Lecture #5
Chemical Exchange

- Topics
  - Introduction
  - Effects on longitudinal magnetization
  - Effects on transverse magnetization
  - Examples

- Handouts and Reading assignments
  - Kowalewski, Chapter 13
  - Levitt, sections 15.5 and 15.6
  - van de Ven, sections 2.4, 2.5, and 6.1.2
Chemical Exchange

• Cross relaxation can lead to exchange of magnetization between coupled spins \( I \) and \( S \).

• However, uncoupled spins can manifest themselves as an apparent coupled spin systems, if the spins are engaged in chemical exchange.

• Consider spins A and B on two molecules undergoing chemical exchange with rate constants \( k_A \) and \( k_B \) respectively.

\[
\begin{align*}
A & \quad \overset{k_A}{\xrightarrow{k_B}} \quad B \\
\frac{1}{\tau_{ex}} &= k_{ex} = \frac{k_A}{k_B}
\end{align*}
\]

- Exchange time
- Exchange rate

• We’ll assume any transition from A to B is instantaneous, but happens at an average rate of \( 1/\tau_{ex} \).
Chemical Exchange Examples

- **Intramolecular:** inorganic phosphate ($^{31}$P MRS)

$$H_2PO_4^- \leftrightarrow HPO_4^{2-} + H^+$$

- **Intramolecular:** water and hydration layers

- **Intermolecular:** CEST

Different chemical shifts

Different correlation times

Different chemical shifts
Chemical exchange and $\tau_c$

- Chemical exchange $\rightarrow$ stochastic modulations $\rightarrow$ relaxation

- Exchange rates ($\mu$s to ms time scales) $\ll$ molecular tumbling
  - Too slow to effect anisotropic interactions such as CSA or dipole coupling
  - Can effect isotropic interactions such as chemical shift or J coupling

- Example: Let spins I and S be J coupled with the bond between them regularly broken by an exchange process.

J-coupling is modulated $\rightarrow$ If $1/\tau_e \gg J$ then $G(\tau) = \langle J(t)J(t+\tau) \rangle = J^2 e^{-|\tau|/\tau_e}$

and $\frac{1}{T_{1,sc}} = \frac{(2\pi J)^2}{2} \frac{\tau_e}{1+\left(\omega_I-\omega_S\right)\tau_e^2}$

Hence, the exchange time can look just like a rotational correlation time!

The name for this particular effect is “scalar relaxation of the 1st kind”. In a few lectures, we’ll see why $J(\omega)$ is probed at $\omega_I-\omega_S$
Longitudinal Magnetization

- Chemical exchange can lead to the flow of longitudinal magnetization between sites.

- Bloch-McConnell equations

\[
\frac{dM_z^A}{dt} = -\frac{M_z^A - M_{z,0}^A}{T_{1A}} - \frac{M_z^A}{\tau_A} + \frac{M_z^B}{\tau_B}
\]

and

\[
\frac{dM_z^B}{dt} = -\frac{M_z^B - M_{z,0}^B}{T_{1B}} - \frac{M_z^B}{\tau_B} + \frac{M_z^A}{\tau_A}
\]

More compactly…

\[
\begin{bmatrix}
\frac{d}{dt} M_z^A \\
\frac{d}{dt} M_z^B
\end{bmatrix} = -
\begin{bmatrix}
\alpha_A & -1/\tau_B \\
-1/\tau_A & \alpha_B
\end{bmatrix}
\begin{bmatrix}
M_z^A - M_{z,0}^A \\
M_z^B - M_{z,0}^B
\end{bmatrix}
\]

with

\[
\alpha_A = \frac{1}{T_{1A}} + \frac{1}{\tau_A}
\]

\[
\alpha_B = \frac{1}{T_{1B}} + \frac{1}{\tau_B}
\]

Note, same form as the Solomon equations for dipolar coupling.
Longitudinal Magnetization

