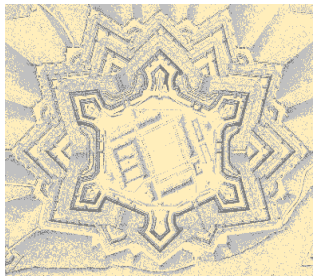
Università del Piemonte Orientale
"Amedeo Avogadro"



Alessandria: La Cittadella

Intensive Programme

"Design, Synthesis and Validation of Imaging Probes"

Torino – September 19-30, 2011

Gd^{III} complexes: mechanisms of action and optimization strategies

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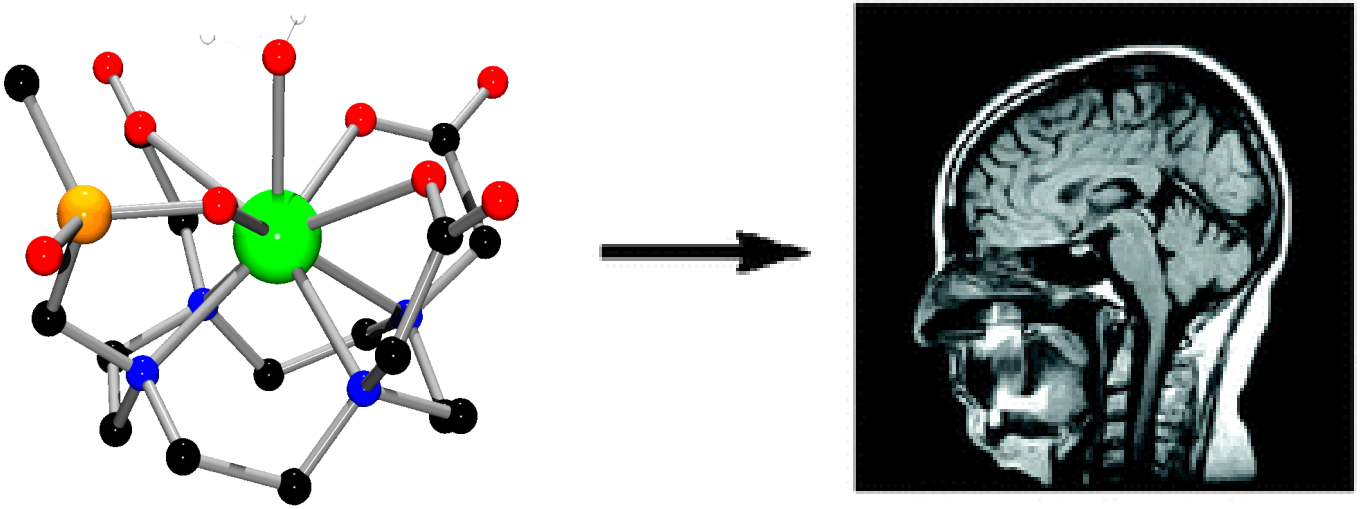
Lanthanides in MRI

"More than 10 million MRI studies are performed with Gd each year"

(P. Caravan, *Chem. Soc. Rev.*, **2006**, *35*, 512)

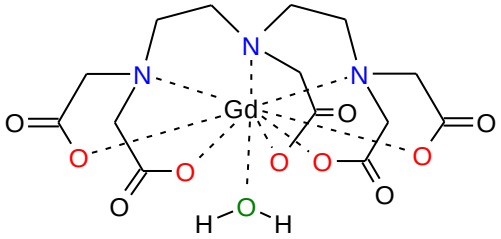


Gd-based T_1 contrast agents:

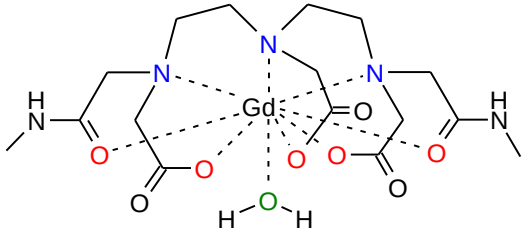
- Increase signal intensity on T_1-weighted images
- Shorten acquisition time
- Improve diagnostic confidence

P. Caravan, *Contrast Media Mol. Imaging.*, **2009**, *4*, 89

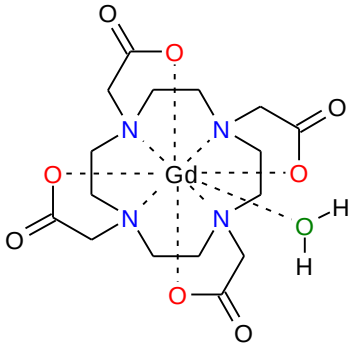
Commercial Agents



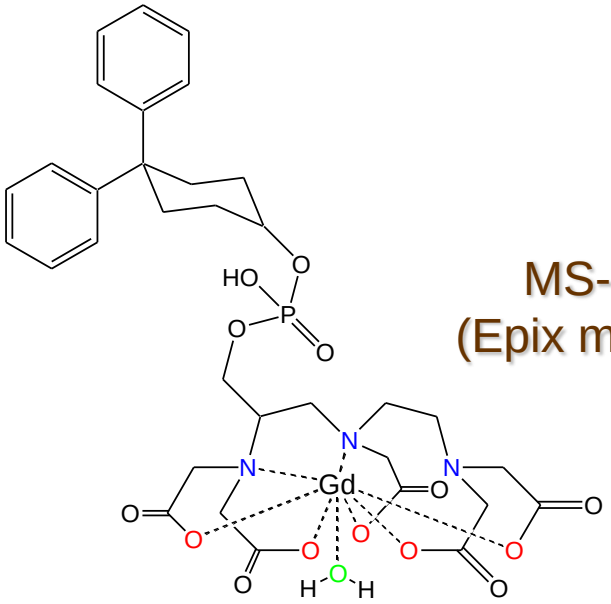
$[Gd(DTPA)(H_2O)]^{2-}$
(Magnevist: Berlex/Schering)



$[Gd(DTPA\text{-}BMA)(H_2O)]$
(Omniscan: Nycomed-Amersham)



$[Gd(DOTA)(H_2O)]^{-}$
(Dotarem: Guerbet)

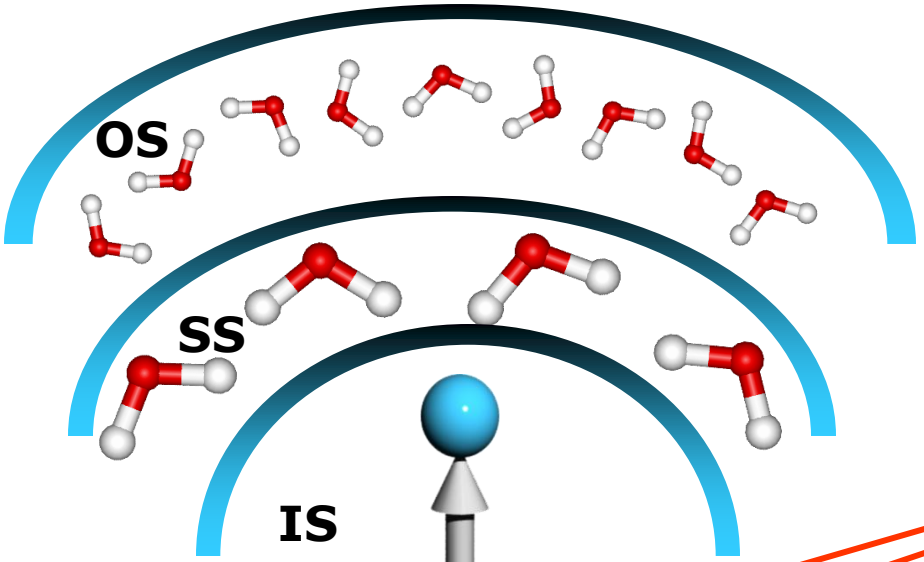


MS-325
(Epix medical)

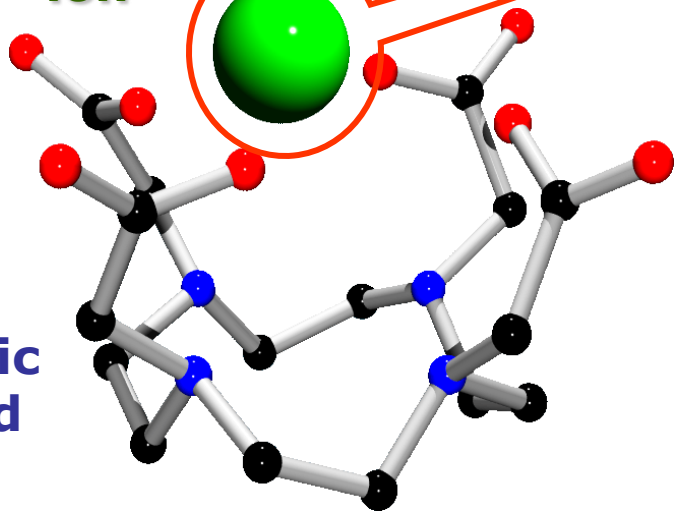
Clinically approved Gd^{III}-based contrast agents

Complex	Brand name	Company	Log K_{GdL}
GdDTPA	Magnevist®	Schering	22.5
GdDOTA	Dotarem®	Guerbet	24.7
GdHPDO3A	ProHance®	Bracco	23.8
GdDO3A-butrol	Gadovist®	Schering	20.8
GdDTPA-BMA	Omniscan®	Nycomed-Amersham	16.8
GdDTPA-BMEA	OptiMARK®	Mallinckrodt	16.8
GdBOPTA	MultiHance®	Bracco	22.6
GdEOB-DTPA	Eovist®	Schering	23.5

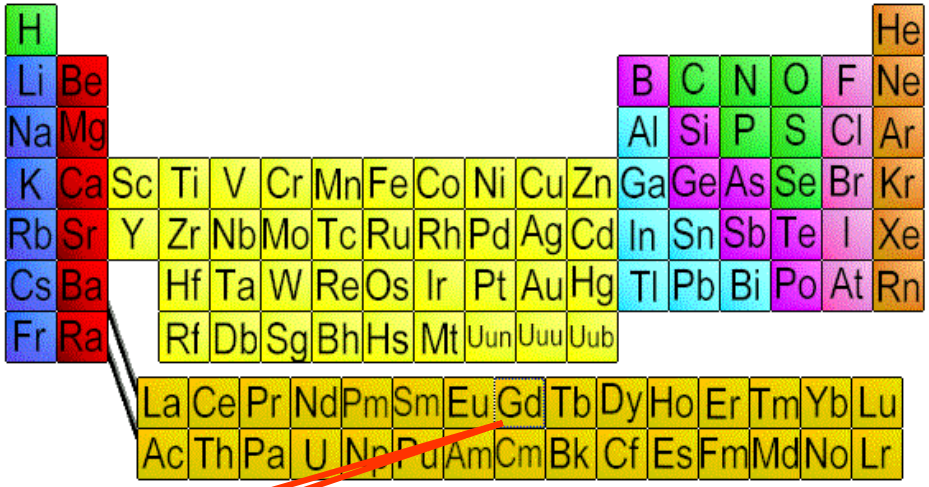
"Anatomy" of a MRI contrast agent



Gd^{3+} ion



organic ligand



- 7 unpaired e$^-$
- Slow electron spin relaxation
- High magnetic moment

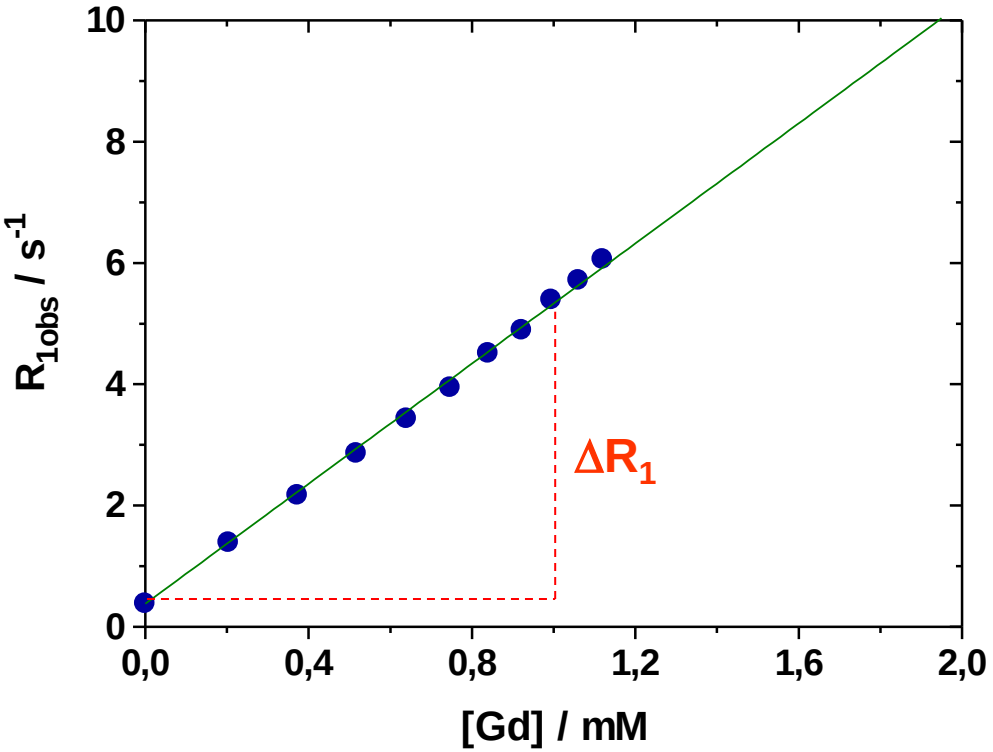
relaxivity – r_1 [mM^{-1} s^{-1}]

