been appreciated.

The accepted idea of how to calculate a stochastically averaged spectrum is universal in the literature of magnetic resonance, underlying the interpretation of average chemical shifts, dipolar couplings, tunnel splittings, quadrupole couplings, and hyperfine interactions. In most situations the number of unknowns is such that it is not possible to verify the form of the stochastic average, but valuable information could be obtained if the correct form were known. If the traditional ideas are generally incorrect, many thousands of experiments need to be reinterpreted with forms of the present theory to in fact obtain the quantitative information on molecular structure that they were designed to yield. Ultimately, the choice of theory will be decided by a preponderance of data. The present work indicates clearly that the issue must be reopened and is a first step in the reexamination of the experimental basis of Eq. 1. Accurate experimental measurements

of systems such as those discussed here will be needed in order to discriminate between the stochastic theories, as opposed to fitting free parameters according to one or the other theory.

Precisely the same issue of how to calculate a stochastic average also arises in the (*ab initio*) theoretical calculation of a measurable spin Hamiltonian from expectation values of the underlying molecular eigenstates, which are almost never sufficiently long-lived to measure individually by magnetic resonance. Application of the correct statistical prescription will often be needed to in fact test experimentally whether the quantum-mechanical part of the calculation is adequate.

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