A Theoretical Application of MAXY NMR for CDₙ Groups

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Liquid-state NMR experiments including edited-pulse angles are widely used to distinguish protonated and deuterated carbonyl groups in complex molecules. One of them is maximum quantum correlation NMR spectroscopy (MAXY NMR), which is very suitable to separate CHₙ groups. The product operator theory is used for the analytical description of these experiments for weakly coupled spin systems. In this study, the MAXY NMR experiment is applied for weakly coupled ISₙ (I = 1/2; S = 1; n = 1, 2, 3) spin systems using the product operator theory. A theoretical discussion and experimental suggestions for sub-spectral editing of CDₙ groups are also presented.

Key words: MAXY NMR; Product Operator Theory; Spin-1.

1. Introduction

In complex molecules, liquid-state NMR experiments including edited-pulse angles are widely used to distinguish protonated and deuterated carbonyl groups. These experiments can be classified into two subgroups as ¹³C and ¹H NMR experiments. ¹³C NMR experiments are based on polarization transfer from a high natural abundance nucleus to a low natural abundance nucleus to increase the sensitive enhancement of the NMR spectra such as DEPT [1], INEPT [2], SEMUT [3, 4] and POMMIE [5]. ¹H NMR experiments are more useful because of the high natural abundance of the ¹H nucleus such as MAXY [6], DEPT-HMQC [7], RINEPT [8] and reverse-POMMIE [9]. ²H NMR spectroscopy became a powerful technique for different applications such as structure elucidation and deuterium labeling [10, 11]. ¹³C and ²H are the most useful stable isotopes for NMR-detected metabolic labeling experiments [11, 12].

The product operator theory, as a simple quantum mechanical method, has been developed for the analytical description of multiple-pulse NMR experiments on weakly coupled spin systems in liquids [13 – 21]. In this method, the spin operators themselves and their direct products called product operators, are used. For example, product operator description of 2D DEPT J-resolved and SEMUT NMR spectroscopy for weakly coupled ISₙ (I = 1/2; S = 1; n = 1, 2, 3) spin systems are reported elsewhere [22, 23]. A complete product operator theory for the IS (I = 1/2; S = 1) spin system and application to the DEPT-HMQC NMR experiment was recently presented in our previous study [24].

In the POMMIE experiment the first maximum quantum excitation was made for edited detection of CHₙ groups [5]. Then, Bulsing et al. have generated the pulse sequence, called reverse-POMMIE, to observe protons [9]. After some modifications, this technique has been edited and named as maximum quantum correlation (MAXY) NMR spectroscopy by Liu et al. [6]. By using the product operator theory, theoretical and experimental studies of some NMR experiments related to MAXY NMR were performed for CHₙ groups [6, 25 – 31].

In the present study, the MAXY NMR experiment is applied for weakly coupled ISₙ (I = 1/2; S = 1; n = 1, 2, 3) spin systems using the product operator theory. Then, a theoretical discussion and experimental suggestions for sub-spectral editing of CDₙ groups are presented. To the best of our knowledge, this will be the first application of product operator theory to MAXY NMR spectroscopy for CDₙ groups.

2. Theory

The product operator formalism is the expansion of the density matrix operator in terms of matrix representation of angular momentum operators for individual spins. For the IS (I = 1/2; S = 1) spin system,
Evolution of product operators under the rf pulse.

Depending on the pulse experiment, the Cartesian spin system is separated into two spin operators \( \sigma \). For example, the evolution of the two spin operators can be made as follows:

\[
\exp(-iHt)\{|\sigma(0)\rangle\} = A - i(\sigma(0)A) + \frac{1}{2!} \left( H_{A}(\sigma(0)A) + H_{A}(A)\sigma(0) \right) + \frac{1}{3!} \left( H_{A}(H_{A}(\sigma(0)A) + H_{A}(A)\sigma(0)) + H_{A}(H_{A}(\sigma(0)A) + H_{A}(A)\sigma(0)) + H_{A}(A)\sigma(0) \right) + \cdots
\]

where \( A(1) = I_x \sigma_1, A(2) = I_y \sigma_2, A(3) = I_z \sigma_3 \).

\[
\exp(-2\pi J I_z S_x t) = \frac{3}{4} \left( e^{2\pi J I_z S_x t} - I_z \sigma_3 - \frac{1}{2} I_x \sigma_2 \right)
\]

