Electronic Supplementary Material (ESI) for Physical Chemistry Chemical Physics.

Supplementary Information

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

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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:

$$\mathbf{D}(t) = \frac{1}{N(t)} \int_{t'=t_0}^{t} e^{\frac{-(t-t')}{\tau}} \mathbf{D}(t') \quad dt'$$

$$N(t) = \int_{t'=t_0}^{t} e^{\frac{-(t-t')}{\tau}} \quad dt' \tag{1}$$

The second integral N(t) is the norm and τ 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 Δt with t' ={0,...,n Δt} the folding integral (1) can be written in matrix form as follows:

$$\begin{pmatrix} \mathbf{d}_{t_0} \\ \mathbf{d}_{t_1} \\ \vdots \\ \mathbf{d}_{t_n} \end{pmatrix} = \begin{pmatrix} e^{-\frac{0}{\tau}} & 0 & \cdots & 0 \\ e^{-\frac{\Delta t}{\tau}} & e^{-\frac{0}{\tau}} & \cdots & 0 \\ \vdots & \vdots & \vdots & \vdots \\ e^{-\frac{n\Delta t}{\tau}} & e^{-\frac{(n-1)\Delta t}{\tau}} & \cdots & e^{-\frac{0}{\tau}} \end{pmatrix} \begin{pmatrix} \mathbf{D}_{t'_0} \\ \mathbf{D}_{t'_1} \\ \vdots \\ \mathbf{D}_{t'_n} \end{pmatrix} \tag{2}$$

The values on the main diagonal of the matrix in eq. (2) are *1*. 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:

$$\langle \mathbf{D} \rangle_{k\Delta t} = \frac{\mathbf{d}_k}{N_k} \tag{3}$$

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 *1* as elements. From (2) we can write down the following recursion for **d** and N:

$$\begin{aligned}
&\mathbf{d}_0 = \mathbf{D}_0 \\
&\mathbf{d}_{k+1} = \mathbf{d}_i e^{-\frac{\Delta t}{\tau}} + \mathbf{D}_{k+1} \\
&N_0 = 1 \\
&N_{k+1} = N_k e^{-\frac{\Delta t}{\tau}} + 1
\end{aligned} \tag{4}$$

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 $< D >_{k\Delta t}$:

$$\begin{aligned}
&\langle \mathbf{D} \rangle_{t=0} = \mathbf{D}_0 \\
&N_0 = 1 \\
&N_{k+1} = N_k e^{-\frac{\Delta t}{\tau}} + 1 \\
&\langle \mathbf{D} \rangle_{(k+1)\Delta t} = \frac{1}{N_{k+1}} \left(\mathbf{D}_{k+1} + N_k \langle \mathbf{D} \rangle_{k\Delta t} \, e^{-\frac{\Delta t}{\tau}} \right)
\end{aligned} \tag{5}$$

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:

$$A = \sum_i \Delta\chi_i \left[P_4 + P_5 \cos^2 \left(\xi_i \phi + P_6 \left| \Delta\chi_i \right| \right) \right] \tag{6}$$

The derivative to cos(φ) gives:

$$\frac{\partial A}{\partial \cos(\phi)} = \sum_i \Delta\chi_i \left[2P_5 \cos \left(\xi_i \phi + P_6 \left| \Delta\chi_i \right| \right) \cos \left(P_6 \left| \Delta\chi_i \right| \right) \right] \tag{7}$$

If the coupling atoms are denoted with A and B the cos(φ) 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(φ) 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

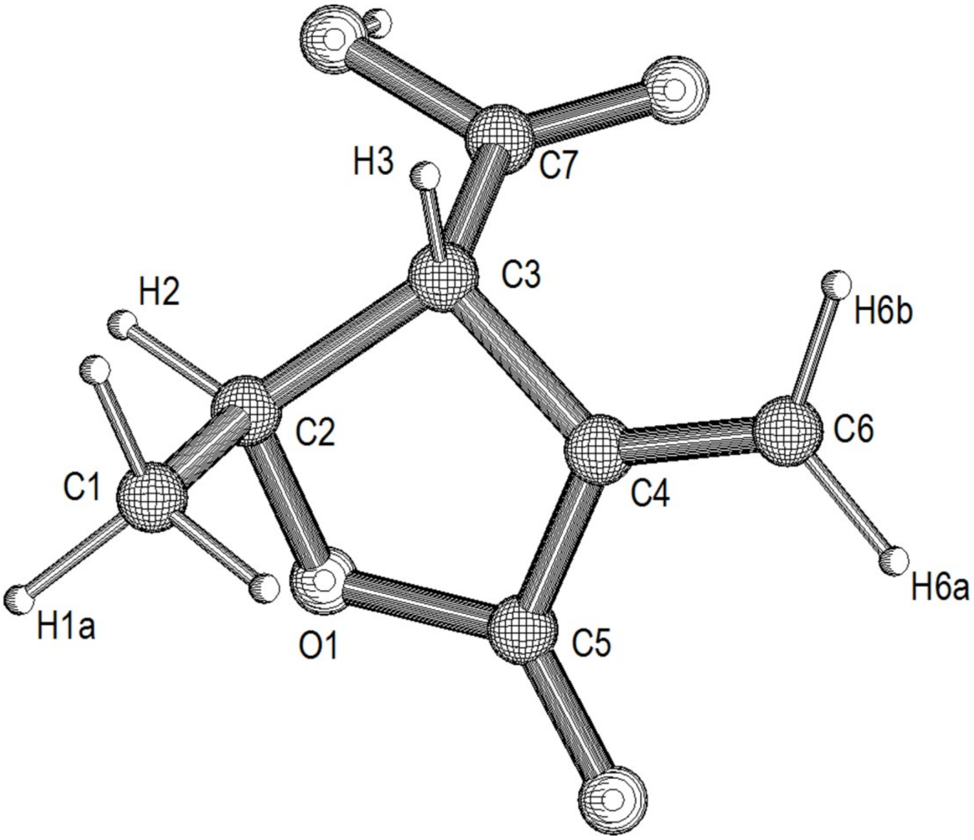

Figure 1: α-Methylene-γ-butyrolactone with numbering of its atoms.

Table 1: Constraints for MDOC Simulations:

Number of Constraints	NMR Data Type	Remarks
7	one bond ^1H-^{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	^3J couplings[1]	Constraints
6	NOE distances[2]	Constraints

Table 2: Simulation parameters for MDOC Simulations

General parameters for the MDOC simulations	
Parameter	Value
Target temperature	300 K
MD time step	0.5 fs
BPT atomic charge calculation	2 fs
Coupling time η to the heat bath	0.02 ps
Memory decay time τ for the property average	200 ps
Time constant ρ for the exponential rise of pseudo-forces	200 ps
Order parameter of the alignment medium S_{am} (dipolar couplings)	0.008

Width and weight parameters for the pseudo forces	
Parameter	Value
Pseudo-force width ΔD 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 ΔD 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 ΔR 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 ΔJ 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] ^{3}J coupling / Hz	MDOC Simulation ^{3}J 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	2.082	-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		

Nr. Values/χ^2: 24/15.4203 = 1.556

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	Error1) / 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/χ^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 $^3J_{HH}$ 0.6 and of $^3J_{CH}$ 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/χ^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

χ^2 7.69

Quality criterion n/χ^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/χ^2 1.03

The experimental NOE distances are obtained from A. Schütz[7]

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, **gauge**}*
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}*

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