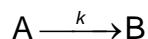# NMR Relaxation

Phenomenology and Experimental Considerations

Review of First-Order Rate Kinetics

Imagine the simple first order process:

$$A \xrightarrow{\ k\ } B$$

The time-dependence of the conversion of A to B depends upon the amount of A present according to the following expression:

$$\frac{\Delta[A]}{\Delta t} = -k[A]$$

or in terms of infinitesimally small variations:

$$\frac{d[A]}{dt} = -k[A]$$

This expression may be rearranged to produce the following

$$\frac{d[A]}{A} = -kdt$$

Integration leads to

$$\int \frac{d[A]}{A} = -k\int dt$$

$$\ln[A] = -kt + C$$

$$[A] = [A]_0\, e^{-kt}$$

k is known as the rate constant of the first-order process or alternatively as the time-constant of the single-exponential reaction.

Nuclear Induction

If a macroscopic sample of magnetically active nuclei is placed in a static magnetic field, a polarization or macroscopic magnetization will be produced *within the sample.* This phenomenon is known as *nuclear induction.*
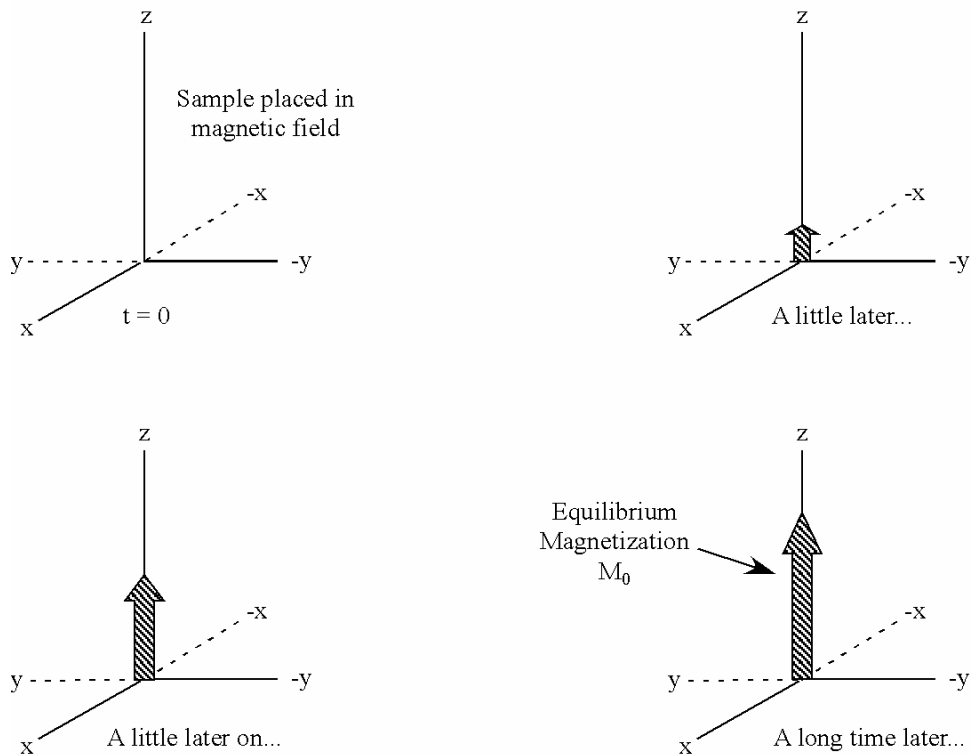
This induced magnetization does not arise instantaneously, but instead accumulates at an exponential rate.

If we define the orientation of the static magnetic field to be along and z-direction, then the induced polarization will also be along the z-axis.

Again, the induced magnetization accumulates at an exponential rate.

$$M(t) \propto 1 - e^{-Rt}$$

A geometrical picture should help us develop a more intuitive sense of the effect:

z

Sample placed in
magnetic field

-x

y

-y

x   t = 0

z

-x

y

-y

x   A little later...

z

-x

y

-y

x   A little later on...

z

Equilibrium
Magnetization
M_0

-x

y

-y

x   A long time later...

## Z-axis Recovery from Perturbation: Longitudinal Relaxation

If we allow such a macroscopic magnetization to establish itself and then apply resonant RF irradiation to tip the vector away from the static field axis, and then monitor the magnitude of the magnetization *along the z-axis* we would find that the system will recover, or *relax* back to the original state at exactly the same rate as for the induction experiment.

A concise mathematical expression for this behavior may be written as:

$$\frac{M(\tau) - M(\infty)}{M(0) - M(\infty)} = e^{-\tau/T_1}$$

wherein *M*(0) is the magnetization immediately following the perturbation, M(∞) is the fully restored equilibrium magnetization and M(τ) is the magnetization at an interval, τ, following the perturbation and T1 is the time constant for the exponential recovery ($1/T_1 = R_1$).

Again, the geometrical analysis may provide a clearer sense of the physics:
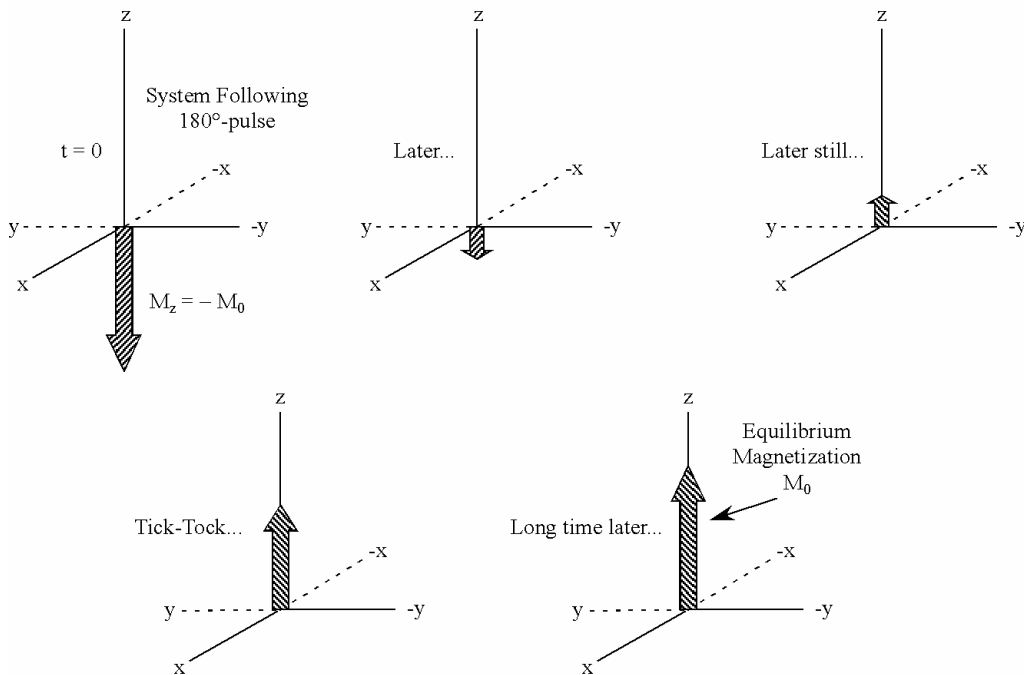
The *rate* of recovery (the relaxation rate) of the magnetization along the z-direction does not depend on the initial state of the system. This means that the relaxation rate along the z-direction does not depend upon the extent of perturbation, i.e., the rate of recovery will not depend on whether we used a 30°- or 60°- or 120° pulses instead of the 180°-pulse.