Then using sine and cosine series,

\[
\exp(-2\pi J I_z S_x t) = \frac{1}{2} \left( e^{2\pi J I_z S_x t} + e^{-2\pi J I_z S_x t} \right)
\]

\[
A(1) = \frac{1}{4} \left( e^{2\pi J I_z S_x t} - e^{-2\pi J I_z S_x t} \right)
\]

\[
A(2) = \frac{1}{4} \left( e^{2\pi J I_z S_x t} + e^{-2\pi J I_z S_x t} \right)
\]

\[
A(3) = \frac{1}{4} \left( e^{2\pi J I_z S_x t} - e^{-2\pi J I_z S_x t} \right)
\]

Thus, the evolution of the product operators can be made as follows:

\[
\exp(-2\pi J I_z S_x t)\{|\sigma(0)\rangle\} = A - i(\sigma(0)A) + \frac{1}{2!} \left( H_{A}(\sigma(0)A) + H_{A}(A)\sigma(0) \right) + \frac{1}{3!} \left( H_{A}(H_{A}(\sigma(0)A) + H_{A}(A)\sigma(0)) + H_{A}(H_{A}(\sigma(0)A) + H_{A}(A)\sigma(0)) + H_{A}(A)\sigma(0) \right) + \cdots
\]

Using the commutation relations, the "spin-spin coupling Hamiltonian" is obtained.

The time dependency of the density matrix is given by:

\[
\sigma(t) = \exp(-iHt)\{|\sigma(0)\rangle\} = \exp(-iHt)\{|0\rangle\langle 0|\}
\]

where \( H \) is the total Hamiltonian, which consists of a magnetic field and a spin-spin coupling Hamiltonian.

Table 2: Table of 16 product operators under the spin coupling Hamiltonian for the spin system (1/2,1/2,1/2) at the rf frequency (i.e. pulse: chemical shift and spin-spin coupling). The Cartesian spin system is separated into two spin operators \( \sigma \). Depending on the pulse experiment, the Cartesian spin system is separated into two spin operators \( \sigma \). In this case there exist 40 product operators. 

<table>
<thead>
<tr>
<th>Product Operator</th>
<th>Evolution of the Product Operator</th>
<th>Evolution of the spin-spin coupling Hamiltonian</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

For more details, refer to [17].
\[
\begin{align*}
S_x & = \frac{1}{2} S_x (c_2 + 1) - \frac{1}{2} S_x (c_2 - 1) + I_z S_x + S_x I_z \\
S_y & = \frac{1}{2} S_y (c_2 + 1) - \frac{1}{2} S_y (c_2 - 1) - I_x S_y + S_y I_x \\
S_z & = \frac{1}{2} S_z (c_2 - 1) - \frac{1}{2} S_z (c_2 + 1) + S_x S_y + S_y S_x \\
I_x & = I_x \quad \text{electric field} \\
I_y & = I_y \quad \text{V DC field} \\
I_z & = I_z \quad \text{magnetic field}
\end{align*}
\]

Table 2. Evolutions of 18 product operators under the spin-spin coupling Hamiltonian \( (2\pi J I, S) \) for the weakly coupled IS \( (I = 1/2; S = 1) \) spin system [24].

\[
\begin{array}{|c|c|}
\hline
\text{Product operator} & \text{Evolution under the spin-spin coupling Hamiltonian} \\
\hline
S_x^2 & \frac{1}{2} S_x^2 (c_2 + 1) - \frac{1}{2} S_x^2 (c_2 - 1) + I_x S_x + S_x I_x \\
S_y^2 & \frac{1}{2} S_y^2 (c_2 + 1) - \frac{1}{2} S_y^2 (c_2 - 1) - I_y S_y + S_y I_y \\
S_z^2 & \frac{1}{2} S_z^2 (c_2 - 1) - \frac{1}{2} S_z^2 (c_2 + 1) + S_x S_y + S_y S_x \\
I_x S_x & I_x S_x \\
I_y S_y & I_y S_y \\
I_z S_z & I_z S_z \\
[I_x, S_x] & [I_x, S_x] + 2I_x S_x, [I_y, S_y] + 2I_y S_y \\
[I_y, S_y] & [I_y, S_y] + 2I_y S_y, [I_z, S_z] + 2I_z S_z \\
[I_z, S_z] & [I_z, S_z] + 2I_z S_z, [I_x, S_x] + 2I_x S_x \\
I_x S_y & I_x S_y \\
I_y S_x & I_y S_x \\
I_z S_y & I_z S_y \\
I_x S_z & I_x S_z \\
I_y S_z & I_y S_z \\
I_z S_z & I_z S_z \\
\hline
\end{array}
\]

Table 3. Evolutions of 9 angular momentum operators under the chemical shift Hamiltonian \( \Omega (S_x) \) for \( S = 1 \) [24].

