Electronic Supplementary Information for

Gadolinium Complexes of Monophosphinic Acid DOTA Derivative Conjugated to Cyclodextrin Scaffolds: Efficient MRI Contrast Agents for Higher Magnetic Fields

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Set of equations used for fitting of relaxometric data.
Fig. S1. (A) SE-HPLC chromatograms of products from reaction of α-CD-(NH₂)₆ with 2 (black), 4 (magenta), 6 (green) and 9 equivs (blue) of DO3APNCS; the reaction mixtures were worked-up by ultrafiltration using membrane with 1 kDa cut-off. (B) Comparison of SE-HPLC chromatograms of product from reaction between β-CD-(NH₂)₇ and 10.5 equivs of DO3APNCS (separated by ultrafiltration using 3 kDa membrane, red) and reaction mixture of β-CD-(NH₂)₇ with 10.5 equivs of DO3APNCS in presence of 20 equivs of benzoate (black). The chromatograms of DO3APABn (blue) and the ditopic byproduct (DO3AP)₂CS (green) are shown for the comparison. The last peak (~27 min) corresponds to the benzoic acid.

Fig. S2. ¹H NMR spectra of the CD–DO3APNCS conjugates. (A) L₆-α-CD; (B) L₇-β-CD.
Fig. S3. MALDI-MS spectra of (LaL)$_6$-α-CD (A) and (YL)$_7$-β-CD (B).

Fig. S4. Suggested solution structure of the L$_7$-β-CD conjugate.
Comparison of steric crowding of conjugates with α and β-cyclodextrins

Let’s suggest that cyclodextrin is a regular cylindrical molecule. For such a case, its circumference is given by:

\[ \text{circ}_{\text{CD}} = n \cdot d_{\text{SU}} \]

where \( n \) is a number of sugar units and \( d_{\text{SU}} \) is mean length of one sugar unit.

The diameter of the cyclodextrin molecule is given by:

\[ d_{\text{CD}} = \frac{\text{circ}_{\text{CD}}}{\pi} \]

Let’s suggest that conjugate has disc geometry. Thus, after conjugation, the diameter is increased by two mean lengths of complex unit, \( d_{\text{complex}} \):

\[ d_{\text{conjug}} = d_{\text{CD}} + 2 \cdot d_{\text{complex}} \]

The circumference of whole conjugate disc is then:

\[ \text{circ}_{\text{conjug}} = \pi \cdot d_{\text{conjug}} = \pi \cdot (d_{\text{CD}} + 2 \cdot d_{\text{complex}}) = \text{circ}_{\text{CD}} + 2 \cdot \pi \cdot d_{\text{complex}} = n \cdot d_{\text{SU}} + 2 \cdot \pi \cdot d_{\text{complex}} \]

The part of circumference available for one complex unit is then:

\[ \frac{\text{circ}_{\text{conjug}}}{n} = d_{\text{SU}} + 2 \cdot \pi \cdot d_{\text{complex}} / n \]

When one is assuming larger \( n+1 \) cyclooligomer, it gives:

\[ \frac{\text{circ}_{\text{conjug}}}{(n+1)} = d_{\text{SU}} + 2 \cdot \pi \cdot d_{\text{complex}} / (n+1), \]

i.e. part of circumference available for complex is decreasing with increasing number of sugar units, and therefore, steric crowding in the disc plane increases. E.g., for typical lengths in the cyclodextrin–DOTA-like conjugate case, the distances are \( d_{\text{SU}} \sim 4.3 \text{ Å} \) and \( d_{\text{complex}} \sim 6 \text{ Å} \), it gives \( \text{circ}_{\text{conjug}} \sim 10.6 \text{ and } 9.7 \text{ Å} \), respectively, for α- and β-cyclodextrin conjugates.
Fig. S5. $^1$H and $^{31}$P($^1$H) NMR spectra of (EuL)$_6$-α-CD (25 °C).