$$f(B, T, q, r, \tau_R, \tau_M, T_{e1,2})$$

[Courtesy of Jakub Rudovsky]

Relaxivity: definitions

$$R_i = [CA]\, r_{ip} + R_{iw} \qquad i = 1,2$$



20 MHz; 298 K

$r_{1p} = 4.95$

$R_{1w} = 0.38$

Commercial Agents

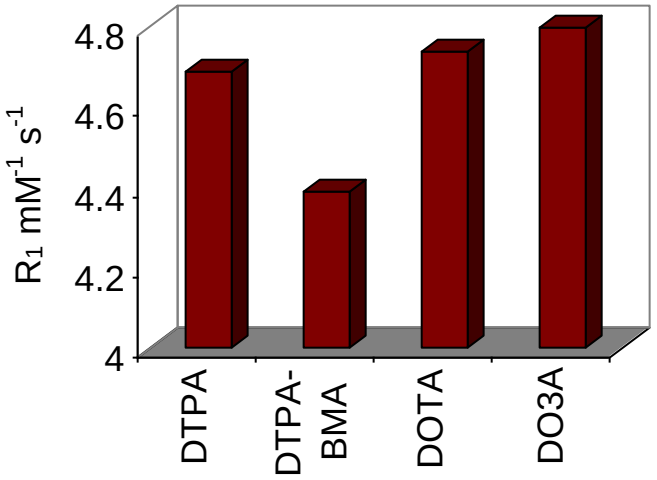
Low relaxivity:

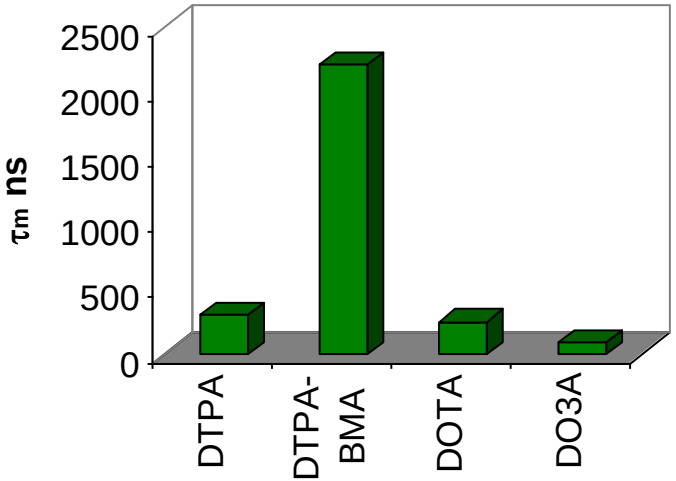
polyaminocarboxylates with $r_1 = 4 – 5\ mM^{-1}s^{-1}$:

- only one inner sphere coordinated water molecule: $q = 1$
- slow water exchange rate : τ_M = 150 to 2500 ns
- fast tumbling molecule : $\tau_R \approx$ ps

Disadvantages:

- injection of gram quantities of Gd complex
- limited to imaging blood streams / liver & kidneys
- do not allow site specific targeting



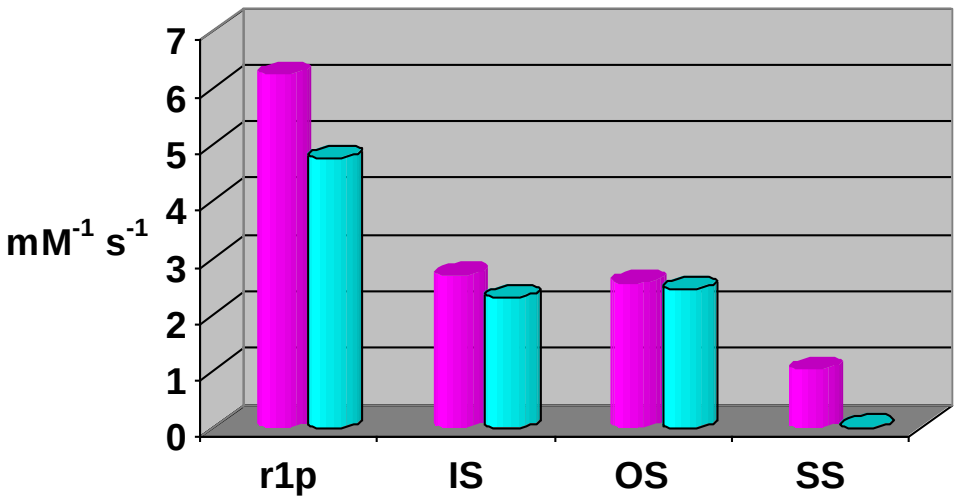


Caravan, P et al. *Chem. Rev.* **1999**, *99*, 2293-2352.

contributions to relaxivity

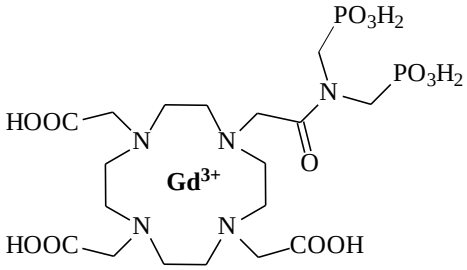
$$r_i = r_{ip}^{IS} + r_{ip}^{OS} + r_{ip}^{SS} \qquad (i = 1, 2)$$

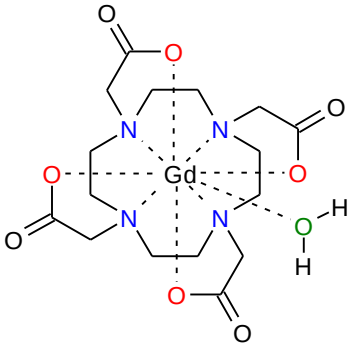
- need to specify magnetic field strength and temperature (... and pH)



DO3A-NP2

DOTA

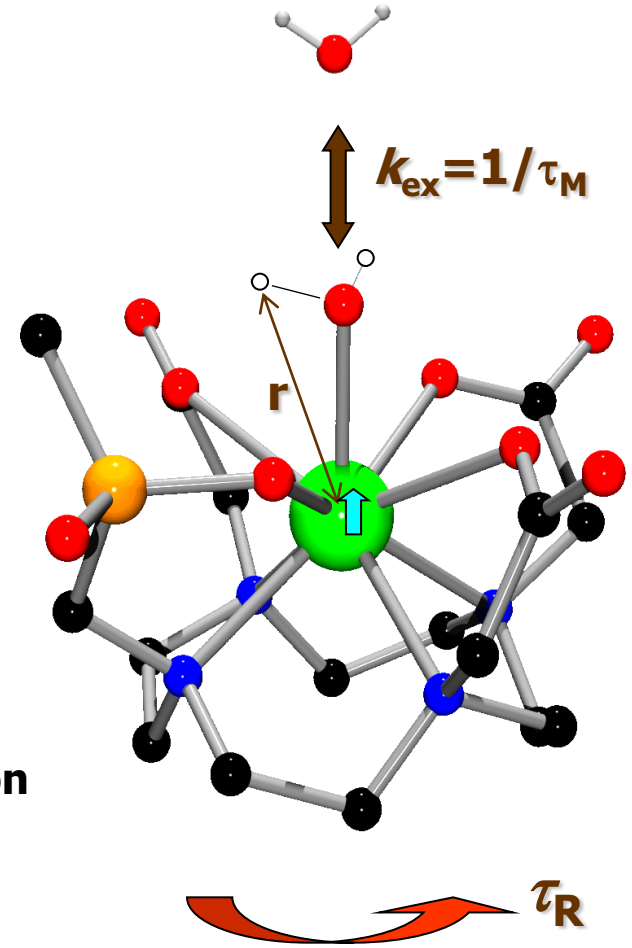




20 MHz – 298 K

Inner-sphere contribution to the relaxivity

$$r_{1p}^{IS} = \frac{[CA]q}{55.6} \frac{1}{T_{1M} + \tau_M}$$



- ***q:*** **n° of metal-bound water molecules**
- τ_M**: their mean residence lifetime**
- T_{1M}**: the longitudinal nuclear magnetic relaxation time of the bound water protons**

Solomon-Bloembergen-Morgan (SBM) equations

$$\frac{1}{T_{1M}} = \frac{2}{15}\frac{\gamma_H^2 g^2 S(S+1)\beta^2}{r_H^6}\left[\frac{3\tau_{C1}}{1+\omega_H^2\tau_{C1}^2} + \frac{7\tau_{C2}}{1+\omega_S^2\tau_{C2}^2}\right]$$

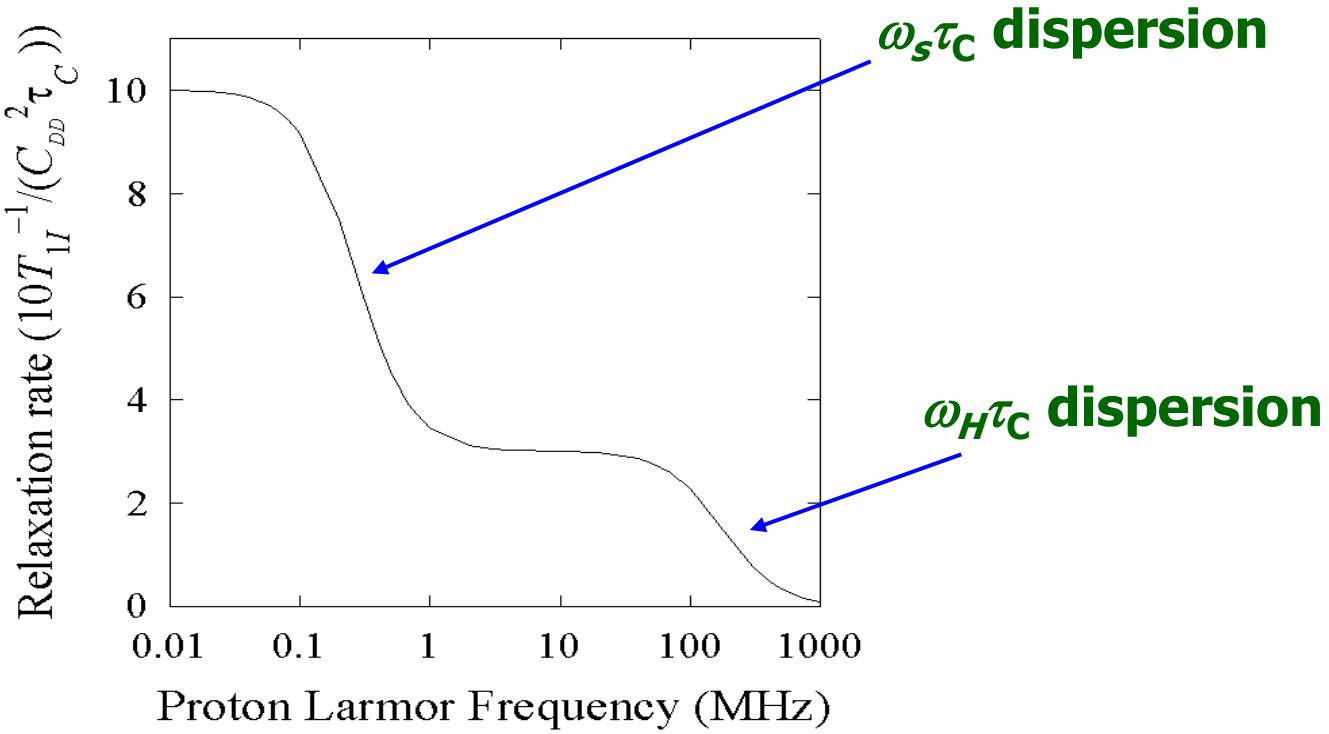
$$\frac{1}{\tau_{Ci}} = \frac{1}{\tau_R} + \frac{1}{\tau_M} + \frac{1}{T_{ie}}$$