\[
\begin{array}{|c|c|}
\hline
\text{Angular momentum operator} & \text{Evolution under the chemical shift Hamiltonian} \\
\hline
S_x & S_x + S_x S_y + S_y S_x \\
S_y & S_y - S_x S_y \\
S_z & S_z \\
[S_x, S_x] & [S_x, S_x] + I_x S_x + S_x I_x \\
[S_y, S_y] & [S_y, S_y] + I_y S_y + S_y I_y \\
[S_z, S_z] & [S_z, S_z] + I_z S_z + S_z I_z \\
S_x^2 & \frac{1}{2} S_x^2 (c_2 + 1) - \frac{1}{2} S_x^2 (c_2 - 1) + S_x S_y + S_y S_x \\
S_y^2 & \frac{1}{2} S_y^2 (c_2 - 1) - \frac{1}{2} S_y^2 (c_2 + 1) - S_x S_y + S_y S_x \\
S_z^2 & \frac{1}{2} S_z^2 (c_2 + 1) - \frac{1}{2} S_z^2 (c_2 - 1) - I_x S_x + I_y S_y \\
\hline
\end{array}
\]

The \( E, I_x, I_y, S_x, S_y \) and \( I_z S_z^2 \) product operators do not change under the spin-spin coupling Hamiltonian for

\[
\text{the IS (} I = 1/2; S = 1 \text{) spin system. Evolutions for the rest 18 product operators are obtained in our previous work [24]. They are presented in Table 2. For } S = 1, \text{ evolutions of nine angular momentum operators under the chemical shift and the r.f. pulse Hamiltonians are given in Tables 3 and 4, respectively [24].}
\]

At any time during the experiment, the ensemble averaged expectation value of the spin angular momentum, e.g. for \( I_x \), is

\[
\langle I_x \rangle = \text{Tr}[I_x \sigma(t)],
\]

where \( \sigma(t) \) is the density matrix operator calculated from (2) at any time. As \( \langle I_x \rangle \) is proportional to the magnitude of the y-magnetization, it represents the signal detected on the y-axis. In order to estimate the free induction decay (FID) signal of a multiple-pulse NMR experiment, the density matrix operator should be obtained at the end of the experiment.

3. Results

For the product operator description of the MAXY NMR experiment, the pulse sequence illustrated in Fig. 1 is used [6], where the density matrix operator at each stage of the experiment is labeled with numbers, and \(^{13}\text{C}\) is treated as spin \( I \) and \(^2\text{H}\) (D) as spin \( S \). In
the pulse sequence, $\Delta$ is the coupling evolution delay, $\Delta'$ is a short compensation delay and $t$ is the acquisition time. The optimum value of $\Delta$ is $1/(2I_{IS})$ for this experiment. Starting from the density matrix operator at thermal equilibrium, one should apply the required Hamiltonians during the pulse sequence and obtain the density matrix operator at the end of the experiment. For multi-spin systems, to follow these processes by hand becomes too difficult. In order to overcome this problem, a computer program written in Mathematica is used. Thus, the density matrix operators at the end of the experiment are obtained for different spin systems such as $IS, IS_2$ and $IS_3$ ($I = 1/2$; $S = 1, 2$).

### 3.1. IS Spin System

For the IS spin system,

$$\sigma_1 = S_x,$$

(11)

is the density matrix operator at thermal equilibrium, and then we obtain

$$\sigma_2 = -S_y, \quad (12)$$

$$\sigma_3 = -2I_xS_x, \quad (13)$$

$$\sigma_4 = 2I_yS_x, \quad (14)$$

$$\sigma_5 = -2I_x[S_y, S_z]_+, \quad (15)$$

$$\sigma_6 = 2I_x[S_x, S_z]_+. \quad (16)$$

At this point all spins are excited to their possible highest heteronuclear multiple-quantum level. Then,

$$\sigma_{10} = 2I_x[S_x, S_y]_+ + c_\theta + 2I_x[S_x, S_z]_+ + s_\theta, \quad (17)$$

$$\sigma_{13} = -2I_x[S_x, S_y]_+ c_\theta + S_x s_\theta, \quad (18)$$

$$\sigma_{14} = -2I_x[S_x, S_y]_+ c_\theta + S_x s_\theta - S_x s_\theta s_S + 2I_x S_y^2 c_\theta + 2I_x S_y^2 c_\theta + S_x s_\theta, \quad (19)$$