Some interesting limiting cases…

Case 1: slow exchange  \( \tau_A^{-1} + \tau_B^{-1} \ll T_{1A}^{-1} + T_{1B}^{-1} \)  \( \Rightarrow \)  \( \alpha_A \approx T_{1A}^{-1}, \alpha_B \approx T_{1B}^{-1} \)

Case 2:  \( T_{1B}^{-1} \gg \tau_A^{-1}, \tau_B^{-1} \gg T_{1A}^{-1} \)  \( \Rightarrow \)  \( \alpha_A \approx \tau_A^{-1}, \alpha_B \approx T_{1B}^{-1} \)

Almost all relaxation at site B

Case 3: site B has very rapid relaxation and very small population, e.g. free water rapidly exchanging with a small pool of bound water.

\[
\alpha_A = \frac{1}{T_{1A}} + \frac{p_B}{p_A T_{1B} + p_B \tau_A}
\]

fractional pool sizes

Important case for water in tissue as well as contrast agents
Transverse Magnetization

- Chemical reactions can have profound effects on NMR linewidths, with the effects strongly dependent on the exchange rate.
Lineshape Calculations

• Modified Bloch equations with coupling:

\[
\frac{dM_x^A}{dt} = -\frac{1}{T_2^A} M_x^A + \cos(\Omega_A t) M_y^A - k_A M_x^A + k_B M_x^B \\
\frac{dM_y^A}{dt} = -\frac{1}{T_2^A} M_y^A - \sin(\Omega_A t) M_x^A - k_A M_y^A + k_B M_y^B
\]

(analogous equations for the B spin)

• Using \( M_{xy} = M_x + iM_y \), compact notation for both A and B spins:

\[
\frac{dM_{xy}^A}{dt} = -(i\Omega_A + 1/T_2^A) M_{xy}^A - k_A M_{xy}^A + k_B M_{xy}^B \\
\frac{dM_{xy}^B}{dt} = -(i\Omega_B + 1/T_2^B) M_{xy}^B - k_B M_{xy}^B + k_A M_{xy}^A
\]

Similar to the Bloch-McConnell equations, but now for transverse magnetization.
Lineshape Calculations

• Rewriting…

\[
\frac{d\vec{M}_{xy}}{dt} = L\vec{M}_{xy}
\]

where \( L = -\Omega + k \)

and

\[
\Omega = \begin{pmatrix}
  i\Omega_A + 1/T_2^A & 0 \\
  0 & i\Omega_B + 1/T_2^B
\end{pmatrix}
\]

\[
k = \begin{pmatrix}
  -k_A & k_B \\
  k_A & -k_B
\end{pmatrix}
\]

• Solution:

\[
\vec{M}_{xy}(t) = e^{Lt} \vec{M}_{xy}(0)
\]
Slow Intermediate Exchange

• Before giving the general solution, let’s look at two special cases.

• Spin A (similar for spin B)  \( \rightarrow \) Slow exchange: \( |\Omega_A - \Omega_B| >> k_A,k_B \)

\[
\frac{dM_{xy}^A}{dt} = -\left( i\Omega_A + \frac{1}{T_{2_{app}}^A} \right) M_{xy}^A \quad \Rightarrow \quad \frac{1}{T_{2_{app}}^A} = \frac{1}{T_{2}^A} + k_A
\]

\( M_{xy} \) for species involved in slow exchange: (a) t=0, (b) t=T

Linebroadening due to chemical exchange. As \( k_A \) increases lines get broader.
Fast Exchange

- Fast exchange: $\left| \Omega_A - \Omega_B \right| \ll k_A, k_B$

- In many ways, the opposite of slow exchange.
  - Spins hop back and forth so fast that we observe a single resonance at the weighted average chemical shift:
    $$\Omega = f_A \Omega_A + f_B \Omega_B$$
    where $f_A$ and $f_B$ are the molar fractions of A and B