Note that although the *rate* depends only upon the relative change in the amplitude, as we saw in the analysis of the first-order reaction, the *actual value* of the observable depends upon both the rate and the initial value of the observable.

Relaxation in the XY-Plane: Transverse Relaxation

In the preceding example we monitored the relaxation effects following an inversion pulse, a 180°-pulse. Consider an alternative experiment in which we apply a 90°-pulse and again monitor the response of the system.

If we monitor the recovery along the z-direction we would measure the exact same rate as in the previous example.

If in this same experiment we were to monitor the amplitude of the magnetization along either the x- or y-directions, we would again find that the rate of change was exponential.

We would also discover that the rate of change along the x-direction was exactly the same as the rate of change along the y-direction.

Finally, we would find that rate of change in the x- or y-directions would differ from the rate at which magnetization recovered along the z direction.

Specifically, we would observe that the amplitude of the magnetization decreased at a *faster* rate in the xy-direction that the z-direction.

The results are shown schematically summarized below:
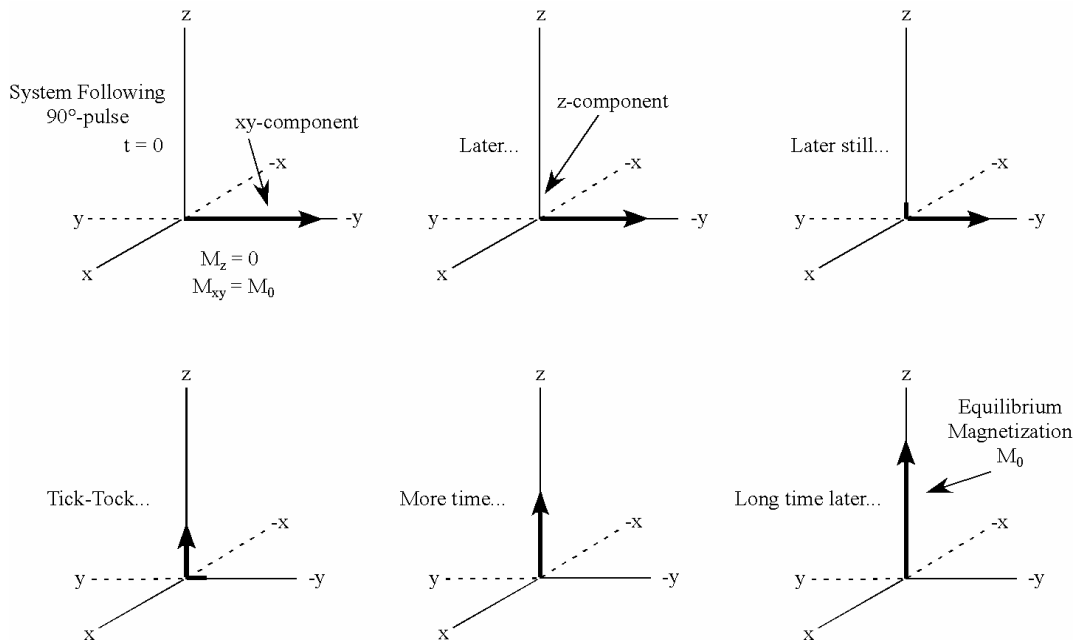
Bloch's Equations

A phenomenological equation is one that is derived to account for experimentally observed behavior. Contrast this with a theoretical equation that expresses predicted behavior based on a hypothetical model.

Bloch generated as series of expressions that account for observed dynamics of the macroscopic magnetization. The resulting expressions are known as Bloch's equations:

$$\frac{d}{dt}M(t) = \gamma M(t) \times B(t) - R\left[M(t) - M_0\right]$$

M_0 is the equilibrium value of M (its value in the absence of perturbations), and the inherent *time-dependence* of the components is emphasized.

In Cartesian coordinate space, the magnetization may be decomposed into a series of differential equations along the x-, y- and z-axes:

$$\frac{d}{dt}M_x = \gamma\left(M_y B_0 + M_z \sin(\omega t)\right) - \frac{M_x}{T_2}$$

$$\frac{d}{dt}M_y = -\gamma\left(M_x B_0 + M_z \cos(\omega t)\right) - \frac{M_y}{T_2}$$

$$\frac{d}{dt}M_z = -\gamma\left(M_x \sin(\omega t) - M_y \cos(\omega t)\right) - \frac{M_z - M_0}{T_1}$$

Note that Bloch's equations imply first-order relaxation, i.e., the recovery from perturbation is single-exponential.

We may also write Bloch's equations in matrix form. In this case, *M(t)* is a vector which may be written as:

$$M(t) = \begin{pmatrix} M_x(t) \\ M_y(t) \\ M_z(t) \end{pmatrix} = \begin{pmatrix} M_x(t) & M_y(t) & M_z(t) \end{pmatrix}$$

B(t) is also a vector and in general may be written as

$$B(t) = \begin{pmatrix} B_x(t) & B_y(t) & B_z(t) \end{pmatrix}$$

If we consider only the applied static magnetic field, we may write:

$$B = \begin{pmatrix} 0 & 0 & B_0 \end{pmatrix}$$

This expression indicates that the magnetic field has no time-dependence and is aligned along the z-direction.

In the more general sense we might include additional fields due to RF pulses, in this case we would write

$$B = \begin{pmatrix} B_1 \cos(\omega t) & -B_1 \sin(\omega t) & B_0 \end{pmatrix}$$

the explicit time-dependence of the B_1 field (RF) is included via the trigonometric factor, e.g., it is an oscillating field.