$$\left(\frac{1}{T_{1e}}\right)^{\mathrm{ZFS}} = \frac{1}{25}\Delta^2\tau_{\mathrm{v}}\left\{4S(S+1)-3\right\}\left(\frac{1}{1+\omega_{\mathrm{S}}^2\tau_{\mathrm{v}}^2} + \frac{4}{1+4\omega_{\mathrm{S}}^2\tau_{\mathrm{v}}^2}\right)$$

$$\left(\frac{1}{T_{2e}}\right)^{\mathrm{ZFS}} = \Delta^2\tau_{\mathrm{v}}\left[\frac{5.26}{1+0.372\omega_{\mathrm{S}}^2\tau_{\mathrm{v}}^2} + \frac{7.18}{1+1.24\omega_{\mathrm{S}}\tau_{\mathrm{v}}}\right]$$

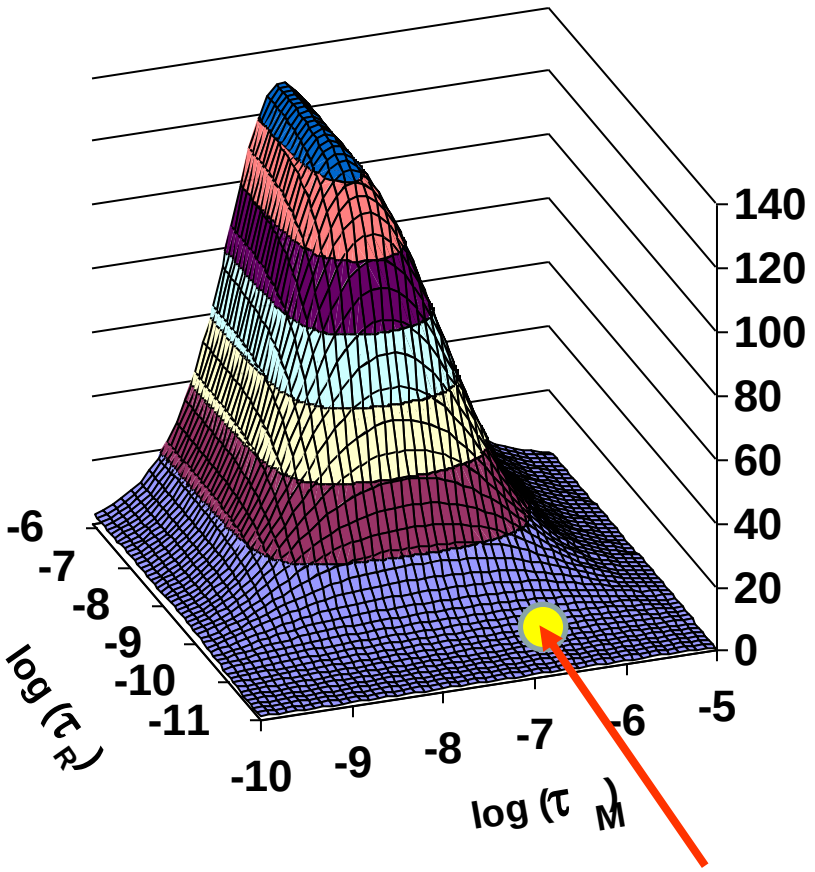
Solomon equation

$$\frac{1}{T_{1M}} = \frac{2}{15}\frac{\gamma_H^2 g^2 S(S+1)\beta^2}{r_H^6}\left[\frac{3\tau_{C1}}{1+\omega_H^2\tau_{C1}^2} + \frac{7\tau_{C2}}{1+\omega_S^2\tau_{C2}^2}\right]$$

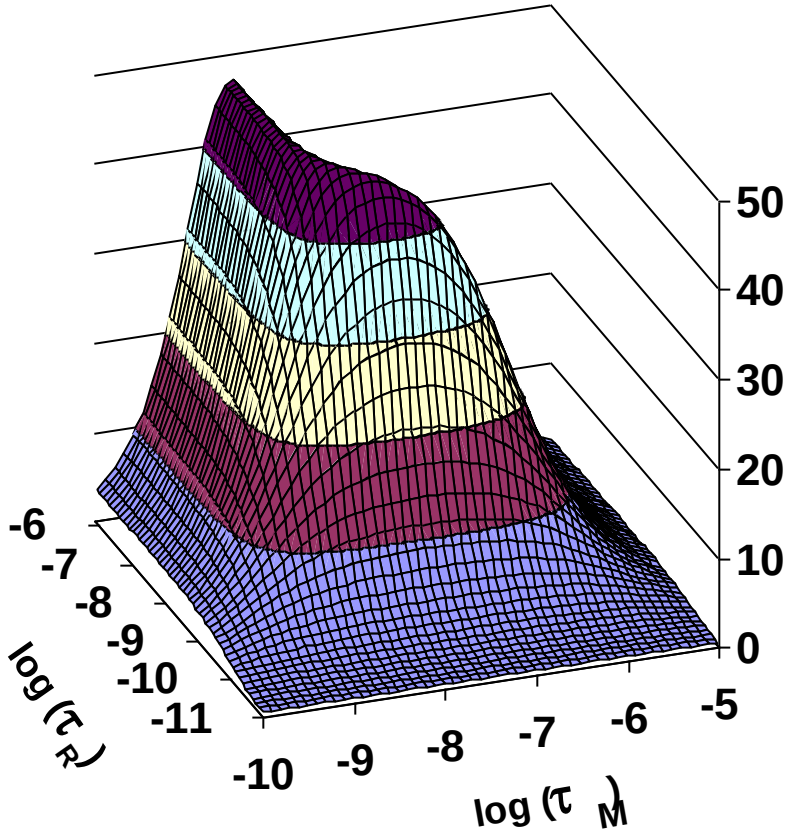


Dependence of r_{1p} on molecular parameters and B_0

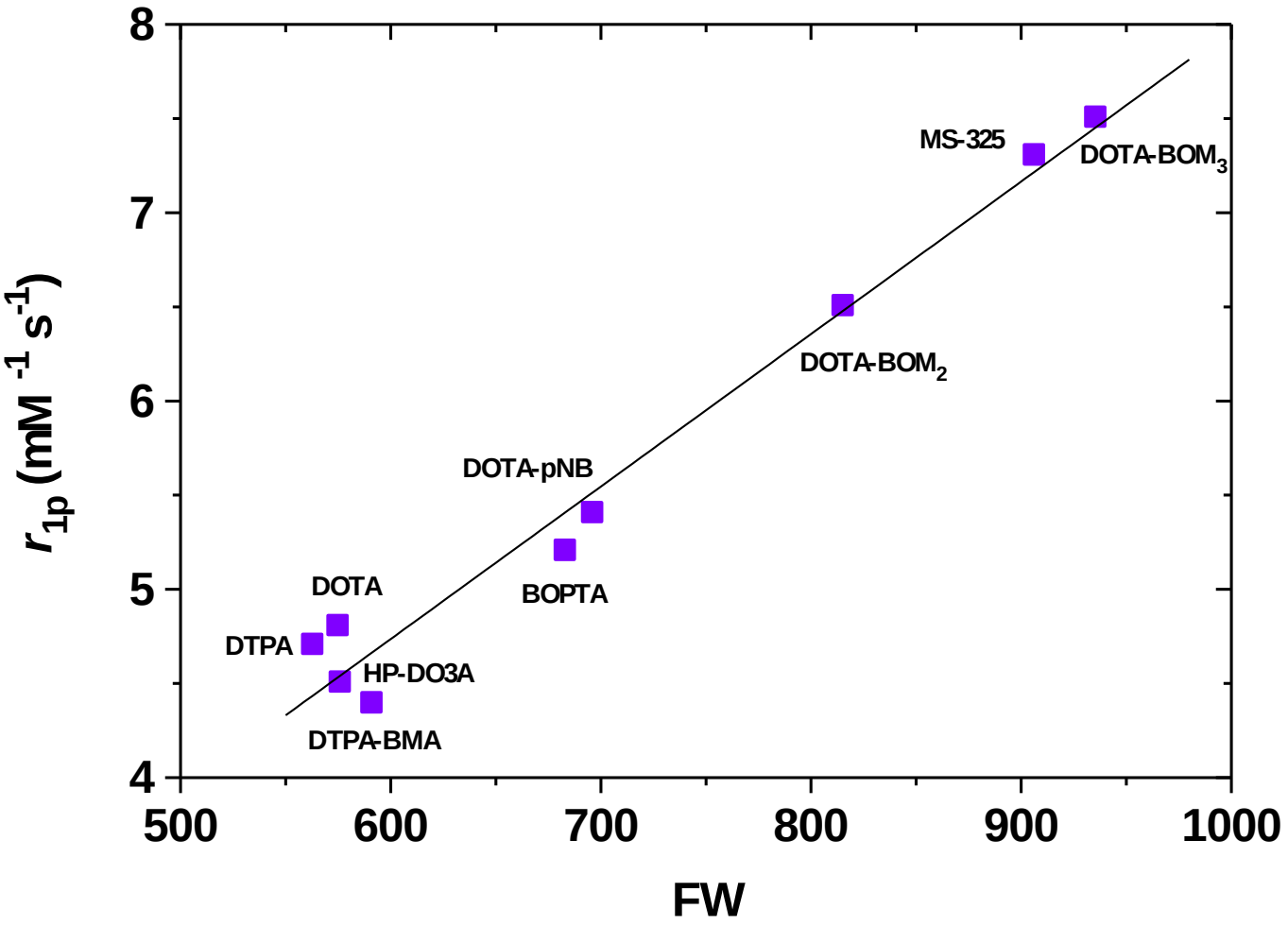
0.5 T / q=1 / r = 3.0 Å



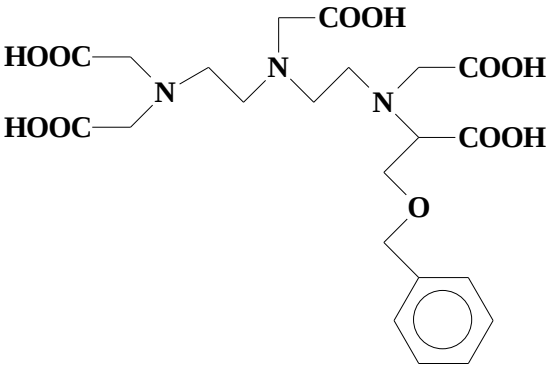
1.5 T / q=1 / r = 3.0 Å



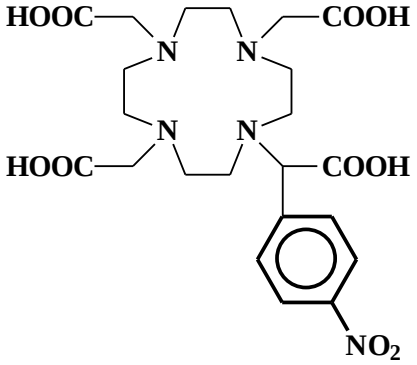
Rotational dynamics



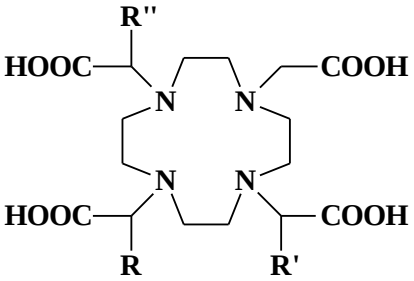
Plot of the relaxivity (20 MHz and 25°C) for monoaquo polyaminocarboxylate Gd(III) complexes versus molecular weight. The correlation coefficient R is 0.988



