Supplementary Information

The Simulation of NMR Data of Flexible Molecules - Sagittamide A as Example for MD Simulations with Orientational Constraints

Ulrich Sternberg, Pavleta Tzvetkova and Claudia Muhle-Goll

1 Formulae of MDOC Methods

1.1 The recursion Formula for the Time Average with an Exponential Decaying Memory Function

The time average of all components the dipolar tensor \( D \) is calculated using the following exponentially decaying memory function:

\[
D(t) = \frac{1}{N(t)} \int_{t'=0}^{t} e^{-\frac{(t-t')}{\tau}} D(t') \, dt'
\]

\[
N(t) = \int_{t'=0}^{t} e^{-\frac{(t-t')}{\tau}} \, dt'
\]

The second integral \( N(t) \) is the norm and \( \tau \) the memory time constant. This folding integral transforms the original function \( D(t') \) to the new time scale \( t \). Introducing \( n \) discrete equidistant time steps \( \Delta t \) with \( t = \{0,...,n \Delta t\} \) the folding integral (1) can be written in matrix form as follows:

\[
\begin{pmatrix}
\mathbf{d}_0 \\
\mathbf{d}_1 \\
\mathbf{M} \\
\mathbf{d}_n
\end{pmatrix}
= 
\begin{pmatrix}
1 & 0 & L & 0 \\
e^{-\frac{\Delta t}{\tau}} & 1 & 0 & L \\
M & M & M & M \\
e^{\frac{n \Delta t}{\tau}} & e^{\frac{(n-1) \Delta t}{\tau}} & L & e^{-\frac{\Delta t}{\tau}}
\end{pmatrix}
\begin{pmatrix}
\mathbf{D}_0 \\
\mathbf{D}_1 \\
\mathbf{M} \\
\mathbf{D}_n
\end{pmatrix}
\]

(2)

The values on the main diagonal of the matrix in eq. (2) are \( I \). To obtain the final \( <D>_{k\Delta t} \) values (\( <>t \) indicates the time average) the elements of the column on the left side have to be divided by the norm:

\[
<\mathbf{D}>_{k\Delta t} = \frac{\mathbf{d}_k}{N_k}
\]

(3)

The vector of the norm values can be obtained by replacing the column vector on the right side of equation (2) with a vector containing only \( I \) as elements. From (2) we can write down the following recursion for \( \mathbf{d} \) and \( N \):

\[
\begin{pmatrix}
\mathbf{d}_0 \\
\mathbf{d}_1 \\
\mathbf{M} \\
\mathbf{d}_n
\end{pmatrix}
= 
\begin{pmatrix}
1 & 0 & L & 0 \\
e^{-\frac{\Delta t}{\tau}} & 1 & 0 & L \\
M & M & M & M \\
e^{\frac{n \Delta t}{\tau}} & e^{\frac{(n-1) \Delta t}{\tau}} & L & e^{-\frac{\Delta t}{\tau}}
\end{pmatrix}
\begin{pmatrix}
\mathbf{D}_0 \\
\mathbf{D}_1 \\
\mathbf{M} \\
\mathbf{D}_n
\end{pmatrix}
\]
\[ \mathbf{d}_k = \mathbf{D}_0 \]
\[ \mathbf{d}_{k+1} = \mathbf{d}_k e^{\frac{N}{\Delta t}} + \mathbf{D}_{k+1} \]
\[ N_0 = 1 \]
\[ N_{k+1} = N_k e^{\frac{\Delta t}{\tau}} + 1 \]  \hspace{1cm} (4)

In this version the norm \( N_i \) has to be stored together with \( \mathbf{d}_k \). Depending on resources and the speed of memory access it may be favorable to run the recursion directly using \( < \mathbf{D} >_{k\Delta t} \):

\[ < \mathbf{D} >_{\Delta t=0} = \mathbf{D}_0 \]
\[ N_0 = 1 \]
\[ N_{k+1} = N_k e^{\frac{\Delta t}{\tau}} + 1 \]  \hspace{1cm} (5)

\[ < \mathbf{D} >_{\Delta t=(k+1)\Delta t} = \frac{1}{N_{k+1}} \left( \mathbf{D}_{k+1} + N_k < \mathbf{D} >_{k\Delta t} e^{\frac{\Delta t}{\tau}} \right) \]

The sum within the parenthesis is calculated before the recursion of the norm is executed. The exponential factor has to be calculated only once at the beginning of the recursion.