The *relaxation operator*, R, accounts for the propensity of the magnetic moment to reestablish its equilibrium polarization subsequent to its perturbation by an external source.

The general form of R may be written equivalently as a *relaxation matrix* as shown below:

$$R = \begin{pmatrix} m_{xx} & m_{xy} & m_{xz} \\ m_{xy} & m_{yy} & m_{yz} \\ m_{zx} & m_{zy} & m_{zz} \end{pmatrix} = \begin{pmatrix} R_{xy} & 0 & 0 \\ 0 & R_{xy} & 0 \\ 0 & 0 & R_z \end{pmatrix} = \begin{pmatrix} 1/T_2 & 0 & 0 \\ 0 & 1/T_2 & 0 \\ 0 & 0 & 1/T_1 \end{pmatrix}$$

The nonzero elements of R correspond to the rates of decay/recovery of the macroscopic magnetic moment (polarization), which we observe to be a single exponential.
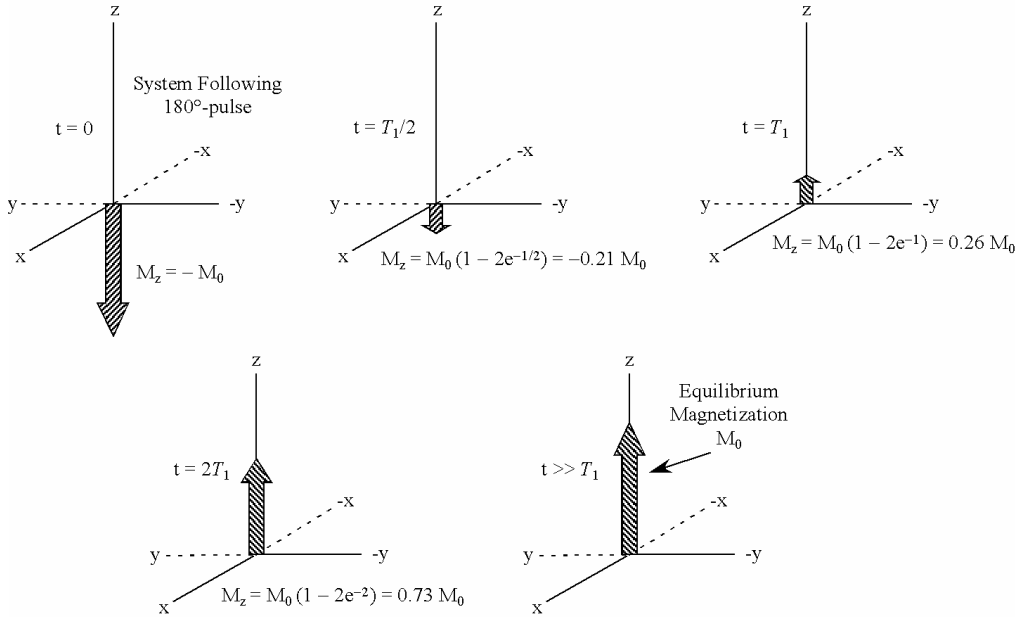
The relaxation rates parallel, $1/T_1$, and perpendicular, $1/T_2$, to the direction of the external magnetic field are distinct, as per common observation.

Relaxation in the z-direction is named longitudinal relaxation or spin-lattice relaxation and the time-constant is T_1.
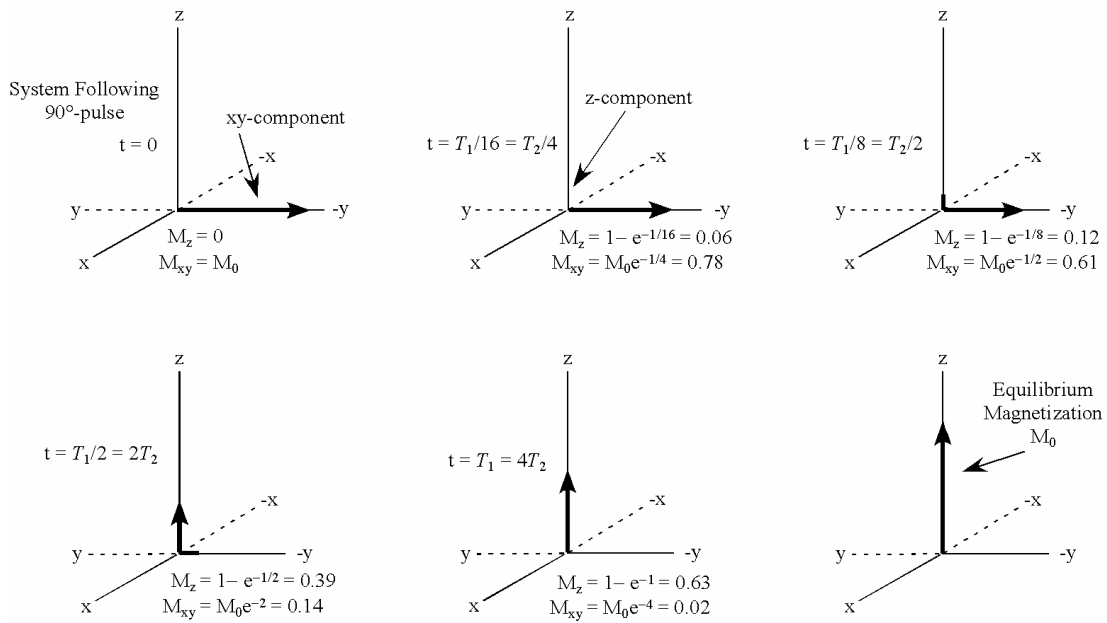
Relaxation in the xy-plane is named transverse relaxation or spin-spin relaxation.

We can now reconsider the phenomena of relaxation again with a more quantitative view.