Fig. S6. $^1$H NMRD profiles of the (GdL)$_6$-α-CD conjugate and the magnetically diluted species, (GdL)(LaL)$_5$-α-CD and (GdL)$_3$(LaL)$_3$-α-CD, acquired at 25 °C (relaxivity calculated per one Gd$^{3+}$ ion).
Table S1. MALDI-MS data for (LaL)_6-α-CD.

<table>
<thead>
<tr>
<th>Found m/z</th>
<th>Ion°</th>
<th>Formula</th>
<th>Calculated m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>5212.8</td>
<td>[(LaL)_6-α-CD+7H]^+</td>
<td>C_{174}H_{253}La_{6}N_{36}O_{72}P_{6}S_{6}^+</td>
<td>5211.84 (100.0 %)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5210.84 (86.3 %)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>5212.85 (52.2 %)</td>
</tr>
<tr>
<td>4640.6</td>
<td>[(LaL)_3-α-CD+La+3H]^+</td>
<td>C_{151}H_{210}La_{6}N_{31}O_{64}P_{6}S_{6}^+</td>
<td>4639.65 (100.0 %)</td>
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<td></td>
<td>4640.66 (85.2 %)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>4641.66 (58.9 %)</td>
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<tr>
<td>4504.8</td>
<td>[(LaL)_3-α-CD+6H]^+</td>
<td>C_{151}H_{222}La_{6}N_{31}O_{64}P_{6}S_{6}^+</td>
<td>4503.77 (100.0 %)</td>
</tr>
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<td></td>
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<td></td>
<td>4504.77 (99.7 %)</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>4502.77 (58.4 %)</td>
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<tr>
<td>3932.6</td>
<td>[(LaL)_4-α-CD+La+2H]^+</td>
<td>C_{128}H_{188}La_{5}N_{31}O_{64}P_{6}S_{6}^+</td>
<td>3932.58 (100.0 %)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>3933.59 (74.6 %)</td>
</tr>
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<td>3931.58 (66.1 %)</td>
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<tr>
<td>3225.5</td>
<td>[(LaL)_3-α-CD+La+H]^+</td>
<td>C_{105}H_{157}La_{4}N_{21}O_{48}P_{6}S_{6}^+</td>
<td>3225.52 (100.0 %)</td>
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<td></td>
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<td>3224.51 (85.2 %)</td>
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<td>3226.52 (66.6 %)</td>
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° As the complexing unit of DO3AP^Ah is four-valent acid, the (LaL) complex unit in the formulas above means the fully deprotonated species with one negative charge, i.e. (LaL)^-.

Table S2. MALDI MS data for (YL)_7-β-CD.

<table>
<thead>
<tr>
<th>Found m/z</th>
<th>Ion°</th>
<th>Formula</th>
<th>Calculated m/z</th>
</tr>
</thead>
<tbody>
<tr>
<td>5730.9</td>
<td>[(YL)_7-β-CD+8H]^+</td>
<td>C_{203}H_{295}N_{42}O_{84}P_{7}S_{7}Y_{7}^+</td>
<td>5730.98 (100.0%)</td>
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<td>5729.98 (99.0%)</td>
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<td></td>
<td></td>
<td>5728.98 (82.2%)</td>
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<tr>
<td>5159.8</td>
<td>[(YL)_6-β-CD+Y+4H]^+</td>
<td>C_{180}H_{261}N_{37}O_{76}P_{6}S_{6}Y_{7}^+</td>
<td>5158.79 (100.0%)</td>
</tr>
<tr>
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<td></td>
<td>5157.79 (81.3%)</td>
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<td>5159.80 (53.8%)</td>
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<tr>
<td>5073.9</td>
<td>[(YL)_6-β-CD+7H]^+</td>
<td>C_{180}H_{264}N_{37}O_{76}P_{6}S_{6}Y_{6}^+</td>
<td>5072.91 (100.0%)</td>
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<td>5071.91 (88.9%)</td>
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<td>5073.91 (87.0%)</td>
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<tr>
<td>4501.7</td>
<td>[(YL)_5-β-CD+Y+3H]^+</td>
<td>C_{157}H_{230}N_{32}O_{68}P_{6}S_{5}Y_{6}^+</td>
<td>4501.72 (100.0%)</td>
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<tr>
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<td>4500.72 (94.5%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4499.72 (52.8%)</td>
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</table>