BOPTA

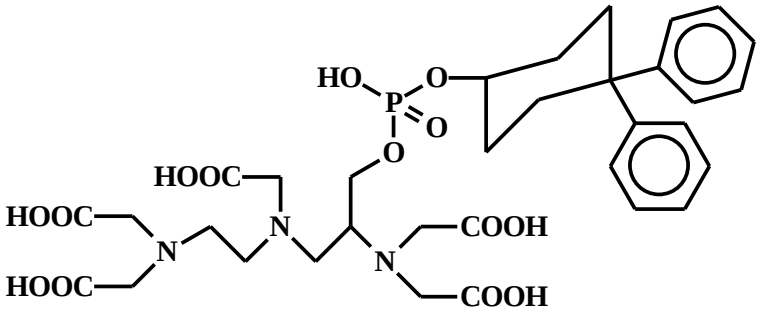


DOTA-pNB



DOTA-(BOM)$_2$
(R = H, R',R'' = -CH$_2$OCH$_2$C$_6$H$_5$)

DOTA-(BOM)$_3$
(R,R',R'' = -CH$_2$OCH$_2$C$_6$H$_5$)

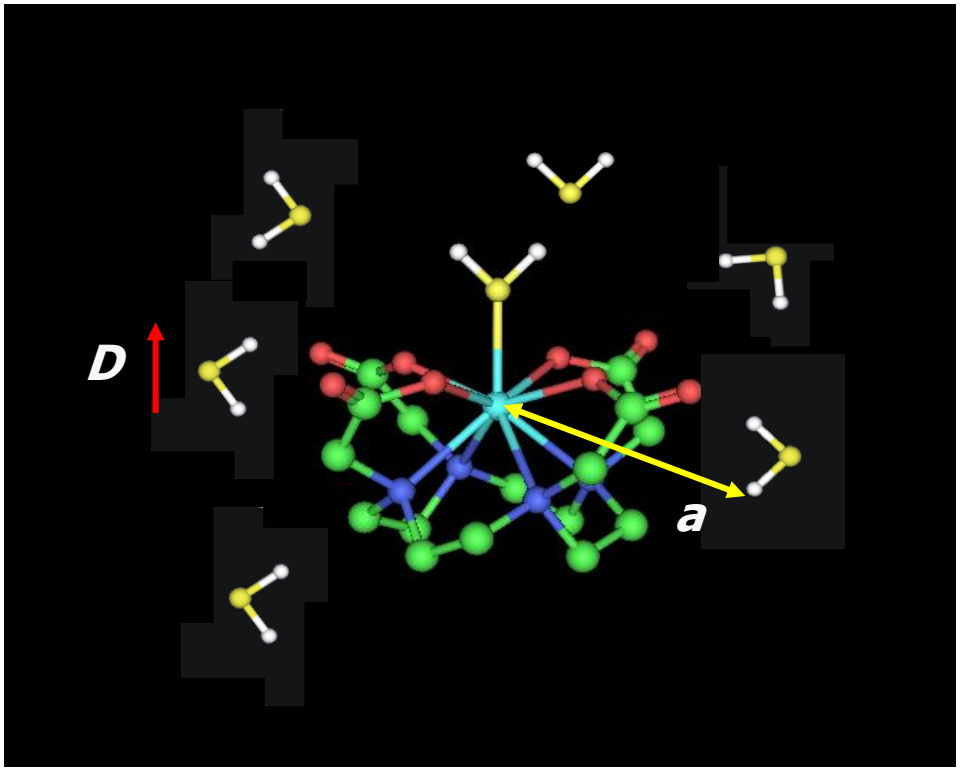


MS-325

Outer-sphere contribution to the relaxivity

→ **translational diffusional model of Freed**

modulation of the dipolar interaction of the paramagnetic centre with the water molecules diffusing next to the surface of the complex

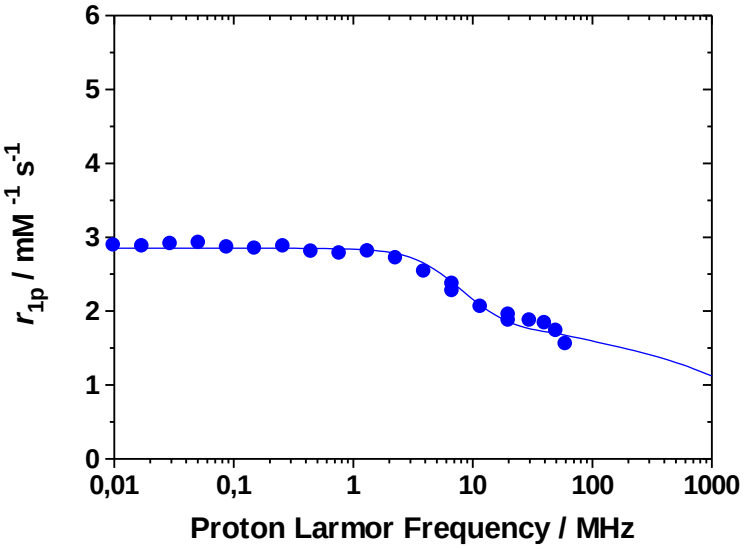


Outer-sphere contribution to the relaxivity

$$r_{1p}^{OS} = C^{OS}\left(\frac{1}{aD}\right)\left[7J(\omega_S) + 3J(\omega_H)\right]$$

$$J(\omega) = \mathrm{Re}\left[\frac{1 + 1/4\left(i\omega\tau_d + \frac{\tau_d}{T_{je}}\right)^{1/2}}{1 + \left(i\omega\tau_d + \frac{\tau_d}{T_{je}}\right)^{1/2} + 4/9\left(i\omega\tau_d + \frac{\tau_d}{T_{je}}\right) + 1/9\left(i\omega\tau_d + \frac{\tau_d}{T_{je}}\right)^{3/2}}\right]$$

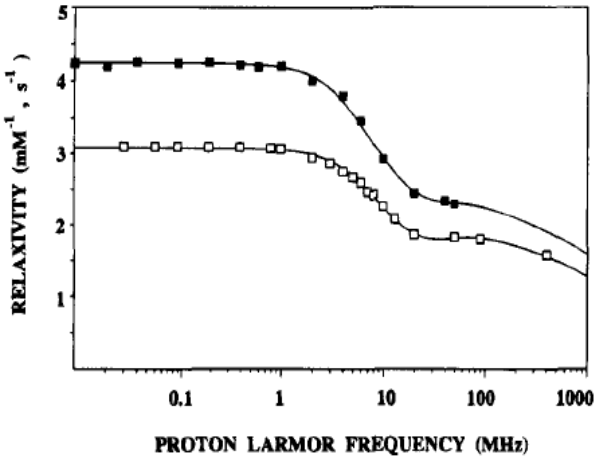
with $j = 1,2$; $\tau_d = a^2/D$

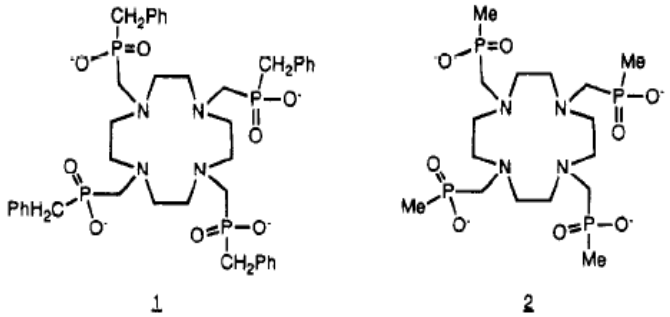


q = 0
a = 4.2 Å
D = 2.24x10^{-5} cm^2 s^{-1}

298 K

Outer-sphere contribution to the relaxivity





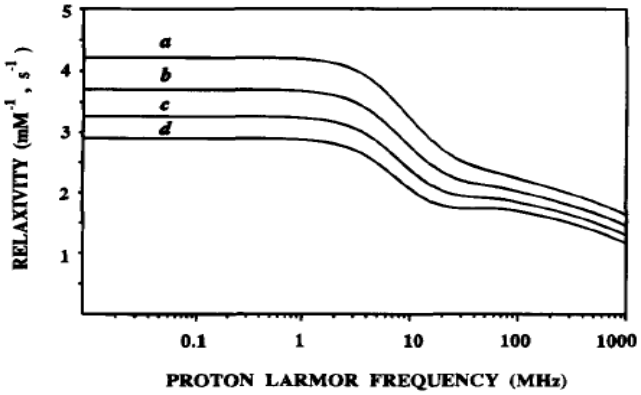


Figure 4. Simulated outer sphere NMRD profiles for values of the distance a of 3.6 (a), 3.9 (b), 4.2 (c), and 4.5 Å (d). Values typical of Gd(III) complexes were utilized for the other parameters: $\tau_{SO} = 80$ ps; $\tau_V = 15$ ps; $D = 2.0 \times 10^{-5}$ cm^2 s^{-1}.

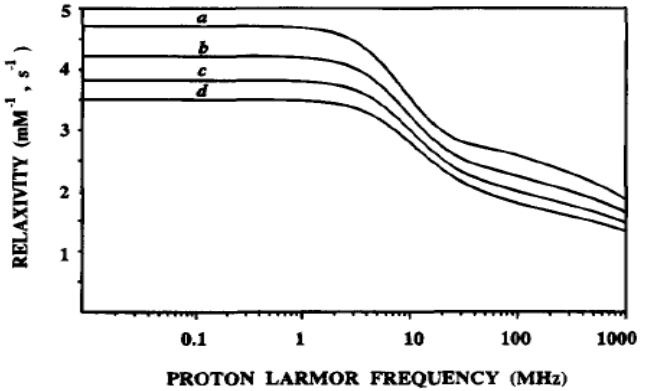


Figure 5. Simulated outer sphere NMRD profiles for values of the diffusion coefficient D of 1.7×10^{-5} (a), 2.0×10^{-5} (b), 2.3×10^{-5} (c), and 2.6×10^{-5} cm^2 s^{-1} (d). Values typical of Gd(III) complexes were utilized for the other parameters: $\tau_{SO} = 80$ ps; $\tau_V = 15$ ps; $a = 3.6$ Å.