Longitudinal Relaxation

System Following 180°-pulse

$t = 0$
$M_z = -M_0$

$t = T_1/2$
$M_z = M_0 (1 - 2e^{-1/2}) = -0.21 \, M_0$

$t = T_1$
$M_z = M_0 (1 - 2e^{-1}) = 0.26 \, M_0$

$t = 2T_1$
$M_z = M_0 (1 - 2e^{-2}) = 0.73 \, M_0$

$t \gg T_1$
Equilibrium Magnetization M_0

Transverse Relaxation

System Following 90°-pulse

$t = 0$
xy-component
$M_z = 0$
$M_{xy} = M_0$

$t = T_1/16 = T_2/4$
z-component
$M_z = 1 - e^{-1/16} = 0.06$
$M_{xy} = M_0 e^{-1/4} = 0.78$

$t = T_1/8 = T_2/2$
$M_z = 1 - e^{-1/8} = 0.12$
$M_{xy} = M_0 e^{-1/2} = 0.61$

$t = T_1/2 = 2T_2$
$M_z = 1 - e^{-1/2} = 0.39$
$M_{xy} = M_0 e^{-2} = 0.14$

$t = T_1 = 4T_2$
$M_z = 1 - e^{-1} = 0.63$
$M_{xy} = M_0 e^{-4} = 0.02$

Equilibrium Magnetization M_0

Experimental Determination of T_1: Gated Inversion Recovery Experiment

The gated inversion recovery pulse sequence (IR) makes use of a 180°(x)-pulse followed by a delay during which time T_1 relaxation occurs, and is followed by a 90°(x)-pulse which allows the recovered magnetization to be measured:
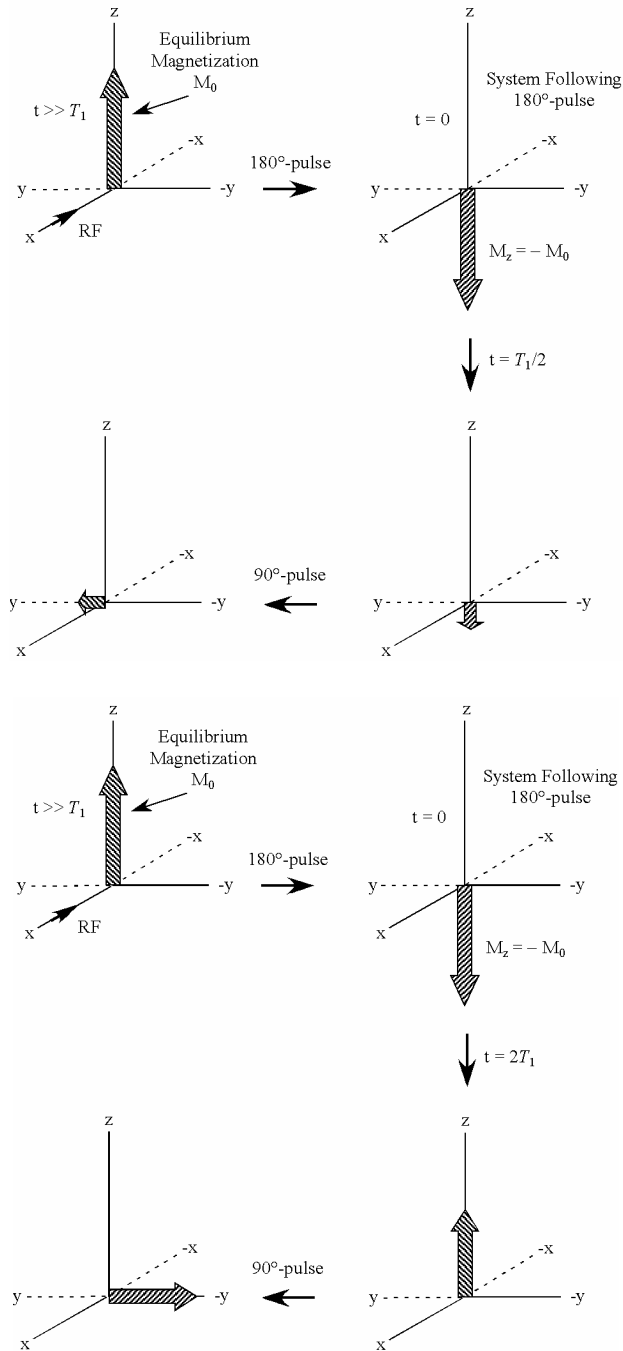
The IR experiment is repeated with an array of delays, τ, between the 180°-pulse and 90°-pulse that cover the range from complete inversion through complete recovery.

It is inconvenient to write vector diagrams and a shorthand notation has been adopted to describe pulse sequences:

$$T_d \; - \; 180^{\circ}_x \; - \; \tau \; - \; 90^{\circ}_x \; - \; \text{detect(FID)}$$

wherein T_d represents a delay interval during which the spin system returns to (virtually complete) equilibrium.

In the inversion recovery experiment, typically 10-20 delays are employed to support robust fitting of the intensity versus time data.

We can rearrange our original expression predicting the recovery of longitudinal magnetization following a perturbation to generate a method for analyzing the IR results:

$$\frac{M(\tau) - M(\infty)}{M(0) - M(\infty)} = e^{-\tau/T_1}$$

$$M(\tau) - M(\infty) = \left(M(0) - M(\infty)\right) e^{-\tau/T_1}$$

$$M(\tau) = M(\infty) + \left(M(0) - M(\infty)\right) e^{-\tau/T_1}$$

The expression above remains completely general, under the specific conditions of the IR experiment, $M(0)$ should be identical to $-M(\infty)$, in which case we obtain:

$$M(\tau) = M(\infty) + \left(M(0) - M(\infty)\right) e^{-\tau/T_1}$$

$$= M(\infty) + \left(-M(\infty) - M(\infty)\right) e^{-\tau/T_1}$$

$$= M(\infty) + \left(-2M(\infty)\right) e^{-\tau/T_1}$$

$$M(\tau) = M(\infty)\left(1 - 2e^{-\tau/T_1}\right)$$

In addition to the variable delay between the 180°-pulse and 90°-pulse we must also use an additional delay between experiments to insure that the spin system is at equilibrium at the beginning of each experiment.