° As the complexing unit of DO3AP^Ah is four-valent acid, the (YL) complex unit in the formulas above means the fully deprotonated species with one negative charge, i.e. (YL)^-.

Table S3. Luminescence lifetimes of the (Eu/TbL)_7-β-CD complexes and related compounds (Eu: λ_ex 396 nm, λ_em 595 and 616 nm; Tb: λ_ex 353 nm, λ_em 488 and 544 nm).

<table>
<thead>
<tr>
<th>Compound</th>
<th>(\tau (H_2O) / \mu s)</th>
<th>(\tau (D_2O) / \mu s)</th>
<th>(q^a)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>(EuL)_7-β-CD</td>
<td>815</td>
<td>2240</td>
<td>0.82/0.64</td>
<td>this work</td>
</tr>
<tr>
<td>(TbL)_7-β-CD</td>
<td>1750</td>
<td>2730</td>
<td>0.86/0.73</td>
<td>this work</td>
</tr>
<tr>
<td>Eu^{III}-DO3AP^Ah</td>
<td>680</td>
<td>2110</td>
<td>1.05/0.90</td>
<td>this work</td>
</tr>
<tr>
<td>Tb^{III}-DO3AP^Ah</td>
<td>1620</td>
<td>2850</td>
<td>1.12/1.03</td>
<td>this work</td>
</tr>
<tr>
<td>Eu^{III}-DOTA</td>
<td>625</td>
<td>1890</td>
<td>1.12/0.98</td>
<td>ref.[1]</td>
</tr>
<tr>
<td>Tb^{III}-DOTA</td>
<td>1515</td>
<td>2560</td>
<td>1.13/1.05</td>
<td>ref.[1]</td>
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</tbody>
</table>

\(q^a\) Hydration numbers calculated according to Horrocks[^2]/Parker[^1] equations.
Table S4. $^{17}$O NMR relaxometric data of (GdL)$_6$-$\alpha$-CD and (GdL)$_7$-$\beta$-CD at 54.3 MHz (i.e. $^1$H 400 MHz, 9.40 T).

<table>
<thead>
<tr>
<th>$T$ / K</th>
<th>$r_1$ / s$^{-1}$ mM$^{-1}$</th>
<th>(GdL)$_6$-$\alpha$-CD</th>
<th>$r_2$ / s$^{-1}$ mM$^{-1}$</th>
<th>$\omega$ / rad s$^{-1}$ mM$^{-1}$</th>
<th>$r_1$ / s$^{-1}$ mM$^{-1}$</th>
<th>(GdL)$_7$-$\beta$-CD</th>
<th>$r_2$ / s$^{-1}$ mM$^{-1}$</th>
<th>$\omega$ / rad s$^{-1}$ mM$^{-1}$</th>
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<tbody>
<tr>
<td>283.2</td>
<td>2.217</td>
<td>16.38</td>
<td>-13.25</td>
<td>2.278</td>
<td>16.20</td>
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<td>298.0</td>
<td>1.618</td>
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<td>-13.84</td>
<td>0.826</td>
<td>3.895</td>
<td>-13.29</td>
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<td>306.7</td>
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<td>0.637</td>
<td>2.667</td>
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<td>0.367</td>
<td>1.345</td>
</tr>
<tr>
<td>316.2</td>
<td>0.981</td>
<td>5.821</td>
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<td>0.367</td>
<td>1.345</td>
<td>-11.16</td>
<td>0.367</td>
<td>1.345</td>
</tr>
</tbody>
</table>

Table S5. $^1$H NMR relaxivities of (GdL)$_6$-$\alpha$-CD and (GdL)$_7$-$\beta$-CD.