are obtained. In the last density matrix operator, only the second term contributes to the signals, as acquisition is taken along $y$-axes for spin $S$. Now, it is necessary to obtain the $\sum_{n=1}^{n} Tr[S_n O]$ values of observable product operators indicated by $O$. For the $IS_n$ ($I = 1/2$; $S = 1, 2$; $n = 1, 2, 3$) spin systems, $\sum_{n=1}^{n} Tr[S_n O]$ values of all observable product operators are calculated by a computer program in Mathematica. The results are given in Table 5. Using Table 5,

$$M_c(t) \propto \langle S_y \rangle = Tr[S_c \sigma_{14}] = 4s_\theta c_\theta \quad (20)$$

is obtained. In the above and following equations, $s_{n\theta} = \sin(n\theta)$, $c_{n\theta} = \cos(n\theta)$, $c_{n\theta} = \cos(n\Omega_c t)$ and $s_{n\theta} = \sin(n\Omega_c t)$.

### 3.2. IS$_2$ Spin System

For the IS$_2$ spin system, $\sigma_1$ is the density matrix operator at thermal equilibrium:

$$\sigma_1 = S_{1z} + S_{2z}, \quad (21)$$

22 observable terms are obtained at the end of the experiment:

$$\sigma_{14} = \frac{1}{2}(2S_{1y} + 2S_{2y} - S_{1y}S_{2y}^2 - S_{1x}S_{2y})$$

$$- S_{1y}S_{2y}^2 - S_{1y}S_{2y}^2) s_\theta c_\theta$$

$$- \frac{1}{2}(S_{1y}S_{2x}^2 + S_{1y}S_{2y} + S_{1y}S_{2y} + S_{1y}S_{2y}) c_\theta s_\theta c_\theta$$

$$- \frac{1}{2}(S_{1y}S_{2x}^2 - S_{1y}S_{2y} + S_{1y}S_{2y} - S_{1y}S_{2y}) s_\theta c_\theta c_\theta$$

$$- \frac{1}{2}(S_{1y}S_{2x}^2 - S_{1y}S_{2y} + S_{1y}S_{2y} - S_{1y}S_{2y}) c_\theta s_\theta c_\theta$$

$$+ 2I_x S_y^2 c_\theta + 2I_x S_y^2 c_\theta + S_x s_\theta - S_x s_\theta s_S + 2I_x S_y^2 c_\theta + 2I_x S_y^2 c_\theta + S_x s_\theta, \quad (19)$$

<table>
<thead>
<tr>
<th>Spin system</th>
<th>Product operators ($O$)</th>
<th>$\sum_{n=1}^{n} Tr[S_n O]$</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS</td>
<td>$S_x$</td>
<td>4</td>
</tr>
<tr>
<td>IS$_2$</td>
<td>$S_x + S_y$</td>
<td>16</td>
</tr>
<tr>
<td>IS$_3$</td>
<td>$S_x + S_y + S_z$</td>
<td>22</td>
</tr>
</tbody>
</table>

Table 5. Results of $\sum_{n=1}^{n} Tr[S_n O]$ calculations for some of the observable product operators for the $IS_n$ ($I = 1/2$; $S = 1$; $n = 1, 2, 3$) spin systems ($j = x, y$ and $k = x, y$).
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Fig. 2. Relative signal intensity of MAXY NMR for CD₂, CD₃ and CD₄ groups as function of the pulse angle \( \theta \).

\[
-\frac{1}{2}(S_{1z}S_{2z} + S_{1z}S_{2z} - S_{1z}S_{2z} - S_{1z}S_{2z})
\]

\[
\cdot c_{\theta} s_{\theta} s_{\theta} c_{\theta} s_{\theta} c_{\theta}.
\]  

(22)

Using the trace values for the observable terms given in Table 5,

\[
M_r(t) \propto \langle S_{1y} \rangle + \langle S_{2y} \rangle = \text{Tr}[S_{1y} \sigma_{14}] + \text{Tr}[S_{2y} \sigma_{14}],
\]  

(23)

\[
\langle S_{1y} \rangle + \langle S_{2y} \rangle = 8(s_{\theta} c_{\theta} s_{\theta} c_{\theta} - 2c_{\theta} s_{\theta} c_{\theta})
\]  

(24)

is obtained.

3.3. IS₃ Spin System

For the IS₃ spin system, applying the same procedure, 188 observable terms are obtained at the end of the experiment by using the computer program. Using the trace values in Table 5,

\[
\langle S_{1y} \rangle + \langle S_{2y} \rangle + \langle S_{3y} \rangle
\]

\[
= 12(s_{\theta} c_{\theta} s_{\theta} c_{\theta} - 4c_{\theta} s_{\theta} c_{\theta} + 4c_{\theta} s_{\theta} c_{\theta})
\]  

(25)

is found.