The delay, T_d, used between experiments must be > 5 T_1 intervals:

$$M(\tau) = M(\infty)(1 - 2e^{-\tau/T_1}) = M(\infty)\left(1 - 2e^{-5}\right) = 0.99 M(\infty)$$

In a properly recorded IR experiment, the observed magnetization varies from -M_0 to +M_0, thus producing a $2M_0$ range in amplitude. Alternative methods such as saturation recovery produce only an amplitude range of M_0. The challenges associated with proper implementation of IR are significant however. First, there is the issue of setting a proper recovery delay (T_d), which must be greater than $5 \times T_1$ values. This dependency compromises the sensitivity of the experiment. More subtle, but of equal importance is the fact that accurate fitting of the data requires that the value of $M(\infty)$ be established, e.g., measurement of the intensity of the magnetization at recovery intervals approaching $5 \times T_1$, which likewise defeats sensitivity. Both of these considerations can be compensated by employing a three parameter fit to the data:

$$M(\tau) = M(\infty) + \left(M(0) - M(\infty)\right)e^{-\tau/T_1}$$

An important alternative of the inversion recovery approach is due to Ray Freeman and Howard Hill known as the Freeman-Hill modification (FHIR). This experiment combines conventional gated inversion recovery with a second simple observe experiment. The timing diagram of this experiment is given as:

$$T_d \ - \ 180^{\circ}_x \ - \ \tau \ - \ 90^{\circ}_x \ - \ \text{FID}_1$$
$$T_d \qquad\qquad - \qquad\qquad \text{FID}_2$$

Data from the two experiments are combined in the host computer memory as the difference between FID_2 and FID_1. The result of the modification is that the time dependence of the recovery is converted into the following form:

$$\text{FID}_2 - \text{FID}_1 = M(\infty) - M(\infty)(1 - 2e^{-t/T_1}) = M(\infty) - M(\infty) + M(\infty)e^{-t/T_1} = 2M(\infty)e^{-t/T_1}$$

There are several advantages to the FHIR approach. Establishing the values of $M(0)$ and $M(\infty)$ are no longer necessary. Waiting for full recovery of equilibrium magnetization is likewise no longer necessary since the response of the system is truly exponential, e.g., selection of $T_d < 5 \times T_1$ only scales the sensitivity of the experiment. Finally, if the recovery if biphasic, the data could be fitted using 4 parameters as opposed to 6 (generally impossible).

Experimental Determination of T_2: CPMG variation of the Hahn Echo

Although in principle the measurement of the transverse relaxation could be derived from a simple 90°-detect pulse scheme, complication in the measurement of T_2 arises due to Larmor precession and the limited spatial homogeneity of the sample chamber.

If we consider a sample composed of spins in a single chemical environment, i.e., a single chemical shift, then we could set our carrier frequency to that exact resonance.

In such a situation, if we applied an exact 90°(x)-pulse then the spins would be rotated exactly onto the the –y-axis as we have previously seen:

x-polarized RF pulse causes magnetization
to rotate towards -y axis
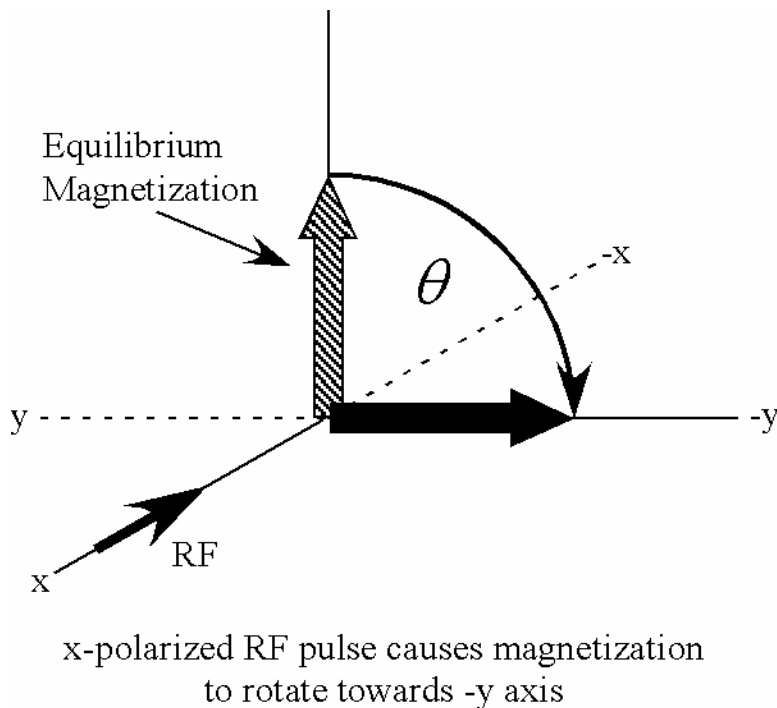
In our perfect-world experiment, the magnitude of the magnetization along the y-direction would decrease without complication, due to T_2 relaxation as we have already noted.

In a real-world experiment however, the magnetic field in different parts of the sample varies due to the finite field homogeneity.

Thus spins in the various regions of the sample cell have different Larmor frequencies:

$$\omega = -\gamma B_{eff} = -\gamma \left(B_0 + \Delta B_0 \right)$$

wherein ΔB_0 represents microscopic field gradients.

In a standard lock-in detection system, spins with resonance frequencies that are higher than the carrier frequency rotate in one sense, while spins with resonance frequencies lower than the carrier frequency rotate in the opposite sense:
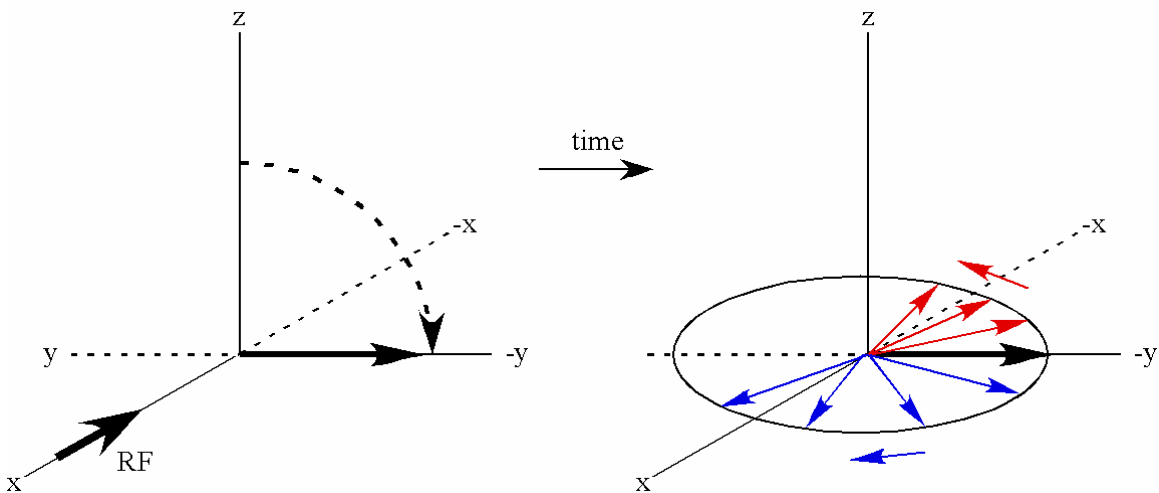

In a simple experiment the decrease in measured magnitude (intensity) will thus be the sum of an artifactual component arising from finite field homogeneity (inhomogeneous broadening) and the actual T_2 relaxation. Distinguishing these effects is critical to accurate measurement of T_2.