<table>
<thead>
<tr>
<th>$B$ / MHz</th>
<th>$r_1$ / s$^{-1}$ mM$^{-1}$</th>
<th>(GdL)$_6$-$\alpha$-CD</th>
<th>$B$ / MHz</th>
<th>$r_1$ / s$^{-1}$ mM$^{-1}$</th>
<th>(GdL)$_7$-$\beta$-CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>298.2 K</td>
<td>0.0100</td>
<td>24.6</td>
<td>310.2 K</td>
<td>0.0100</td>
<td>28.5</td>
</tr>
<tr>
<td>0.0164</td>
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<td>23.02</td>
<td>0.0147</td>
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<td>22.60</td>
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<tr>
<td>0.0267</td>
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<td>23.63</td>
<td>0.0214</td>
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<tr>
<td>0.0438</td>
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<td>0.0314</td>
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<td>22.38</td>
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<tr>
<td>0.0716</td>
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<td>23.01</td>
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<td>22.58</td>
</tr>
<tr>
<td>0.117</td>
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<td>23.02</td>
<td>0.0674</td>
<td>28.67</td>
<td>22.61</td>
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<td>0.191</td>
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<td>22.23</td>
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<td>22.58</td>
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<td>3.66</td>
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<td>9.56</td>
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<td>14.28</td>
<td>18.32</td>
<td>13.63</td>
</tr>
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</table>

Table S6. $^1$H NMR relaxivities of (GdL)$_6$-$\alpha$-CD and (GdL)$_7$-$\beta$-CD measured at clinical fields (1.5 and 3.0 T) compared with values predicted by analysis of $^1$HNMRD profile (in italics). Values of relaxivity are suggested to be loaded by ESD’s of approximately ±1 s$^{-1}$ mM$^{-1}$ due to range of averaged voxels, and principal error in ensuring temperature stability.

<table>
<thead>
<tr>
<th>$B$ / MHz</th>
<th>$r_1$ / s$^{-1}$ mM$^{-1}$</th>
<th>(GdL)$_6$-$\alpha$-CD</th>
<th>$B$ / MHz</th>
<th>$r_1$ / s$^{-1}$ mM$^{-1}$</th>
<th>(GdL)$_7$-$\beta$-CD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5</td>
<td>63.9</td>
<td>17.8(18.8)</td>
<td>15.3(14.8)</td>
<td>19.8(20.2)</td>
<td>14.2(15.9)</td>
</tr>
<tr>
<td>3.0</td>
<td>128.8</td>
<td>13.2(12.6)</td>
<td>12.5(13.7)</td>
<td>12.6(13.7)</td>
<td>12.7(12.3)</td>
</tr>
</tbody>
</table>
Simultaneous fit of 1H NMRD and 17O T1, T2 and dwr NMR data
Molecular tumbling modelled by Lipari-Szabo approach

IndVars: T,B
DepVars: R1H,lnT1O,lnT2O,dwr

All possible parameters:
tv0,Ev,delta,n,tm0,Hm,tr0l,tr0lH,tr0g,Erl,Erg,RLS,ro,rh,rhos,acc,khi,Cout,nss,tm0ss,Hmss
It is necessary to choice in maximum 20 of them, otherwise Scientist breaks
Params: tv0,Ev,delta,n,tm0,Hm,tr0l,tr0g,Erl,Erg,RLS,ro,rh,rhos,acc,khi,Cout,nss,tm0ss,Hmss

Notes
Temperature is in Kelvins
Magnetic field is in Larmor frequencies
Relaxivities and shifts are given per millimolar solution
"ln" means natural logarithm
Pm is molar fraction of coordinated water, Pm = q*c(Gd)/55.56