### 1.2 Coordinate Derivative of the Altona Equation

For the force field the derivative of the Altona equation\(^5\) is needed. The Altona correction term has the form:

\[ A = \sum_i \Delta \chi_i \left[ P_2 + P_3 \cos^2 \left( \xi_i \phi + P_5 |\Delta \chi_i| \right) \right] \]  \hspace{1cm} (6)

The derivative to \( \cos(\phi) \) gives:

\[ \frac{\partial A}{\partial \cos(\phi)} = \sum_i \Delta \chi_i \left[ 2 P_2 \cos \left( \xi_i \phi + P_5 |\Delta \chi_i| \right) \cos \left( P_5 |\Delta \chi_i| \right) \right] \]  \hspace{1cm} (7)

If the coupling atoms are denoted with A and B the \( \cos(\phi) \) is calculated from a scalar product of the unit vectors that are perpendicular to A-C-C and C-C-B. Finally we have only to perform the derivative of \( \cos(\phi) \) with respect to the coordinates of the atoms A-C-C-B. In the case of the Altona equation A and B are H atoms and in the case of the correction term of Palermo et al.\(^6\) atom A is a hydrogen and atom B a carbon atom.
2. Fife-membered ring Lactone

2.1 Structure and NMR Data

Figure 1: α-Methylene-γ-butyrolactone with numbering of its atoms.

Table 1: Constraints for MDOC Simulations:

| Number of Constraints | NMR Data Type                                      | Remarks                                                                 |
|-----------------------|---------------------------------------------------|-------------------------------------------------------------------------|
| 7                     | one bond $^1$H-$^{13}$C RDC values$^1$             | Orientational constraints                                              |
| 8                     | long range RDC values$^1$                          | Orientational constraints                                              |
| 8                     | long range RDC values without experimental signs$^1$ | Predicted from the other constraints in a preliminary MDOC simulation and used as constraints in subsequent final simulations |
| 2                     | $^3$J couplings$^1$                                | Constraints                                                             |
| 6                     | NOE distances$^2$                                  | Constraints                                                             |
Table 2: Simulation parameters for MDOC Simulations

| Parameter                                                                 | Value       |
|---------------------------------------------------------------------------|-------------|
| Target temperature                                                        | 300 K       |
| MD time step                                                              | 0.5 fs      |
| BPT atomic charge calculation                                             | 2 fs        |
| Coupling time $\eta$ to the heat bath                                     | 0.02 ps     |
| Memory decay time $\tau$ for the property average                          | 200 ps      |
| Time constant $\rho$ for the exponential rise of pseudo-forces            | 200 ps      |
| Order parameter of the alignment medium $S_{am}$ (dipolar couplings)       | 0.008       |

| Parameter                                                                 | Value       |
|---------------------------------------------------------------------------|-------------|
| Pseudo-force width $\Delta D$ for the one bond CH couplings               | 0.5 Hz      |
| Weight parameter $k_D$ (one bond couplings - in kJ mol$^{-1}$ Hz$^{-1}$)  | 0.0003      |
| Pseudo-force width $\Delta D$ for the one long range couplings            | 0.5 Hz      |
| Weight parameter $k_D$ (long range couplings- in kJ mol$^{-1}$ Hz$^{-1}$) | 0.01        |
| Pseudo-force width $\Delta R$ for the NOE distance constraints            | 0.2 Å       |
| Weight parameter $k_R$ (NOE distances - in kJ mol$^{-1}$ Å$^{-1}$)         | 1.2         |
| Pseudo-force width $\Delta J$ for the $^3J_{HH}$ coupling constraints     | 1.0 Hz      |
| Weight parameter $k_J$ ($^3J_{HH}$ couplings - in kJ mol$^{-1}$ Hz$^{-1}$) | 5.0         |
| Total MD duration                                                         | 80 ns       |

2.2 Results of MDOC Simulations

Table 3: Comparison of experimental and MDOC simulated $^3J_{HH}$ and $^3J_{CH}$ couplings

| Coupling Atom A | Coupling Atom B | Experiment$^1$ $^3J$ coupling / Hz | MDOC Simulation $^3J$ coupling / Hz | Estimated Error$^1$ / Hz |
|-----------------|-----------------|-------------------------------------|-------------------------------------|-------------------------|
| H3              | H2              | 6.4                                 | 7.369                               | 1.0                     |
| H3              | C1_CH3          | 5.11                                | 4.747                               | 1.0                     |