Inorg. Chem. **1994,** *33,* 4696−4706

Separation of the *inner* and *outer sphere* contributions

measurement of the T-dependency of r_{1p} at a fixed frequency

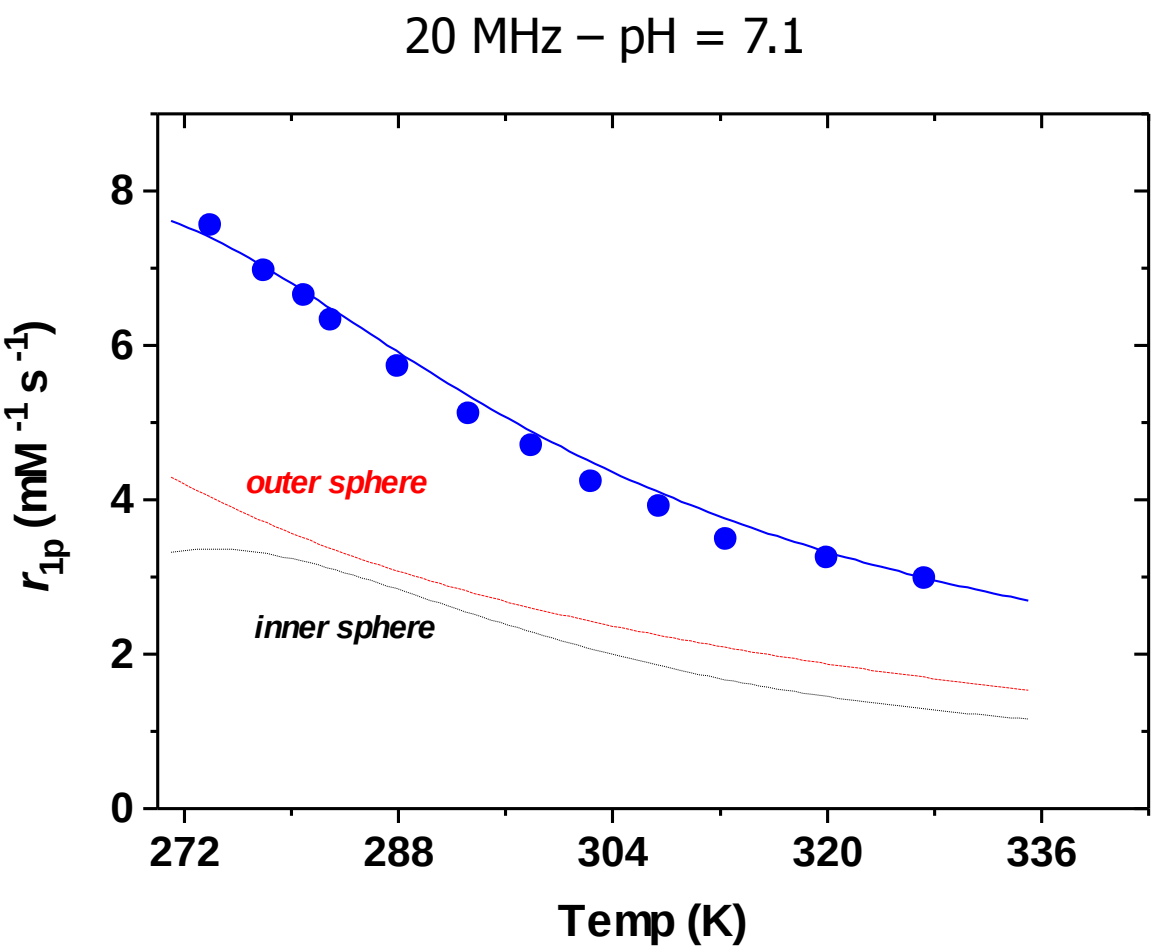
- the *outer sphere* relaxivity increases by lowering T because of the increase of D and of $T_{1,2e}$
- the T-dependence of r_{1p}^{IS} depends on the relative values of T_{1M} and τ_M:

$$r_{1p}^{IS} = \frac{[CA]q}{55.6} \frac{1}{T_{1M} + \tau_M}$$

i. $\tau_M < T_{1M}$ (fast exchange regime)

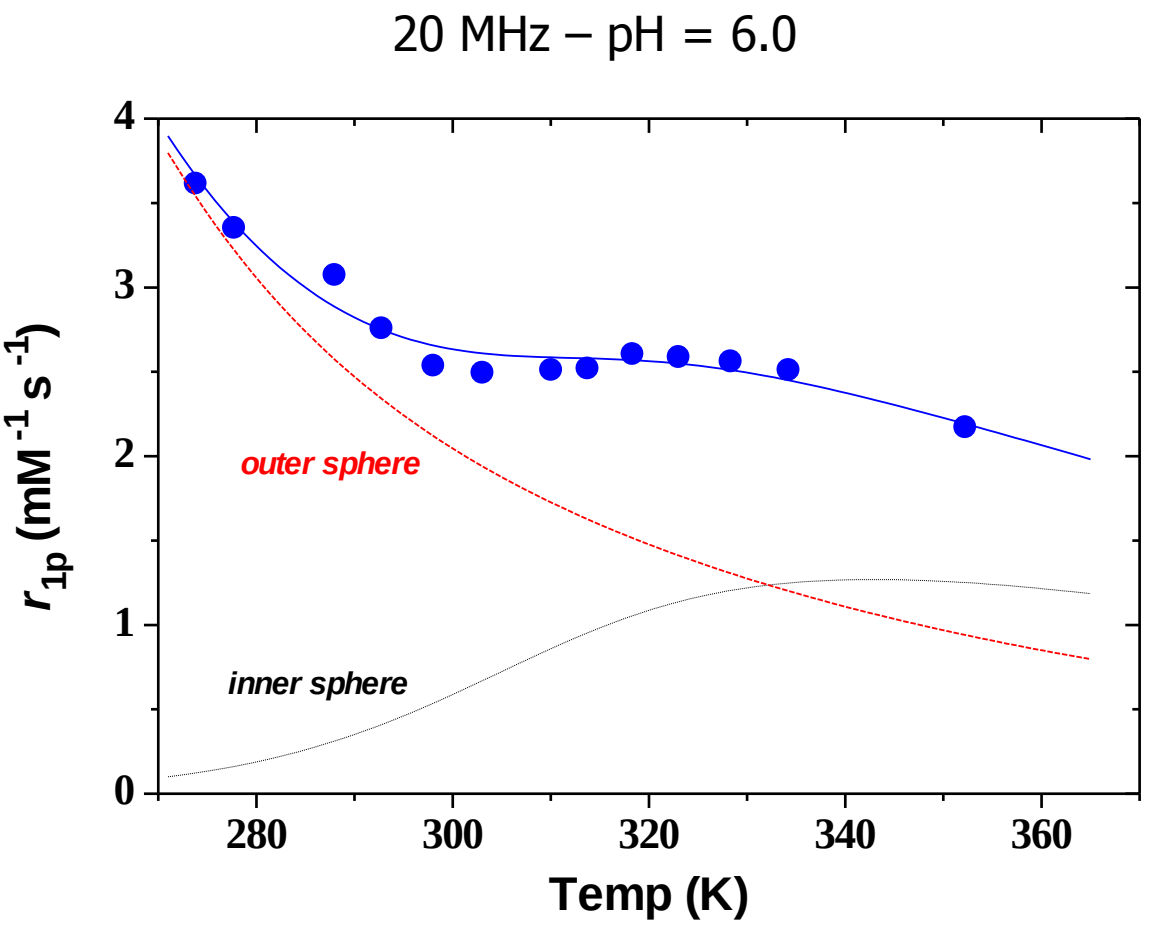
ii. $\tau_M \geq T_{1M}$ (slow/intermediate exchange regime)

$\tau_M < T_{1M}$: fast exchange regime



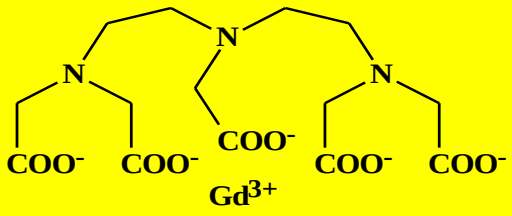
Na[Gd(DOTA)]