The experiment is named the *Carr-Purcell-Meiboom-Gill* experiment, CPMG more commonly, and the approach is based on the original spin-echo technique invented by Erwin Hahn.

Imagine a system that contains multiple spins with different chemical shifts. In this situation, perhaps none of the spins may resonate at the carrier frequency. These spins will precess about the z-axis in the same ways as we have just discussed.

Hahn discovered that the direction of the precession could be reversed by applying a 180°-pulse – this experiment has become known as the Hahn spin-echo experiment because the intensity of monitored magnetization appears to first decrease and the increase again.

The Spin-Echo Experiment
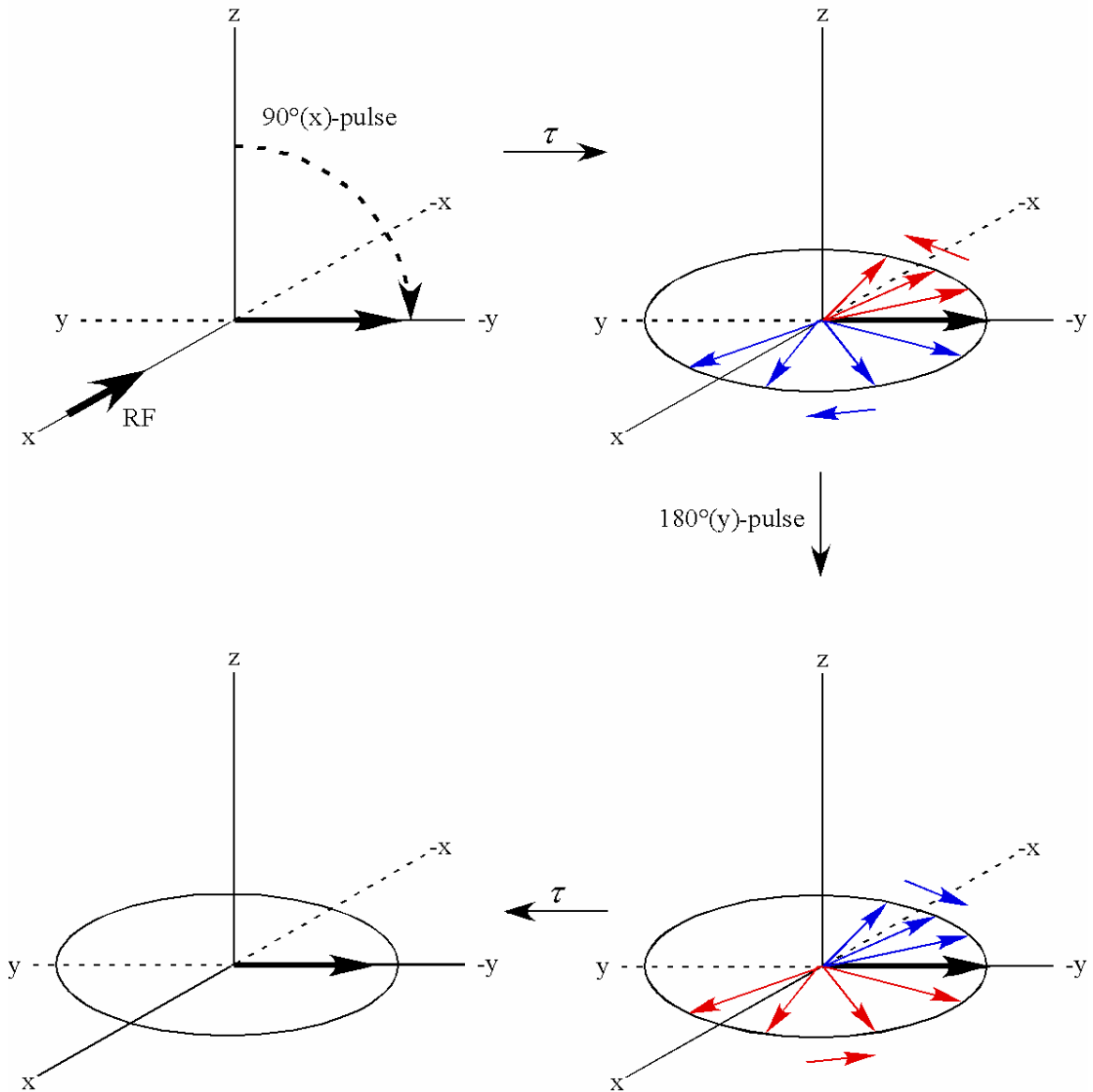
In this experiment, the amplitude of magnetization recovered at the end of the sequence is not the original amount but is less due to T_2 relaxation:

$$M_{xy}(t) = M(\infty)e^{-2\tau/T_2}$$

wherein 2τ is the interval during which time the spins are allowed to precess in the xy-plane.

In our shorthand notation we would write this sequence as:

$$90^{\circ}_x \: - \: \tau \: - \: 180^{\circ}_y \: - \: \tau \: - \: \text{detect}$$

In the CPMG variant, the $(\tau \: - \: 180^{\circ}_y \: - \: \tau)$ component of the Hahn echo is repeated, thus allowing an array of time intervals to be produced.

The CPMG sequence may thus be written as:

$$90^{\circ}_x \: - \: \left(\tau \: - \: 180^{\circ}_y \: - \: \tau \right)_n \: - \: \text{detect}$$

The total length of the transverse relation interval will thus be defined by the length of a CPMG-cycle multiplied by the number of cycles.

Origins of NMR Relaxation: Motional Coupling

A careful analysis of the interaction of light and matter; which lies beyond the scope of the current discussion, leads to the conclusion that a spin subjected to a fluctuating magnetic field will be induced to undergo transitions between all available energy levels at a rate that is proportional to the intensity of field.