  - Linebroadening due to chemical exchange. As $k_A$ and $k_B$ increases line gets sharper.
    $$\frac{1}{T_{2_{\text{app}}}} = \frac{1}{T_2} + \Delta \nu \quad \text{with} \quad \Delta \nu \propto \frac{\Delta \Omega^2}{(k_A + k_B)}$$
Detailed Calculations

• Starting with $\tilde{M}_{xy}(t) = e^{Lt}\tilde{M}_{xy}(0)$
• Taking the Fourier Transform and assuming that…

$$k_A >> 1/T_2^A \quad \text{and} \quad k_B >> 1/T_2^B \quad \text{(i.e. chemical exchange is much faster than} \ T_2 \ \text{relaxation)}$$

yields (after considerable algebra):

$$S(\omega) = \frac{f_A f_B (\Omega_A - \Omega_B)^2 \tau_{ex}^{-1}}{(\Omega_A - \omega)^2 (\Omega_B - \omega)^2 + (\bar{\Omega} - \omega)^2 \tau_{ex}^{-2}} M_0$$

where

$$\bar{\Omega} = f_A \Omega_A + f_B \Omega_B, \quad f_A + f_B = 1, \quad \frac{f_A}{f_B} = \frac{k_B}{k_A}, \quad \tau_{ex} = \frac{1}{k_A + k_B}, \quad \frac{1}{\tau_{ex}} = \frac{1}{\tau_A} + \frac{1}{\tau_B} \quad \text{\tau_A = 1/k_A, \ \tau_B = 1/k_B : lifetimes of A and B}$$

\[ A \xrightleftharpoons[k_B]{k_A} B \]
Detailed Calculations

\[ S(\omega) = \frac{f_A f_B (\Omega_A - \Omega_B)^2 \tau_{ex}^{-1}}{(\Omega_A - \omega)^2 (\Omega_B - \omega)^2 + (\Omega - \omega)^2 \tau_{ex}^{-2}} M_0 \]

- Three values of \( \omega \) which correspond to spectral peaks

- \( S(\omega \approx \Omega_A) = \frac{f_A \tau_A}{(\Omega_A - \omega)^2 + \tau_A^{-2}} M_0 \)

  Lorentzian at \( \Omega_A \) with width \( 1/\tau_A = k_A \).

  If \( \tau_A \) is very short, peak very broad.

  \( \rightarrow \) peak visible under slow exchange

- \( S(\omega \approx \Omega_B) \): analysis same as for A.

- \( S(\omega \approx \bar{\Omega}) = \frac{f_A f_B (\Omega_A - \Omega_B)^2 \tau_{ex}}{f_A f_B \tau_{ex}^2 (\Omega_A - \Omega_B)^4 + (\Omega - \omega)^2} M_0 \)

  Lorentzian at \( \bar{\Omega} = f_A \Omega_A + f_B \Omega_B \) increases with \( \tau_{ex} \)

  Linewidth: \( \pi \Delta \nu = f_a f_b (\Omega_a - \Omega_b)^2 \tau_{ex} \)

  \( \rightarrow \) peak visible under fast exchange
2-Spin System with Chemical Exchange

\[ S(\omega) = \frac{f_A f_B (\Omega_A - \Omega_B)^2 \tau_{ex}^{-1}}{(\Omega_A - \omega)^2 (\Omega_B - \omega)^2 + (\bar{\Omega} - \omega)^2 \tau_{ex}^{-2}} M_0 \]
Example 1: Fast Exchange

- $S(\omega) = \frac{f_A f_B (\Omega_A - \Omega_B)^2 \tau^{-1}}{(\Omega_A - \omega)^2 (\Omega_B - \omega)^2 + (\Omega - \omega)^2 \tau^{-2}} M_0$ …derived under assumptions that...
  
  $k_A >> 1/T_2^A$ and $k_B >> 1/T_2^B$ (i.e. chemical exchange much faster than $T_2$)

  Not necessarily true for contrast agents.