$^1$ Experimental error + estimated error of the semi-empirical theory$^5, 6$
Table 4: Comparison of experimental and MDOC simulated RDC for the RS (C2-R and C3-S) structure denoted trans-2b

| Coupling Atom A | Coupling Atom B | Experiment RDC / Hz | MDOC Prediction RDC / Hz | MDOC Simulation RDC / Hz | Difference Exp.-Sim. Hz | Error / Hz |
|-----------------|-----------------|---------------------|--------------------------|--------------------------|-------------------------|------------|
| H2              | C2              | -18.7               | -19.524                  | 0.824                    | 0.5                     |
| H2              | C3              | -0.24               | -0.33                    | 0.09                     | 0.2                     |
| H2              | C7              | 1.6                 | 0.758                    | 1.303                    | 0.297                   | 0.2        |
| H2              | C1_CH3          | -1.6                | -1.533                   | -0.067                   | 0.2                     |
| H2              | H3              | -4.5                | -4.154                   | -0.346                   | 0.2                     |
| H3              | C3              | -32.3               | -32.096                  | -0.204                   | 0.5                     |
| H3              | C2              | -0.9                | -0.945                   | 0.045                    | 0.2                     |
| H3              | C4              | -1                  | -0.747                   | -0.924                   | 0.076                   | 0.5        |
| H3              | C6              | 0.6                 | 0.269                    | 0.331                    | 0.2                     |
| H3              | C7              | -1.9                | -1.250                   | -1.777                   | -0.123                  | 0.2        |
| H3              | C1_CH3          | 2                   | 1.843                    | 0.157                    | 0.5                     |
| H6b             | C6              | 11.1                | 11.319                   | -0.219                   | 0.5                     |
| H6b             | C3              | 1.2                 | 1.107                    | 0.093                    | 0.2                     |
| H6b             | C4              | 3.2                 | 2.110                    | 3.116                    | 0.084                   | 0.2        |
| H6b             | C5              | 0.8                 | 0.397                    | 0.627                    | 0.173                   | 0.5        |
| H6b             | H3              | 1.8                 | 1.922                    | -0.122                   | 0.5                     |
| H1a             | C1_CH3          | -0.73               | -0.925                   | 0.195                    | 0.5                     |
| H1b             | C1_CH3          | -0.73               | -0.91                    | 0.18                     | 0.5                     |
| H1c             | C1_CH3          | -0.73               | -0.907                   | 0.177                    | 0.5                     |
| H6a             | C6              | 3.5                 | 3.249                    | 0.251                    | 0.5                     |
| H6a             | C3              | 0.4                 | 0.292                    | 0.108                    | 0.2                     |
| H6a             | C4              | 2                   | 1.665                    | -0.082                   | 0.5                     |
| H6a             | C5              | 1.9                 | 0.920                    | 1.624                    | 0.276                   | 0.2        |
| H6a             | C7              | 0.01                | 0.128                    | 0.065                    | -0.055                  | 0.2        |

RMS Deviation / Hz: 0.67 / 0.25

Table 5: Comparison of experimental and MDOC simulated NOE distances for the RS (C2-R and C3-S) structure denoted trans-2b

| Atom A | Atom B | NOE Dist.\(^2\) Exp. / Å | NOE Dist. MDOC / Å | Diff. Exp.-Calc. / Å | Error\(^1\) / Å |
|--------|--------|---------------------------|--------------------|----------------------|------------------|
| H2     | H3     | 3.083                     | 2.897              | 0.186                | 0.11             |
| H2     | H1a    | 2.742                     | 2.642              | 0.1                  | 0.05             |
| H2     | H1b    | 2.742                     | 2.636              | 0.106                | 0.05             |
| H2     | H1c    | 2.742                     | 2.637              | 0.105                | 0.05             |
| H3     | H6b    | 3.087                     | 3.054              | 0.033                | 0.11             |
| H3     | H1a    | 2.831                     | 2.857              | -0.026               | 0.11             |
| H3     | H1b    | 2.831                     | 2.857              | -0.026               | 0.11             |
| H3     | H1c    | 2.831                     | 2.857              | -0.026               | 0.11             |

\(^1\) The errors of the NOE distances were estimated according the rules as given by Butts et al.\(^3\). Distances lower than 2.8Å can be determined with an error 0.05Å and longer distances up to 4.5Å with an error of 0.11Å.