QM time-dependent perturbation theory provides us with an expression known as *Fermi's golden rule*:

$$W_{i \to j} \equiv \text{transition probability per unit time}$$

$$= \frac{1}{\hbar^2 t} \int_0^t \int_0^t \langle i | H(t') | j \rangle \langle j | H(t'') | i \rangle e^{-i\omega_{ij}(t'-t'')} dt' dt''$$
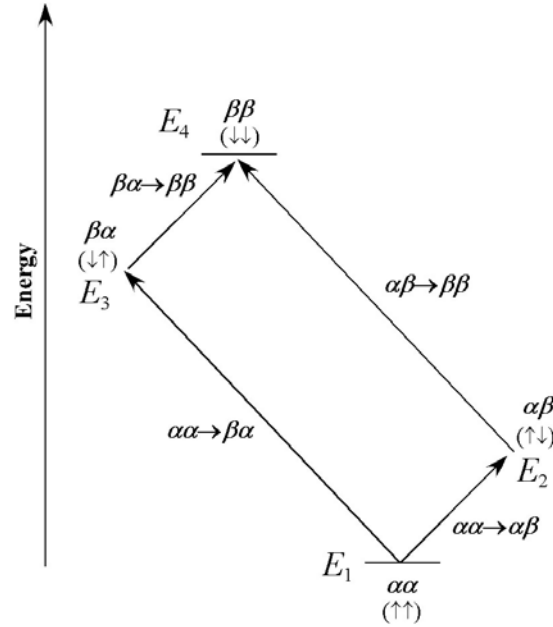
wherein ω_{ij} is the transition frequency (rad s^{-1}).

The expression is the Fourier transform of the Hamiltonian composed with itself and evaluated over time.

This expression is entirely general, and is used to calculate the transition rates stimulated by any sort of time-dependent magnetic field.

The magnetic field may be external, as in the magnetic component of an applied RF pulse or it may arise from within the sample itself dues to modulations of field-spin or spin-spin interactions that are modulated by molecular reorientation.

For a pair of uncoupled spin-1/2 nuclei the W_{ij} may defined with respect to our energy level diagram:

$$W_0 = W\left(\alpha\beta \leftrightarrow \beta\alpha\right)$$

$$W_{1I} = W\left(\alpha\alpha \leftrightarrow \beta\alpha\right); \quad W_{1I}' = \left(\alpha\beta \leftrightarrow \beta\beta\right)$$

$$W_{1S} = W\left(\alpha\alpha \leftrightarrow \alpha\beta\right); \quad W_{1S}' = W\left(\beta\alpha \leftrightarrow \beta\beta\right)$$

$$W_2 = W\left(\alpha\alpha \leftrightarrow \beta\beta\right)$$

In the presence of coupling ($J > 0$), the energy levels, E_1 and E_4 increase while E_2 and E_3 decrease.

The transition rates due to external RF irradiation are given by the following expression:

$$W_{i \rightarrow j} = 2\pi\gamma_I\gamma_S B_1^2 \left\langle i\left|H_{RF}\left(t\right)\right|j\right\rangle^2 \delta\left(\omega_{ij} - \omega_1\right)$$
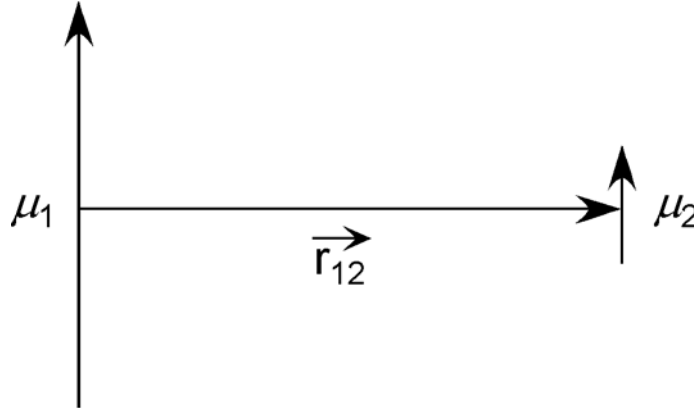
wherein $\delta\left(\omega_{ij} - \omega_1\right)$ is a delta function in frequency.

For spin-1/2 nuclei at moderate applied field strength, the dominant internal field is due to the dipolar interaction. The classical expression for the energy of a pair of point-dipoles is given by:

$$E = \frac{\vec{\mu}_I \cdot \vec{\mu}_S}{r_{IS}^3} - 3\frac{\left(\vec{\mu}_I \cdot \vec{r}_{IS}\right) \cdot \left(\vec{\mu}_S \cdot \vec{r}_{IS}\right)}{r_{IS}^5}$$

wherein $\vec{r}_{IS}$ is the vector joining $\vec{\mu}_I$ and $\vec{\mu}_S$.

The following diagram defines the physical picture:

Transformation from the classical to the QM expression is accomplished using the following substitution:

$$\vec{\mu}_I = \hbar\gamma_I\vec{I}\,; \quad \vec{\mu}_S = \hbar\gamma_S\vec{S}$$

The energy of the interaction in the QM formalism is expressed as a Hamiltonian:

$$H_{dd} = \frac{1}{2}\frac{\gamma_I\gamma_S}{r_{IS}^3}\left(1-3\cos^2\theta\right)\left(3I_zS_z - \vec{I}\cdot\vec{S}\right)$$

wherein we have also converted the expression into polar coordinates, in which θ is the angle between r and the applied magnetic field (assume z-direction).

Note that the interaction energy depends upon the cube of the internuclear distance and the orientation between the two spins and the applied magnetic field.

As the molecule tumbles in solution, the magnitude of the vector between the two dipoles remains constant, but the orientation will clearly change, leading to a modulation of the energy.

The stimulated transition rate may thus be written as:

$$W_{i\to j} = \frac{1}{\hbar^2 t}\int_0^t\int_0^t \langle i|H_{dd}(t')|j\rangle\langle j|H_{dd}(t'')|i\rangle e^{-i\omega_{ij}(t'-t'')}dt'dt''$$

$$W_{i\to j} \propto \int_{-\infty}^{\infty} G(t')e^{-i\omega_{ij}t'}dt' = 2\int_0^{\infty} G(t')e^{-i\omega_{ij}t'}dt'$$

.

The function $G(t)$ reflects the degree to which the molecule reorients in a given time interval, and is thus named the autocorrelation function. The geometric picture commonly employed describes the molecular motion as beginning in some arbitrary instant with a some orientation – at later times the molecule will have tumbled away from its original position

The integral represents a Fourier transformation of the time domain function, $G(t)$, e.g., a frequency-domain representation of the motion.