Reduced times T1,2Or are calculated by:
T1,2Or = (1/Pm)*(1/{T1,2O(Gd-sample)}-1/{T1,2O(blank)})

Reduced frequencies (shifts) dwr are calculated by:
dwr = B*1E-6*(2*pi/c(Gd))*{(shift(O,Gd-sample)-shift(O,blank))- (shift(H,Gd-sample)-shift(H,blank))}
where B is in MHz, c(Gd) is in mM and shifts are in ppm
Alternatively
dwr = (2*pi/c(Gd))*{(shift(O,Gd-sample)-shift(O,blank))- (go/gh)*(shift(H,Gd-sample)-shift(H,blank))}
where shifts are in Hz
Be careful, somebody is fitting using frequency wr calculated by
wr = B*(2*pi/Pm)*{(shift(H,Gd-sample)-shift(H,blank))- (shift(O,Gd-sample)-shift(O,blank))}
(here, shifts are in ppm scale)
Which can be transferred to dwr by
dwr = wr*1e-3/55.56

Parameters and variables used
T - temperature [K]
B - used field [MHz for 1H]
R1H - 1H longitudinal relaxivity [ms-1 mM-1]
R1O - 17O longitudinal relaxivity [ms-1 mM-1]
R2O - 17O transversal relaxivity [ms-1 mM-1]
n - number of water molecules coordinated at Gd
tm0 - water residence time at 298 K [s]
tm0ss - water residence time at 298 K for second sphere [s]
tr0l - local rotation correlation time of Gd-O vector at 298 K [s]
tr0lH - local rotation correlation time of Gd-H vector at 298 K [s]
tr0g - global rotation correlation time at 298 K [s]
trss - rotation correlation time of second sphere [s]
tv0 - correlation time for instantaneous distortion of the metal coordination polyhedron at 298 K [s]
dwr - 17O reduced radial frequency difference of bonded and free water [rad s-1]
delta - Δ2, mean squared fluctuation of ZFS
Erl - rotation free energy (local motion) [kJ mol-1]
Erg - rotation free energy (global motion) [kJ mol-1]
Hm - water exchange free energy [kJ mol-1]
acc - hyperfine Gd-O coupling constant A*hbar
ro - Gd-O distance [m]
rh - Gd-H distance [m]
rhos - shortest Gd-H distance from outer sphere to Gd [m]
RLS - degree of spatial restriction of the local motion
D0 - diffusion coefficient at 298 K
khi - term with quadrupolar coupling constant and asymmetry parameter = χ*(1+(η^2)/3)^0.5
Cout - outer sphere contribution to 17O NMR shift
nss - number of water molecules at second sphere
// rss - Gd-ss distance; sometime simplified that rss=a
// Hmss - water exchange free energy for second sphere contribution

// Physical constants implicitly used
// p - Ludolf's number (π = 3.14159265)
// univ - universal gas constant (R = 8.31441 J mol⁻¹ K⁻¹)
// gh - gyromagnetic ratio of 1H (γH = 2.675E8 rad s⁻¹ T⁻¹)
// go - gyromagnetic ratio of 17O (γO = -3.626E7 rad s⁻¹ T⁻¹)
// gs - electronic gyromagnetic ratio (γs = 1.75977E11 rad s⁻¹ T⁻¹)
// S - multiplicity of Gd (S = 3.5)
// Sz - spin z projection (Sz = 2*S*(S+1) = 31.5)
// mB - Bohr magneton (μB = 9.274E-24 J T⁻¹)
// m0 - vacuum magnetic susceptibility (μ0 = 4πE-7)
// h - Planck constant (h = 6.626071E-34 J s)
// hbar - reduced Planck constant (h/(2*π) = 1.0546E-34 J s rad⁻¹)
// NA - Avogadro constant (NA = 6.023E23 mol⁻¹)
// k - Boltzmann constant (kB = 1.38066E-23 J K⁻¹)
// g - electron g-factor (g = 2.002319304362)