$\tau_M \geq T_{1M}$: slow/intermediate exchange regime

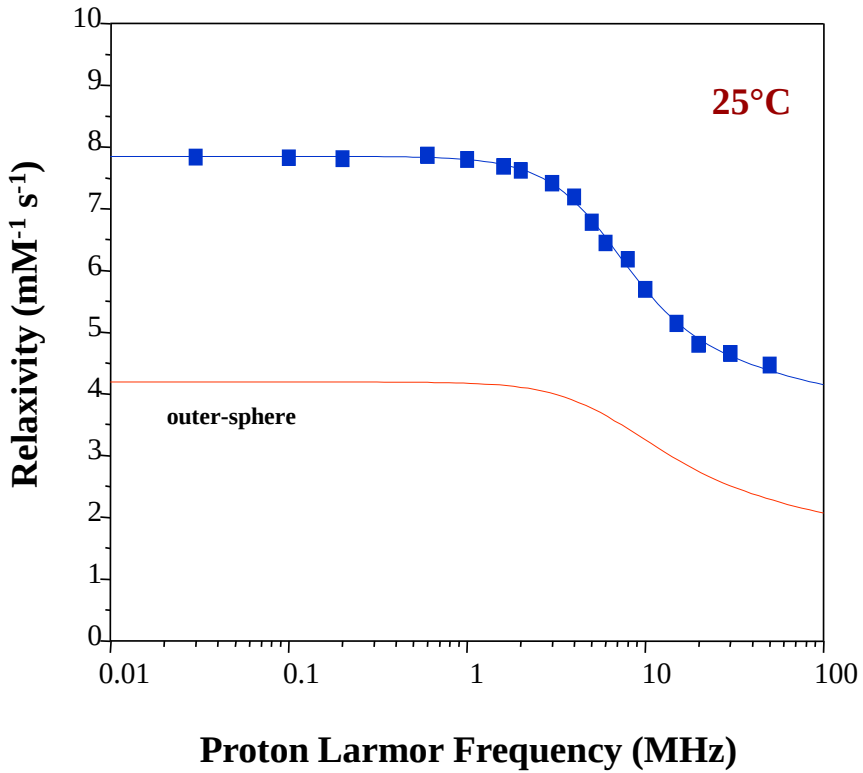


[Gd(DOTAM)]tfl3

NMRD profiles



[Gd(DTPA)(H_2O]$^{2-}$



q = 1

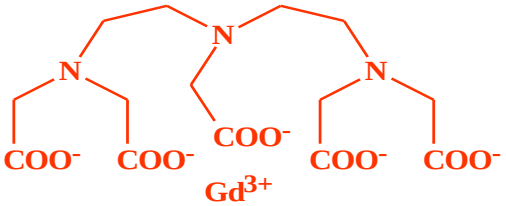
r = 3 Å

τ_R = 70 ps

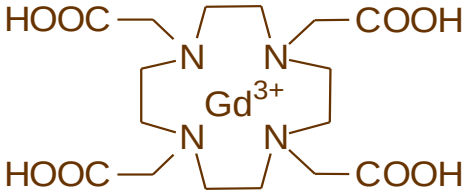
τ_M = 300 ns

$^{0.47}T_{1E}$ = 1 ns

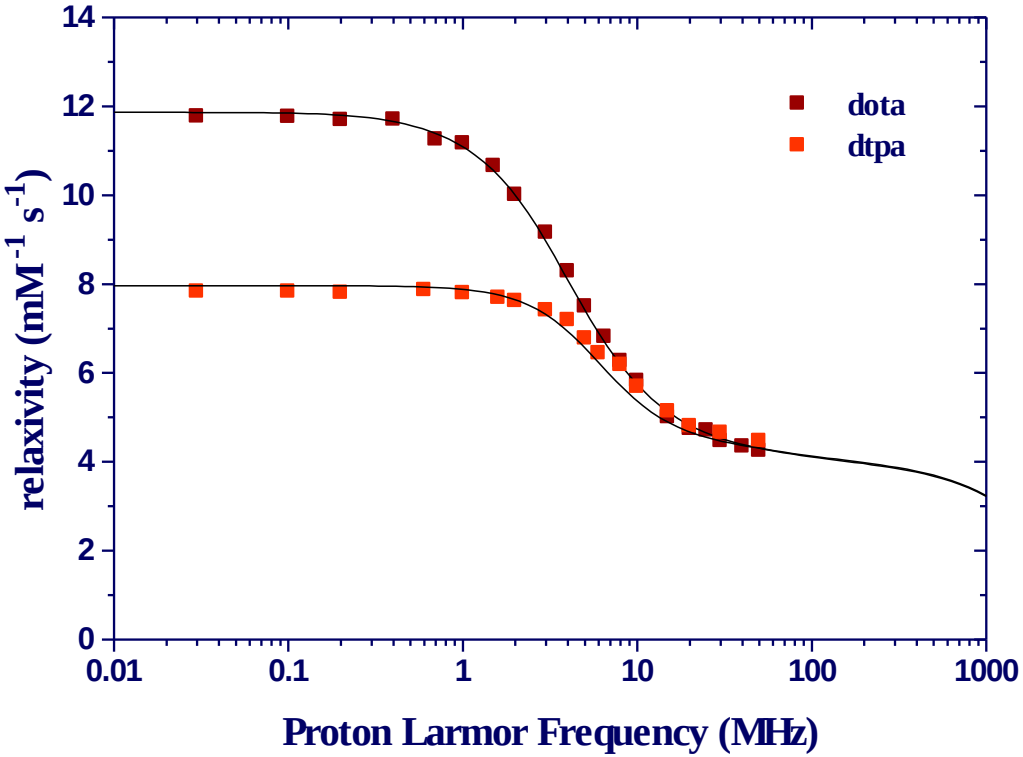
NMRD profiles



dtpa



dota



NMRD parameters

hydration numer q

reorientational correlation time τ_R

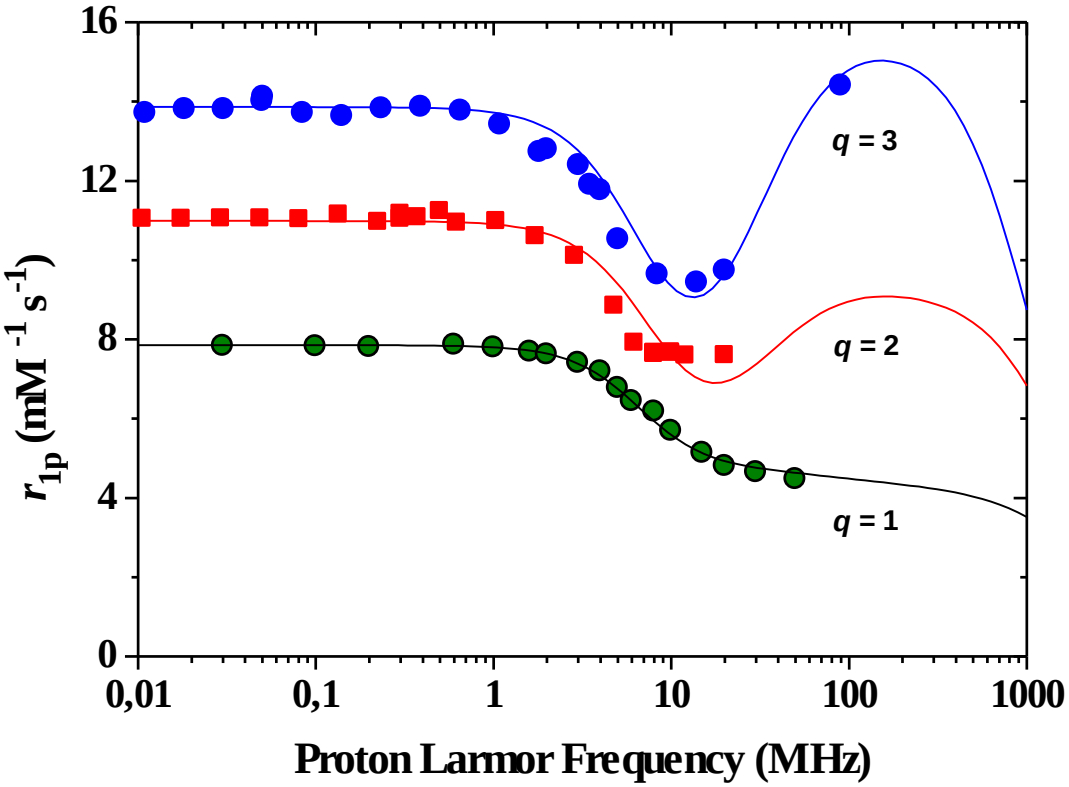
exchange lifetime τ_M

Gd–H_w distance r

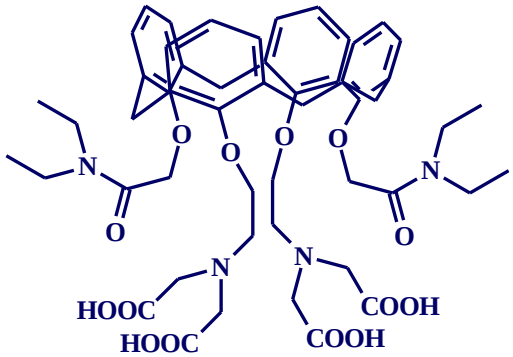
electronic relaxation times (Δ^2 ; τ_V)

a and D (outer sphere)

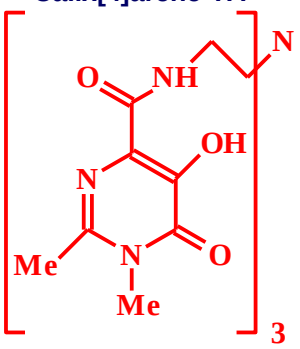
the effect of increasing *q*…



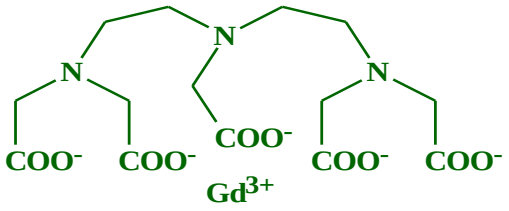
^{1}H NMRD profiles (25°C) of three Gd(III) complexes differing in the number *q* of *inner sphere* water molecules: GdDTPA (open circles), GdHOPY (squares), GdCalix[4]arene (filled circles)



Calix[4]arene-TA



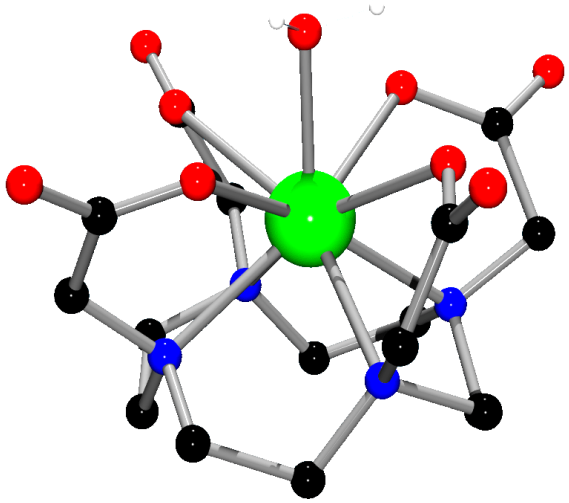
TrenHOPY

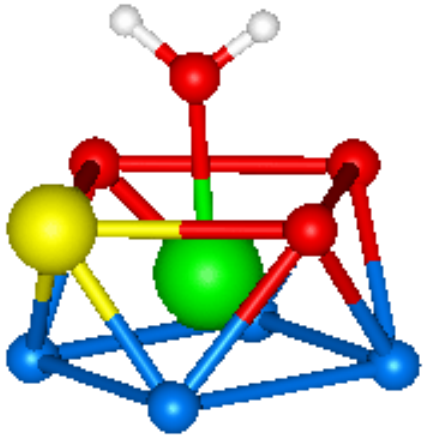


DTPA

the Gd-H_w distance *r*

Estimation from X-ray data? Gd-O_w ≠ Gd-H_w
Gd-Hw dependends from tilt angle of the water molecule





tilt angle: variation with nature of donor groups?

pulsed ENDOR spectra: 3.1±0.1 Å (Caravan et al.)

Rotational dynamics

the reorientational correlation time τ_R

A) Debye-Stokes equation $\tau_R = 4\pi\eta r_{eff}^3/3k_BT$

B) ^{17}O NMRlongitudinal relaxation time of the Gd(III)-bound water molecules

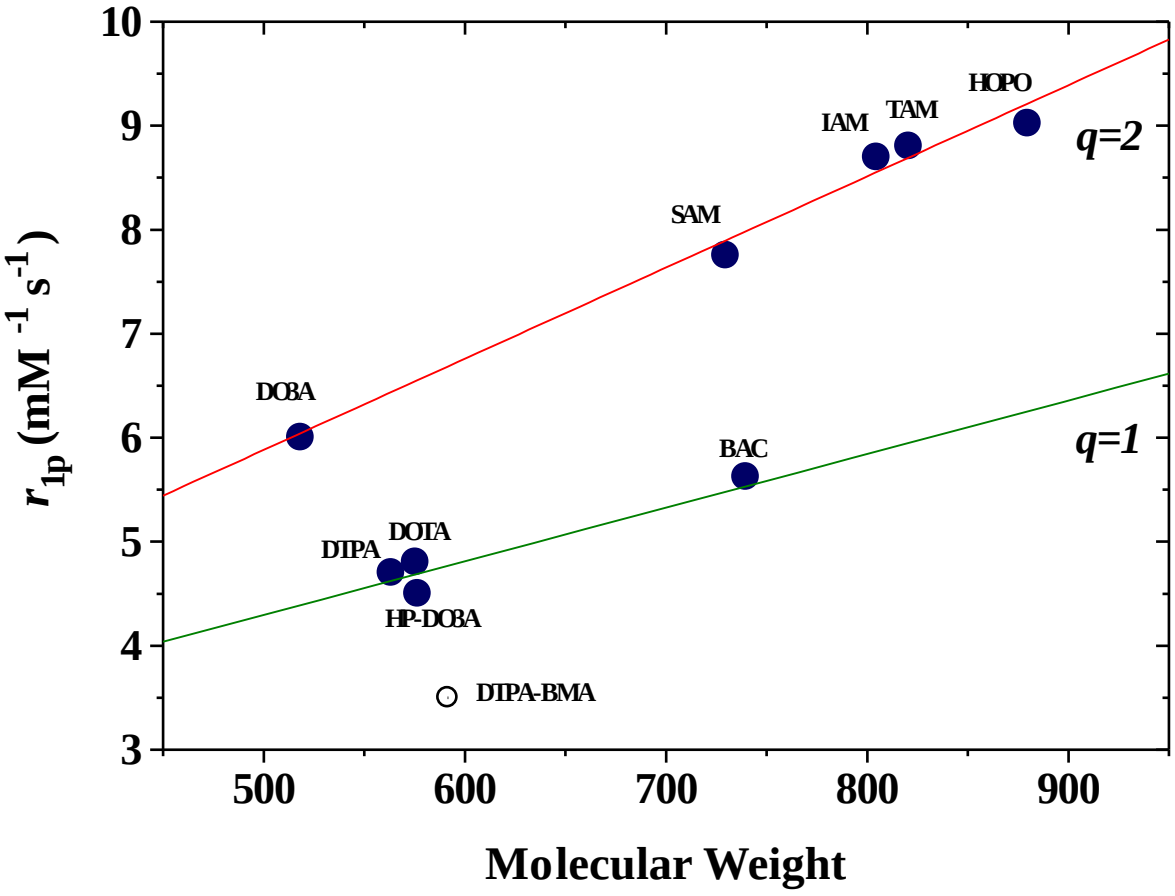
$$\frac{1}{T_{1q}} = \frac{3\pi^2}{10}\left(\frac{2I+3}{I^2(2I-1)}\right)\chi^2\left(1+\eta^2/3\right)\left[0.2\left(\frac{\tau_R}{1+\omega_I^2\tau_R^2}\right)+0.8\left(\frac{\tau_R}{1+4\omega_I^2\tau_R^2}\right)\right]$$