The exact form of the correlation depends upon the nature of the motion. For Brownian motion, $G(t)$, may be suitably modeled as an exponential decay:

$$G(t) = e^{-t/\tau_c}$$

wherein the *correlation time*, τ_c, characterizes the rate of tumbling. For a roughly spherical molecule, hydrodynamic theory predicts that:

$$\tau_c = \frac{\eta V_{eff}}{k_b T}$$

wherein η is the solution viscosity, V_{eff} is the effective molecular volume, k_b is Boltzmann's constant and T is the temperature in K.

The Fourier transform of the correlation function is known as a *spectral density function*, $J(\omega)$, and describes the frequency distribution the motion.

The Fourier transform of an exponential function is a *Lorentzian function*, and thus we may write that:

$$J(\omega) = \frac{C\tau}{1 + \omega^2 \tau^2}$$

The value of the spectral density thus depends both on the transition frequency and the correlation time:
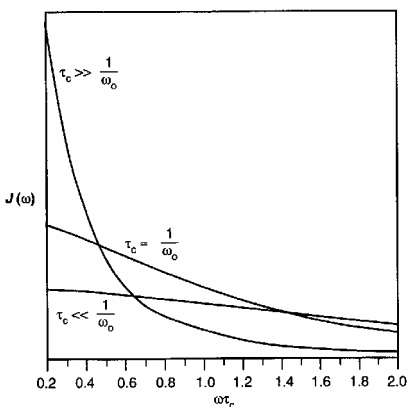

Figure 8.1 from Becker, E.D. (2000) High Resolution NMR. Academic Press, New York

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Notice that for $\omega\tau \ll 1$ that the value of $J(\omega)$ decreases rapidly as a function of $\omega\tau$, whereas for $\omega\tau \gg 1$ the opposite is true.

If we substitute the dipolar coupling Hamiltonian into the transition rate expression, we will obtain the following:

$$W_0 = W(\alpha\beta \leftrightarrow \beta\alpha) \propto \frac{\gamma_I\gamma_S}{r_{IS}^6} J(\omega_I - \omega_S) \approx \frac{\gamma_I\gamma_S}{2r_{IS}^6} J(0) \text{ when I=S}$$

$$W_{1I} = W(\alpha\alpha \leftrightarrow \beta\alpha) \approx W(\alpha\beta \leftrightarrow \beta\beta) \propto \frac{\gamma_I\gamma_S}{r_{IS}^6} J(\omega_I)$$

$$W_{1S} = W(\alpha\alpha \leftrightarrow \alpha\beta) \approx W(\beta\alpha \leftrightarrow \beta\beta) \propto \frac{\gamma_I\gamma_S}{r_{IS}^6} J(\omega_S)$$

$$W_2 = W(\alpha\alpha \leftrightarrow \beta\beta) \propto \frac{\gamma_I\gamma_S}{r_{IS}^6} J(\omega_I + \omega_S)$$

We may now also write the rates (again, rate constants actually) of longitudinal and transverse relaxation in term of these transition rates to obtain the following expressions:

$$R_1^H({}^1H,{}^{13}C) = \frac{1}{T_1} = \frac{C\gamma_H^2\gamma_C^2}{r_{HC}^6}\left[J(\omega_H - \omega_C) + 2J(\omega_H) + J(\omega_H + \omega_C) \right]$$

$$R_1^C({}^1H,{}^{13}C) = \frac{1}{T_1} = \frac{C\gamma_H^2\gamma_C^2}{r_{HC}^6}\left[J(\omega_H - \omega_C) + 2J(\omega_C) + J(\omega_H + \omega_C) \right]$$

$$R_1^H({}^1H,{}^1H) = \frac{1}{T_1} = \frac{C\gamma_H^4}{r_{HH}^6}\left[J(\omega_H) + 4J(2\omega_H) \right]$$

$$R_2^H({}^1H,{}^{13}C) = \frac{1}{T_2} = \frac{C\gamma_H^2\gamma_C^2}{2r_{HC}^6}\left[4J(0) + J(\omega_H - \omega_C) + 3J(\omega_H) + 6J(\omega_C) + 6J(\omega_H + \omega_C) \right]$$

$$R_2^C({}^1H,{}^{13}C) = \frac{1}{T_2} = \frac{C\gamma_H^2\gamma_C^2}{2r_{HC}^6}\left[4J(0) + J(\omega_H - \omega_C) + 3J(\omega_C) + 6J(\omega_H) + 6J(\omega_H + \omega_C) \right]$$

$$R_2^H({}^1H,{}^1H) = \frac{1}{T_2} = \frac{C\gamma_H^4}{2r_{HH}^6}\left[3J(0) + 5J(\omega_H) + 2J(2\omega_H) \right]$$

The frequency dependence of the relaxation rate constants is shown in the figure below:
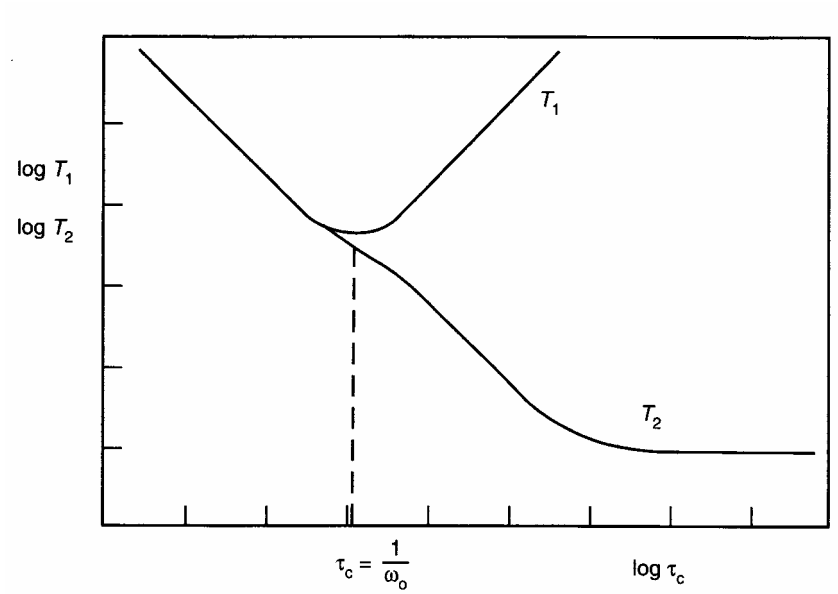

$$\tau_c = \frac{1}{\omega_o}$$

Figure 8.2 from Becker, E.D. (2000) High Resolution NMR. Academic Press, New York.