// Definitions of constants
p=3.14159265
univ=8.31441
gh=2.675E8
go=-3.626E7
gs=1.75977E11
C1=2.4
C2=1.2
C3=5.25
C4=4.7604E-45
C5=3.4274E-59
C6=0.1657
C7=9.5209E-45
C8=0.9475
C9=5.181644E-43
C10=5.796E-19

// Calculation of diffusion coefficient (D)
// Hindman alternative
B1=3.118150E-04
B2=5.062560E+03
B3=1.547920E+02
B4=1.629310E+03
D=(1E-4))/((B1*EXP(B2/T))+(B3*EXP(B4/T)))
// Alternative using activation theory
//D0=25E-10 m² s⁻¹
//ED=22 kJ mol⁻¹
//D0=25E-10
//ED=22E3
//D=D0*exp((ED/univ)*((1/298.15)-(1/T)))
// Definition of molar fraction of coordinated water molecules
P_m = n*1E-3/55.55

// Definition of Larmor (angular) frequencies of 1H (wh), 17O (wo) and electron (ws)
wh = 2*p*1E6*B
wo = 2*p*1E6*B*(go/gh)
ws = 2*p*1E6*B*(gs/gh)

// Eyring equations
\[ t_m = (tm0*298.15/T)\exp((-H_m/univ)*((1/298.15)-(1/T))) \]
\[ t_{mss} = (tm0ss*298.15/T)\exp((-H_{mss}/univ)*((1/298.15)-(1/T))) \]
\[ t_{rl} = tr0l*\exp((-E_r/l/univ)*((1/298.15)-(1/T))) \]
\[ t_{rlH} = tr0lH*\exp((-E_{rlH}/univ)*((1/298.15)-(1/T))) \]
\[ t_r = tv0*\exp((-E_v/univ)*((1/298.15)-(1/T))) \]

// Electronic relaxation times T1e, T2e
// Alternative taking into account only zero field splitting (ZFS)
// McLachlan theory
\[ T_{1e} = (C1*delta*t_v*((1/(1+ws^2*t_v^2))+(4/(1+4*ws^2*t_v^2))))^{-1} \]
\[ T_{2e} = (C2*delta*t_v^3*(3+(5/(1+ws^2*t_v^2))+(2/(1+4*ws^2*t_v^2))))^{-1} \]
// Powell alternative
\[ T_{2e} = (delta*t_v^3((5.26/(1+0.372*ws^2*t_v^2)))+(7.18/(1+1.24*ws^2*t_v^2))))^{-1} \]

// Alternative including spin rotation (SR) term using local rotational time
\[ T_{1e} = (C1*delta*t_v*((1/(1+ws^2*t_v^2))+(4/(1+4*ws^2*t_v^2)))+(dg/(9*trl)))^{-1} \]
\[ T_{2e} = (delta*t_v^3((5.26/(1+(0.372*ws^2*t_v^2)))+(7.18/(1+1.24*ws^2*t_v^2)))+(dg/(9*trl)))^{-1} \]

// Correlation times (t - total, l - local, g - global, e - electronic)
// Dunand suggestion for trlH/trl ratio
\[ t_{rl} = t_{rl}^{-1} \]
\[ t_{rl}^{-1} = (t_{rl}^{-1}+t_{rlH}^{-1})^{-1} \]
\[ t_{cl} = (T_{1e}^{-1}+t_{rl}^{-1}+t_{rlH}^{-1})^{-1} \]
\[ t_{c2l} = (T_{2e}^{-1}+t_{rl}^{-1}+t_{rlH}^{-1})^{-1} \]
\[ t_{c1lH} = (T_{1e}^{-1}+t_{rlH}^{-1}+t_{rlH}^{-1})^{-1} \]
\[ t_{c2lH} = (T_{2e}^{-1}+t_{rlH}^{-1}+t_{rlH}^{-1})^{-1} \]
\[ t_{c1g} = (T_{1e}^{-1}+t_{rl}^{-1}+t_{rlH}^{-1})^{-1} \]
\[ t_{c2g} = (T_{2e}^{-1}+t_{rl}^{-1}+t_{rlH}^{-1})^{-1} \]
\[ t_{1e} = (T_{1e}^{-1}+t_{rl}^{-1}+t_{rlH}^{-1})^{-1} \]
\[ t_{2e} = (T_{2e}^{-1}+t_{rl}^{-1}+t_{rlH}^{-1})^{-1} \]