C) ^{13}C NMR longitudinal relaxation time and NOE on a diamagnetic (Y, La, Lu) analog

$$R_1^{dd} = n\frac{4\gamma_C^2\gamma_H^2\hbar^2 S(S+1)}{3r_{C-H}^6}\tau_R$$

$R_1^{obs}/R_1^{dd} = \eta_{max}/\eta$

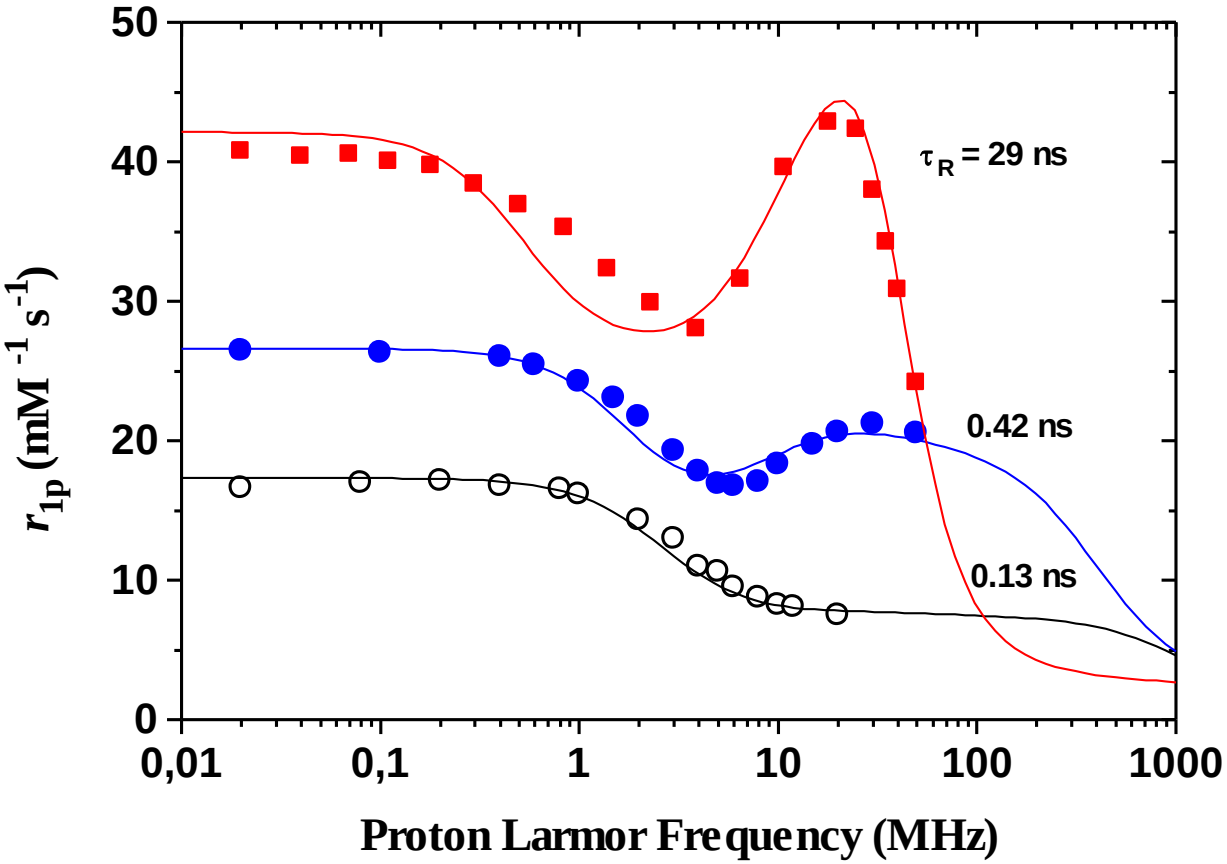
the reorientational correlation time τ_R

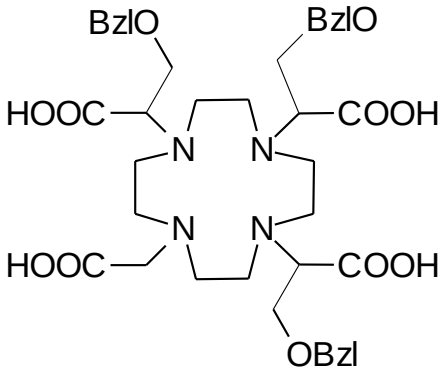


The linear relationship confirms the dependence of r_{1p} on the tumbling rate of the complexes, the close similarity of the outer sphere contributions, and excludes significant variations in the distance values r_{Gd-H}

Inorg. Chem. **2000,** *39,* 5747-5756

the effect of slowing down rotation…





^{1}H NMRD profiles (25°C) of GdDOTA-BOM$_3$ (open circles), its inclusion complex with β-cyclodextrin (filled circles) and of GdDOTA-BOM$_3$-HSA adduct (squares). The different shapes and amplitudes of the profiles are primarily due to the different rotational correlation times of the paramagnetic complexes.

How to increase τ_R?

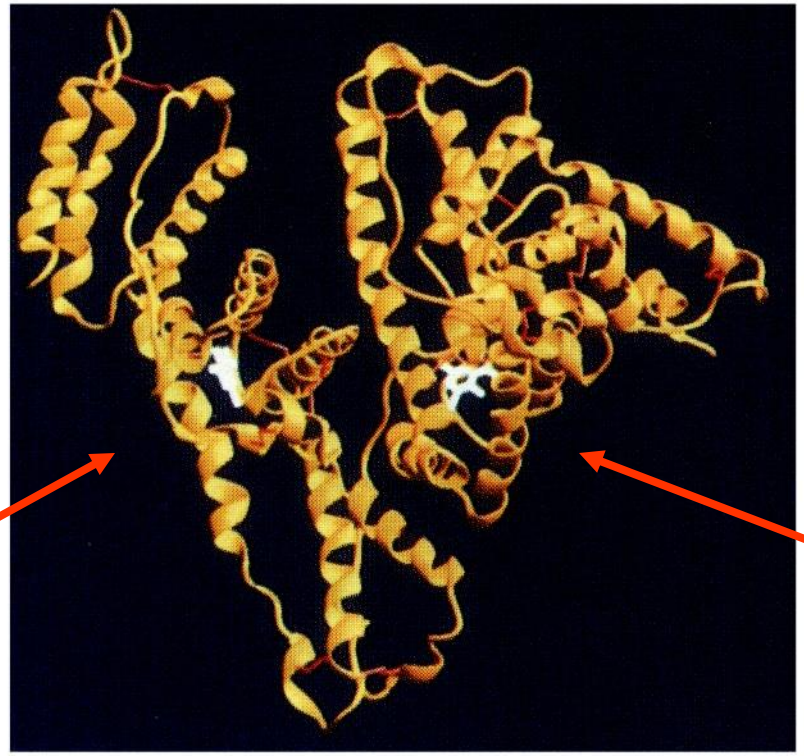
Covalent binding

Non Covalent binding

M = macromolecule

(proteins, synthetic or natural polimers, dendrimers,…)

HSA as target molecule for Gd^{III}-based CAs

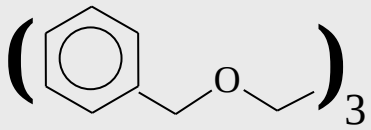


IIIA binding site

IIA binding site

Development of CAs for MR Angiography (MRA)