4. Discussion

The \( \sum_{i=1}^{n} \text{Tr}[S_{iy} \sigma_{14}] \) values obtained in the preceding section for IS, IS₂ and IS₃ spin systems represent the FID signals of MAXY NMR for CD, CD₂ and CD₃ groups, respectively. The \( \sum_{i=1}^{n} \text{Tr}[S_{iy} \sigma_{14}] \) values for the ISₙ \((I = 1/2; S = 1; n = 1, 2, 3) \) spin systems can be generalized as

\[
\sum_{i=1}^{n} \text{Tr}[S_{iy} \sigma_{14}] = 4n(1 - 2c_{\theta}^2)^{n-1}s_{\theta} c_{\theta}.
\]  

(26)

The \( \sum_{i=1}^{n} \text{Tr}[S_{iy} \sigma_{14}] \) values can be normalized by multiplication with \( 6/(4n\text{Tr}(E)) \). Here \( E \) is the unity product operator for the corresponding spin system. Then, normalized values become as follows:

\[
\text{Tr}[S_{y} \sigma_{14}] = s_{\theta} c_{\theta},
\]  

(27)

\[
\sum_{i=1}^{2} \text{Tr}[S_{iy} \sigma_{14}] = \frac{1}{3}(1 - 2c_{\theta})s_{\theta} c_{\theta},
\]  

(28)

\[
\sum_{i=1}^{3} \text{Tr}[S_{iy} \sigma_{14}] = \frac{1}{9}(1 - 2c_{\theta})^2 s_{\theta} c_{\theta}.
\]  

(29)

Normalized \( \sum_{i=1}^{n} \text{Tr}[S_{iy} \sigma_{14}] \) values can be written in a generalized form of

\[
\sum_{i=1}^{n} \text{Tr}[S_{iy} \sigma_{14}] = \frac{1}{3^{n-1}}(1 - 2c_{\theta})^{n-1}s_{\theta} c_{\theta}.
\]  

(30)

The plots of these generalized functions are presented in Figure 2. As seen in this figure, the relative signal intensities of CD, CD₂ and CD₃ groups vary as functions of \( \theta \). In the MAXY NMR experiment of CDₙ groups, the real relative signal intensities found from (26) are given in Table 6. As seen in Table 6 and Fig. 2, when
Table 6. Real relative signal intensities of MAXY NMR experiment of CD₆ groups for several pulse angles θ.

<table>
<thead>
<tr>
<th>Spin system</th>
<th>θ = 30° and 150°</th>
<th>θ = 45° and 135°</th>
<th>θ = 90°</th>
</tr>
</thead>
<tbody>
<tr>
<td>IS(CD)</td>
<td>1</td>
<td>0.707</td>
<td>1</td>
</tr>
<tr>
<td>IS₂(CD₂)</td>
<td>0</td>
<td>1.414</td>
<td>6</td>
</tr>
<tr>
<td>IS₃(CD₃)</td>
<td>0</td>
<td>2.121</td>
<td>27</td>
</tr>
</tbody>
</table>

the experiment is performed for the angle of 30°, only CD groups will be observed, giving a positive signal. For the angle 90°, all CD, CD₂ and CD₃ groups will give positive signals with the real relative signal intensities of 1 : 6 : 27. When the pulse angle is 45°, real relative signal intensities of the CD, CD₂ and CD₃ groups will be 0.707 : 1.414 : 2.121. By comparing their relative signal intensities obtained for the angles of 90° and 45°, one can easily identify CD₂ and CD₃ groups from each other. As a result, the MAXY NMR experiment can be used for sub-spectral editing of CD₆ groups. In deuterium labeling it is of interest to determine whether the methyl group is transferred as a whole, leading to ¹³CD₃-containing compounds, or leading to ¹³CD₂H- or ¹³CDH₂-containing compounds [11, 33]. MAXY NMR of CD₆ groups can be also used for this purpose.

5. Conclusions

The product operator formalism became a useful technique for the analytical description of multiple-pulse and edited-pulse NMR experiments for weakly coupled spin systems including spin-1/2 and spin-1 [6, 13–24]. In this study, by using the product operator theory, an analytical description of the MAXY NMR experiment is presented for ISₙ (I = 1/2; S = 1; n = 1, 2, 3) spin systems. Then, theoretical discussion and experimental suggestions are presented in order to distinguish CD, CD₂ and CD₃ groups from each other.