// Radial frequency difference of bound and free water [rad s-1] (dwm)
dwm = (C6/T)*acc*B

// Spectral density functions for Lipari-Szabo approach
d10 = (RLS*t_{lc1g}((1+wo^2*tc1g^2))*+(1-RLS)*tc1l/(1+wo^2*tc1l^2))
d20 = (RLS*tc2g((1+wo^2*tc2g^2))*+(1-RLS)*tc2l/(1+wo^2*tc2l^2))
q10 = (RLS*trg((1+wo^2*trg^2))*+(1-RLS)*trt/(1+wo^2*trt^2))
q20 = (RLS*trg((1+4*wo^2*trg^2))*+(1-RLS)*trt/(1+4*wo^2*trt^2))
//d1H = (RLS*t_{1c1g}((1+wh^2*tc1g^2))*+(1-RLS)*tc1l/(1+wh^2*tc1l^2))
//d2H = (RLS*tc2g((1+wo^2*tc2g^2))*+(1-RLS)*tc2l/(1+wo^2*tc2l^2))
d1H = (RLS*t_{1c1g}((1+wh^2*tc1g^2))*+(1-RLS)*tc1l/(1+wh^2*tc1l^2))
d2H = (RLS*tc2g((1+wo^2*tc2g^2))*+(1-RLS)*tc2l/(1+wo^2*tc2l^2))
// ******************* 17O longitudinal relaxation *******************
//
// R1 dipolar (pseudocontact) contribution for 17O according to Lipari-Szabo (R1dO)
R1dO=(C7/(ro^6))*(3*d1O+7*d2O)
//
// R1 quadrupolar contribution for 17O according to Lipari-Szabo (R1qO)
R1qO=C8*khi^2*(0.2*q1O+0.8*q2O)
//
// Total T1 relaxation rate/time (R1mO/T1mO)
R1mO=R1dO+R1qO
T1mO=(R1mO)^(-1)
//
// Overall reduced T1 relaxation of 17O (R1O)
lnT1Or=ln(1/(T1mO+tm))
R1O=Pm/(T1mO+tm)

// ******************* 17O transversal relaxation *******************
//
// R2 scalar (contact) contribution for 17O (R2sO)
R2sO=C3*acc^2*((te1*(1+ws^2*te2^2)))
//
// R2 dipolar (pseudocontact) contribution for 17O according to Lipari-Szabo (R2dO)
R2dO=(C4/(ro^6))*(7*d1O+13*d2O)
//
// R2 dipolar (pseudocontact) Curie contribution for 17O (R2cO)
R2cO=(C5*wo^2/(T^2*ro^6))*(4*trg+3*trg/(1+wo^2*trg^2))
//
// Total T2 relaxation rate/time (R2mO/T2mO)
//R2mO=R2sO+R2dO+R2cO
R2mO=R2sO+R2dO
//R2mO=R2sO
T2mO=(R2mO)^(-1)
//
// Overall reduced T2 relaxation of 17O (R2O)
num=(T2mO^(-2))+(T2mO*tm)^(-1)+dwm^2
denom=(tm^(-1)+T2mO^(-1))^2+dwm^2
fract=num/denom
lnT2Or=ln(fract/tm)
R2O=Pm*fract/tm