RMS deviation: 0.094 Å

Quality criterion \(13 / \chi^2\): 0.498
3. Sagittamide A

3.1 Parameter Setup for MDOC simulations

Table 6: Parameters used for the MDOC simulation on Sagittamide A

| Option                        | Parameter          | Remark                        |
|-------------------------------|--------------------|-------------------------------|
| Duration                      | 80 ns              |                               |
| Step                          | 0.5 fs             |                               |
| Temperature                   | 300 K              | Target temperature            |
| Coupling time to thermostat   | 0.02 ps            |                               |
| **NMR Data**                  |                    |                               |
| RDC values                    | 8                  | error 0.5 Hz                  |
| NOE distances                 | 7                  | error 0.2 Å, one value 0.4 Å  |
| J-couplings                   | 13                 | Experimental error of $^{3}J_{HH}$ 0.6 and of $^{3}J_{CH}$ 1 Hz |
| **Pseudo-forces**            |                    |                               |
| Rise time const. of DD pseudo forces | 200 ps     | RDC                           |
| Weight factor for DD pseudo energy | 0.001             | Pseudo-Energy 6.81 kJ/Mol at start |
| Width for DD pseudo energy    | 1 Hz               |                               |
| Memory time constant for DD couplings | 200 ps     | RDC mean value                |
| Weight factor for $^{3}$J-couplings | 4                 |                               |
| Width for $^{3}$J-couplings   | 2.0 Hz             |                               |
| Memory time constant for $^{3}$J-couplings | 200 ps     | $^{3}$J-mean value            |
| Weight factor for R constraints | 0.5              |                               |
| Width for R constraints       | 0.3 Å              |                               |
| Memory time constant for R constraints | 200 ps | NOE distance average          |

In the work on Sagittamide A only one bond $^{1}$H-$^{13}$C dipolar couplings are taken into account as orientational constraints. Therefore we assigned a dipolar tensor to every H-C-bond under investigation. The value of $D = 23.13665$ kHz was calculated for the nuclear distance of 1.093 Å. All calculated $^{1}$H-$^{13}$C dipolar couplings are scaled down by an order parameter of the alignment medium of $S_{am} = 0.004$. 
3.2 Results of the MDOC Simulations

Table 7: Mean Dipolar Couplings of Configuration $a$ of Sagittamide A

| Nr | Atom 1 | Atom 2 | Experimental RDC / Hz | Error / Hz | Calculated RDC / Hz |
|----|--------|--------|-----------------------|------------|---------------------|
| 1  | H10    | C10    | 5.9                   | 0.5        | 5.824               |
| 2  | H9     | C9     | 8.8                   | 0.5        | 8.739               |
| 3  | H8     | C8     | 9.1                   | 0.5        | 8.99                |
| 4  | H7     | C7     | 8                     | 0.5        | 7.745               |
| 5  | H6     | C6     | -2                    | 0.5        | -1.775              |
| 6  | H5     | C5     | 3.5                   | 0.5        | 3.604               |
| 7  | H4a    | C4     | 5                     | 0.5        | 4.672               |
| 8  | H4b    | C4     | 14.1                  | 0.5        | 13.599              |

The experimental RDC values are obtained from Schuetz et al. 4
The off diagonal elements of the calculated mean DD tensors are smaller than 0.025 Hz.
RMS deviation: 0.25 Hz
Quality criterion $n/\chi^2$ 3.94

Table 8: of Mean $^3J$ Couplings of Configuration $a$ of Sagittamide A

| Nr | Atom 1 | Atom 2 | Experimental $^3J$ coupling / Hz | Error / Hz | Calculated value / Hz |
|----|--------|--------|---------------------------------|------------|-----------------------|
| 1  | C10    | H8     | 3.2                             | 1.65       | 2.714                 |
| 2  | C9     | H7     | 0.7                             | 1.65       | 2.618                 |
| 3  | C8     | H10    | 0.7                             | 1.65       | 2.777                 |
| 4  | C7     | H5     | 1.7                             | 1.65       | 2.345                 |
| 5  | C6     | H8     | 1                               | 1.65       | 2.643                 |
| 6  | C5     | H7     | 1.6                             | 1.65       | 2.718                 |
| 7  | H10    | H9     | 1.65                            | 1.25       | 3.731                 |
| 8  | H9     | H8     | 9.4                             | 1.25       | 8.884                 |
| 9  | H8     | H7     | 1.45                            | 1.25       | 2.267                 |
| 10 | H7     | H6     | 7.1                             | 1.25       | 6.441                 |
| 11 | H6     | H5     | 4.8                             | 1.25       | 5.243                 |
| 12 | H5     | H4a    | 2.8                             | 1.25       | 3.647                 |
| 13 | H5     | H4b    | 8.8                             | 1.25       | 8.107                 |