- Some parameters to consider.
  - Chemical shift difference between water when free and when coordinated with the agent/metal.
  - $T_2^B$ of water bound to the agent (typically dominated by the unpaired electron spin).
  - Lifetime, $\tau_B$, of the water in the coordination sphere of the contrast agent.

- To be discussed in detail later…
Example 2: Intermediate Exchange

Chemical exchange saturation transfer (CEST)
Example 3: Fast Exchange

- $\text{H}_2\text{PO}_4^- \rightleftharpoons \text{HPO}_4^{2-} + \text{H}^+$ (inorganic phosphate)
  - $\Omega_A = 3.2 \text{ ppm}$  $\Omega_B = 5.7 \text{ ppm}$
- Under fast exchange, the $^{31}$P peak will be at $\bar{\Omega} = f_A \Omega_A + f_B \Omega_B$
- Henderson-Hasselbach relationship
  $$\text{pH} = \text{pK}_A + \log\left(\frac{f_A}{1 - f_A}\right)$$
- Combining the above and expressing things in terms of chemical shift yields …
  $$\text{pH} = \text{pK}_A + \log\left(\frac{\omega - \Omega_A}{\Omega_B - \omega}\right)$$

\[
\begin{align*}
\text{H}_2\text{PO}_4^- & \rightleftharpoons \text{HPO}_4^{2-} + \text{H}^+ \\
\text{pH} & = \text{pK}_A + \log\left(\frac{f_A}{1 - f_A}\right) \\
\Delta \delta_{P_i} & = 3.2 \text{ ppm} \\
\Delta \delta_{P_i} & = 5.7 \text{ ppm}
\end{align*}
\]
What acid is forming to drive down the pH?
Example 4: Fast Exchange

Temperature mapping via water chemical shift

The resonance frequency of the in vivo water $^1$H peak is known to shift with temperature at a rate of ~0.01 ppm/°C. This effect can be explained via a two-site exchange process.
Temperature mapping with H$_2$O

• The earliest reference I found was Hindman JC, “Proton Resonance Shift of Water in the Gas and Liquid States”, *J. Chemical Physics*, 44, 4583 (1966).

• Hydrogen bonds decrease the electron density at the involved proton site and hence lead to a positive frequency shift.

• Liquid water can be modeled as a mixture of two components: a hydrogen-bonded “ice-like” fraction and a non-hydrogen-bonded monomeric fraction.

• The chemical shifts for these two components, which are in fast exchange, are…

  shielding constant for monomeric water, $\sigma_w \approx -0.4 \times 10^{-6}$

  shielding constant hydrogen-bonded water, $\sigma_p \approx \sigma_w - 5.5 \times 10^{-6}$
Temperature mapping with $\text{H}_2\text{O}$

- Under fast exchange, water chemical shift is $\bar{\Omega} = f_A \Omega_A + f_B \Omega_B$
- Combining with the data provided below,

<table>
<thead>
<tr>
<th>Temp (°C)</th>
<th>Thermal</th>
<th>Shielding</th>
<th>Dielectric</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>(0.155)</td>
<td>(0.155)</td>
<td>0.16</td>
</tr>
<tr>
<td>25</td>
<td>0.19</td>
<td>0.21</td>
<td>0.19</td>
</tr>
<tr>
<td>50</td>
<td>0.22</td>
<td>0.26</td>
<td>0.22</td>
</tr>
<tr>
<td>75</td>
<td>0.25</td>
<td>0.31</td>
<td>0.25</td>
</tr>
<tr>
<td>100</td>
<td>0.29</td>
<td>0.35</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Table VI. Calculation of the fraction of zero-bonded water from thermal, dielectric, and chemical-shielding data.

yields a water proton frequency shift of $\Delta \approx 0.008 \text{ ppm/°C.}$

What would we expect to see if the hydrogen-bonded and zero-bonded water were NOT in fast exchange?
Next Lecture: In vivo water