// ******************* 17O chemical shift *******************
//
// Contribution of os (dwos) and total reduced frequency (dwr)
dwos=Cout*dwm
dwr=Pm*((dwm/((tm/T2mO+1)^2+(tm*dwm)^2))+dwos)

// ******************* 1H longitudinal relaxation *******************
//
// R1 inner sphere dipolar (pseudocontact) contribution for 1H according to Lipari-Szabo (R1dH, R1His)
R1dH=(C9/(rh^6))*(3*d1H+7*d2H)
T1mH=(R1dH)^(-1)
R1His=Pm/(T1mH+tm)
//
// R1 outer sphere contribution for 1H according to Freed (R1Hos);
// i - 1H nucleus, s - Gd3+ electron
tau=rhos^2/D
\[ z_{2i} = (\tau/T_{1e}) + ([0,1]*wh*\tau) \]
\[ z_{2s} = (\tau/T_{2e}) + ([0,1]*ws*\tau) \]
\[ os_{1} = \text{Re}\left( \frac{(1+0.25*(z_{2i}^{0.5})}{(1+z_{2i}^{0.5}+(4/9)*z_{2i}+(1/9)*(z_{2i}^{1.5}))} \right) \]
\[ os_{2} = \text{Re}\left( \frac{(1+0.25*(z_{2s}^{0.5})}{(1+z_{2s}^{0.5}+(4/9)*z_{2s}+(1/9)*(z_{2s}^{1.5}))} \right) \]
\[ R_{1Hos} = \text{Re}\left( \frac{C_{10}/(\rho*\Delta)}{3*os_{1}+7*os_{2}} \right) \]

\[
// R_{1} \text{ second sphere dipolar contribution for } 1H (R_{1Hss}) \\
tc_{1ss} = (T_{1e}^{-1}+tr_{ss}^{-1})^{-1} \\
tc_{2ss} = (T_{2e}^{-1}+tr_{ss}^{-1})^{-1} \\
R_{1dHss} = \left( \frac{C_{9}/(\rho*\Delta)}{3*tc_{1ss}/(1+wh^2*tc_{1ss}^2)+(7*tc_{2ss}/(1+ws^2*tc_{2ss}^2))} \right) \\
T_{1ms} = R_{1dHss}^{-1} \\
P_{ms} = n_{ss}*1E-3/55.55 \\
R_{1Hss} = P_{ms}/(T_{1ms}+tm_{ss}) \\
//
// Overall \text{ R}_{1} \text{ proton relaxivity } (R_{1H}) \\
// R_{1H} = R_{1His}+R_{1Hos}+R_{1Hss} \\
R_{1H} = R_{1His}+R_{1Hos} \\

\[
// \text{ Estimation of parameters} \\
// tv_{0}, Ev, delta, dg, n, tm_{0}, Hm, tr_{0I}, tr_{0H}, tr_{0g}, Er_{I}, Er_{IH}, Erg, RLS, ro, rh, a, acc, khi, Cout, n_{ss}, tm_{0ss}, Hm_{ss} \\
tv_{0} = 9.08E-12 \\
Ev = 1000 \\
delta = 0.0509E20 \\
dg = 0.11 \\
n = 1 \\
tm_{0} = 1.25E-8 \\
Hm = 45E3 \\
tr_{0} = 220E-12 \\
// tr_{0H} = 220E-12 \\
tr_{0g} = 1950E-12 \\
Er_{I} = 22E3 \\
// Er_{IH} = 22E3 \\
Erg = 22E3 \\
RLS = 0.37 \\
ro = 2.5E-10 \\
rh = 3.1E-10 \\
\rho_{os} = 3.5E-10 \\
acc = -3.18E6 \\
khi = 7.58E6 \\
Cout = 0.0 \\
n_{ss} = 0 \\
tm_{0ss} = 1E-9 \\
Hm_{ss} = 10E3 \\
tr_{ss} = 1E-10 \\

References