The experimental $^3J$ coupling values are obtained from Schuetz et al. 4
The $^3J_{HH}$ couplings are calculated using the method of Haasnoot et al. 5 and the $^3J_{CH}$ couplings according to Palermo et al. 6. The time mean value was calculated using the equations (5) and (6).
The error was estimated as the sum of the experimental error and the RMS deviation of the prediction 5, 6.
Root mean square deviation: 1.60 Hz
$\chi^2$ 7.69
Quality criterion $n/\chi^2$ 1.70
Table 9: Distance Constraints of Configuration a of Sagittamide A

| Nr | Atom 1 | Atom 2 | NOE Distance / Å | Error / Å | Calculated Distance / Å |
|----|--------|--------|------------------|-----------|------------------------|
| 1  | H10    | H9     | 2.4              | 0.2       | 2.508                  |
| 2  | H10    | H8     | 2.9              | 0.2       | 2.941                  |
| 3  | H8     | H7     | 2.4              | 0.2       | 2.37                   |
| 4  | H8     | H6     | 3.1              | 0.4       | 2.977                  |
| 5  | H8     | H5     | 2.45             | 0.2       | 2.951                  |
| 6  | H7     | H5     | 2.9              | 0.2       | 2.917                  |
| 7  | H6     | H5     | 2.6              | 0.2       | 2.551                  |

RMS Deviation / Å: 0.20
Quality criterion n/χ²: 1.03

The experimental NOE distances are obtained from A. Schütz⁷
Calculated NOE mean values according to Torda et al.⁸ (see eq. (12) of the paper).

3.3 Full statistics of the torsion angles C7 to C10

The analysis is performed using Mathematica. The following matrix contains the population of the combination of torsion states. The torsion angles are counted within two regions: values between -120 and 120° are regarded as gauche and the values between +/- 120 and +/-180 are counted as trans.

Table 10: Populations of combinations of torsion angles of the bonds C5 to C9
{ C7-C8-C9-C10, C6-C7-C8-C9, C5-C6-C7-C8, C4-C5-C6-C7 }

| Probability / % | Torsion angle combination                      |
|-----------------|-------------------------------------------------|
| 22.0            | {trans, trans, trans, gauche}                   |
| 18.0            | {trans, trans, gauche, trans}                   |
| 14.6            | {trans, trans, trans, trans}                    |
| 14.4            | {trans, trans, gauche, gauche}                  |
| 8.7             | {trans, gauche, trans, gauche}                  |
| 7.2             | {trans, gauche, gauche, gauche}                 |
| 5.6             | {trans, gauche, gauche, trans}                  |
| 3.8             | {trans, gauche, trans, trans}                   |
| 1.2             | {trans, gauche, trans, gauche}                  |
| 1.1             | {gauche, gauche, trans, gauche}                 |
| 0.9             | {gauche, trans, trans, gauche}                  |
| 0.7             | {gauche, gauche gauche, gauche}                 |
| 0.6             | {gauche, gauche, gauche, trans}                 |
| 0.5             | {gauche, gauche, trans, trans}                  |
| 0.4             | {gauche, trans, trans, trans}                   |
| 0.3             | {trans, gauche, trans, trans}                   |

⁷C. M. Thiele, A. Marx, R. Berger, J. Fischer, M. Biel, and A. Giannis; Determination of the Relative Configuration of a Five-Membered Lactone from Residual Dipolar Couplings, Angew. Chem. Int. Ed. 2006, 45, 4455 –4460. Supporting Information added 2009.
⁸A. Kolmer, L. J. Edwards, I. Kuprov, C. M. Thiele; Conformational analysis of small organic molecules using NOE and RDC data: A discussion of strychnine and a-methylene-c-butyrolactone; Journal of Magnetic Resonance 2015 261 101–109.
3 C. P. Butts, C. R. Jones, E. C. Towers, J. L. Flynn, L. Appleby and N. J. Barron; Interproton distance determinations by NOE – surprising accuracy and precision in a rigid organic molecule; Org. Biomol. Chem., 2011, 9, 177 -184.
4 A. Schuetz, J. Junker, A. Leonov, O. F. Lange, T. F. Molinski, and C. Griesinger; Stereochemistry of Sagittamide A from Residual Dipolar Coupling Enhanced NMR; Supplementary material; J. Am. Chem. Soc. 2007 129 15114-15115.
5 C. A. G. Haasnoot, F. A. A. M. de Leew and C. Altona; The Relationship between Proton-Proton NMR Coupling Constants and Substituent Electronegativities; Tetrahedron 1980 36 2783-2792.
6 G. Palermo, R. Riccio, and G. Bifulco; Effect of Electronegative Substituents and Angular Dependence on the Heteronuclear Spin-Spin Coupling Constant $^3J_{C,H}$: An Empirical Prediction Equation Derived by Density Functional Theory Calculations; J. Org. Chem. 2010, 75, 1982–1991.
7 A. Schütz, private communication
8 A. E. Torda, and W. F. van Gunsteren, Computer Physics Communications 1991, 62, 289-296.