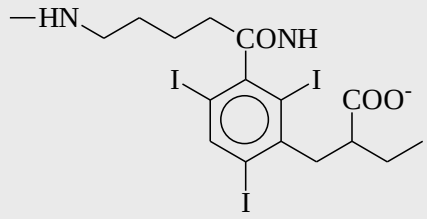
Non covalent binding to HSA



$K_A = 2 \cdot 10^4\ M^{-1}$

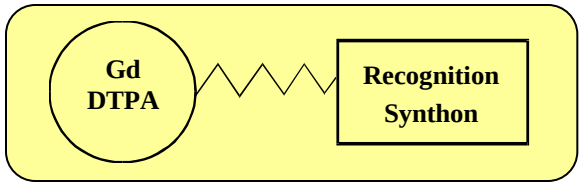
$r_1^b = 44.0\ s^{-1}mM^{-1}$

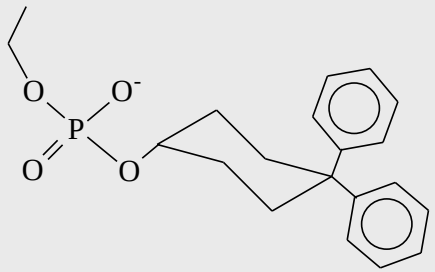
25°C - 0.47 T



$K_A = 4.5 \cdot 10^3\ M^{-1}$

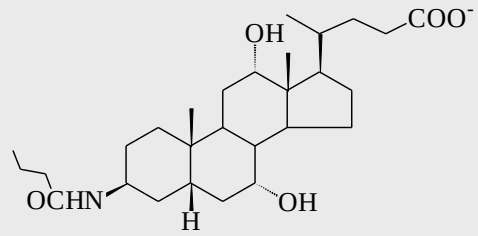
$r_1^b = 19.9\ s^{-1}mM^{-1}$





$K_A = 9 \cdot 10^4\ M^{-1}$

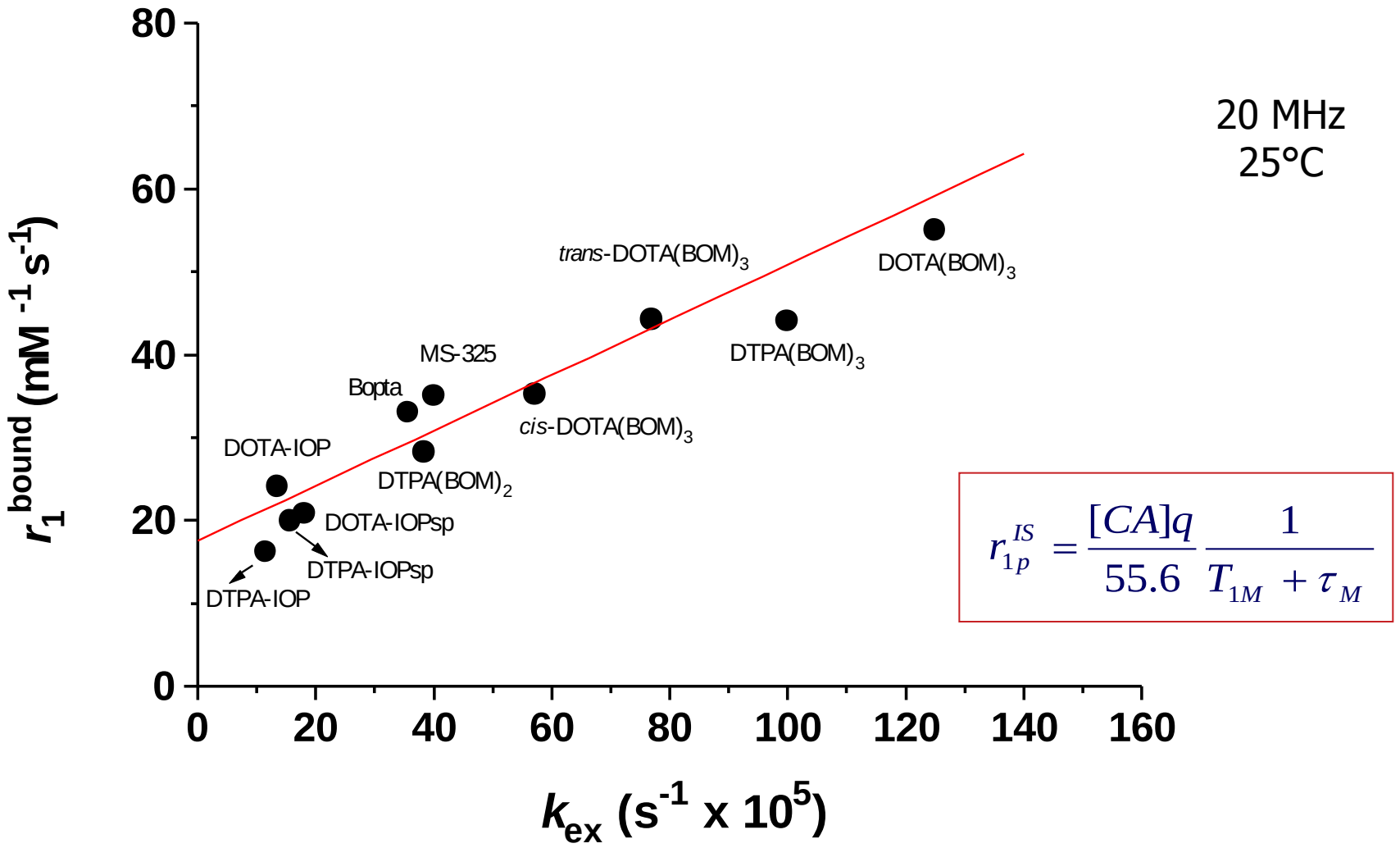
$r_1^b = 37.2\ s^{-1}mM^{-1}$



$K_A = 3.2 \cdot 10^4\ M^{-1}$

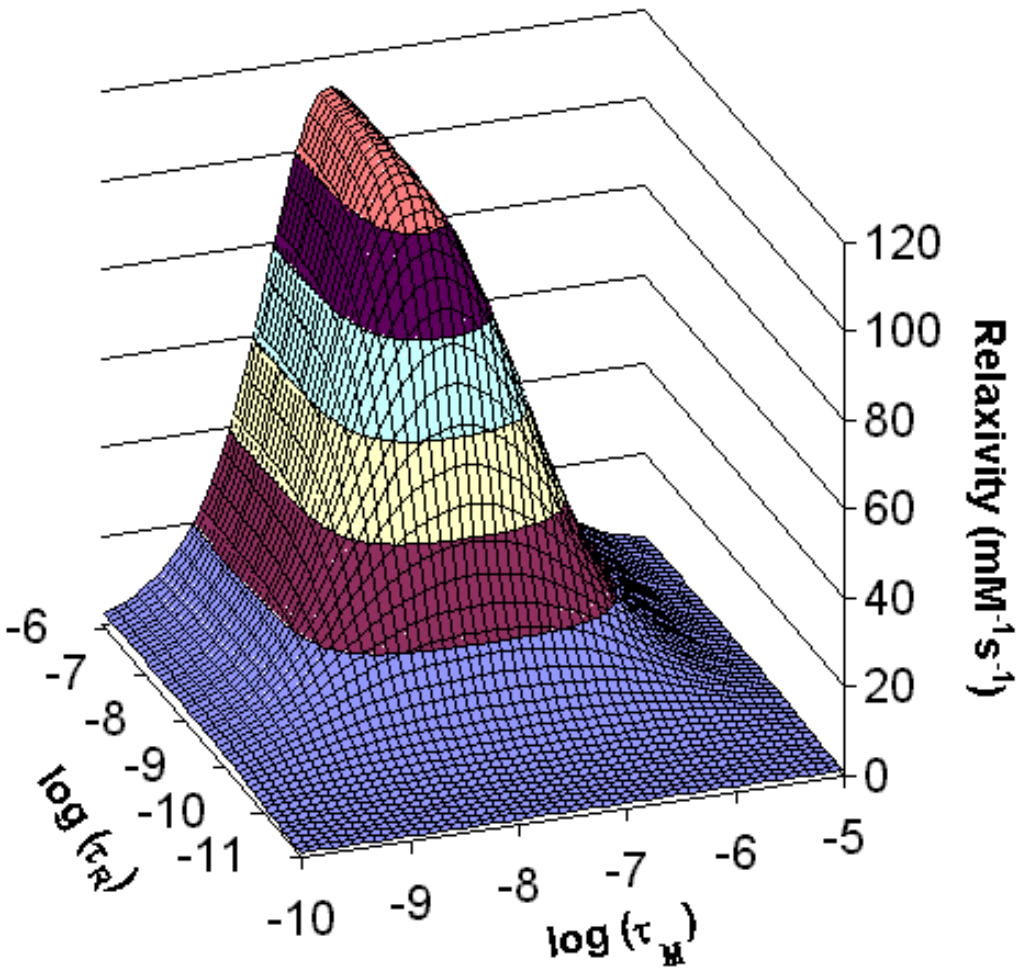
$r_1^b = 25.7\ s^{-1}mM^{-1}$

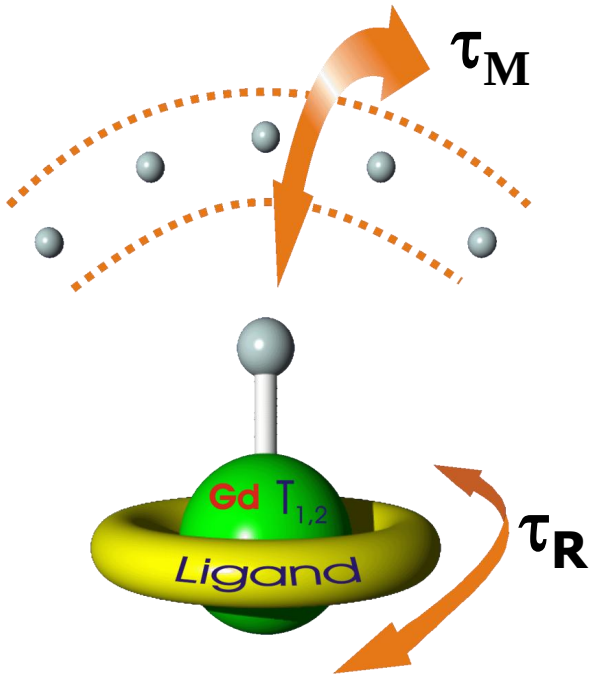
Non-covalent HSA conjugates



Aime, S.; Botta, M.; Fasano, M.; Terreno, E., *Protein-Bound Metal Chelates*, in *The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging*, (A. E. Merbach, É Tóth, Eds.), Wiley: New York, 2001

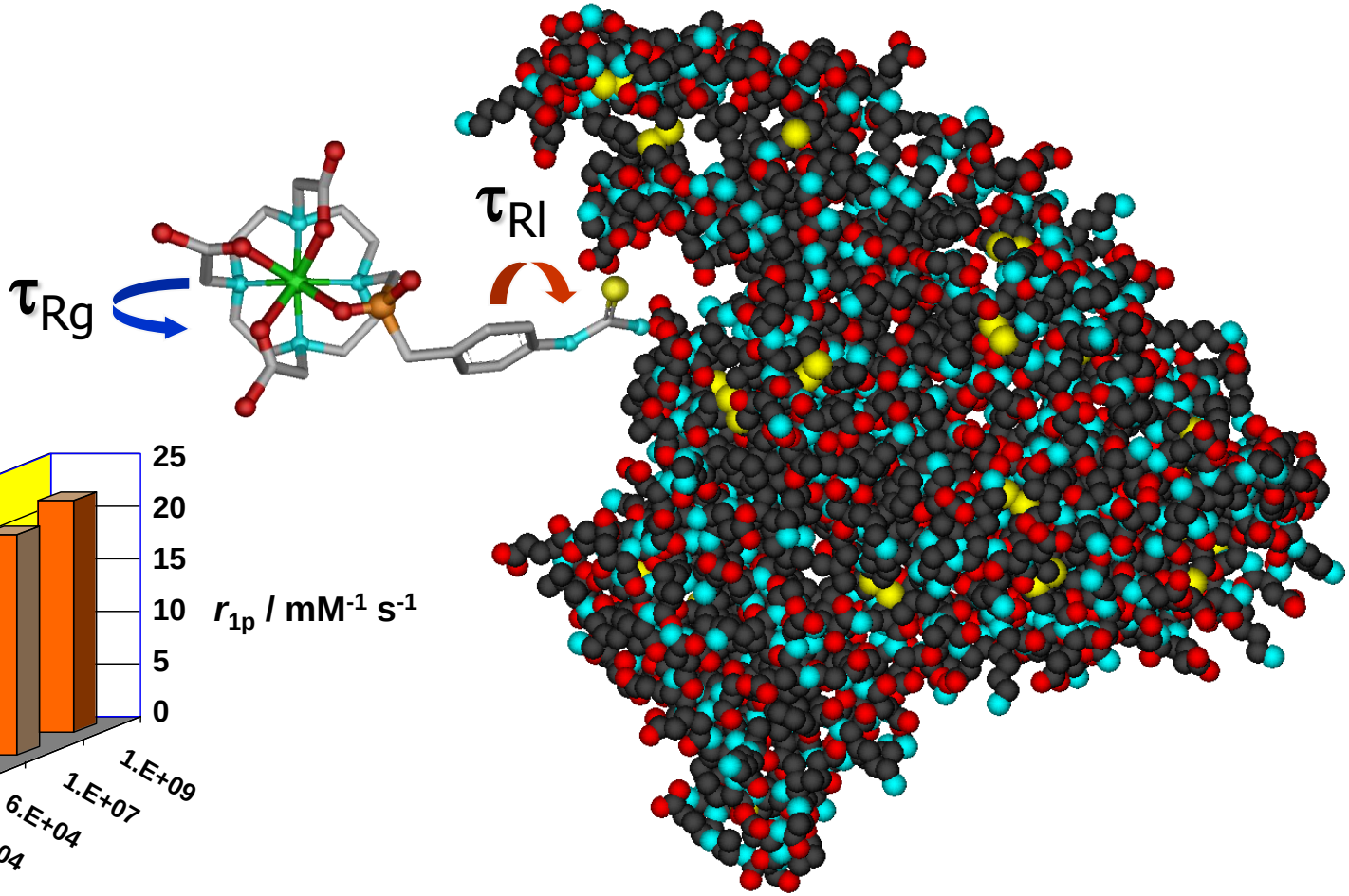
the limiting factors: rotation and exchange…





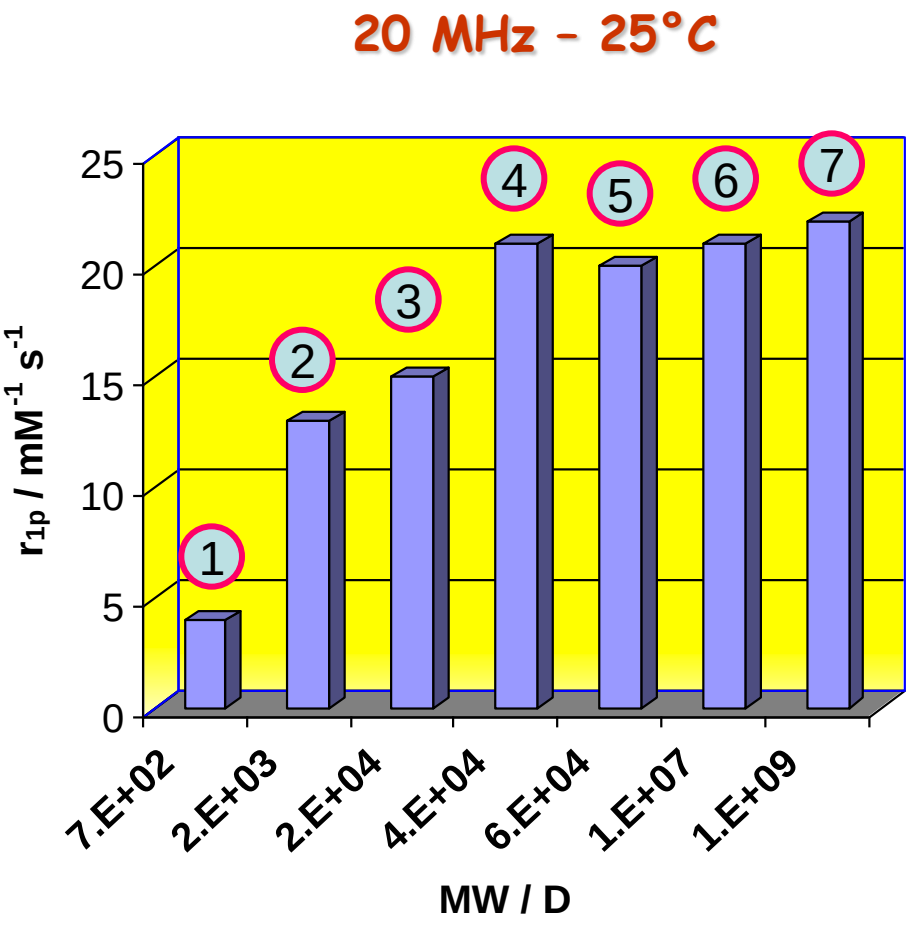
The problem of internal rotation

another limiting factor



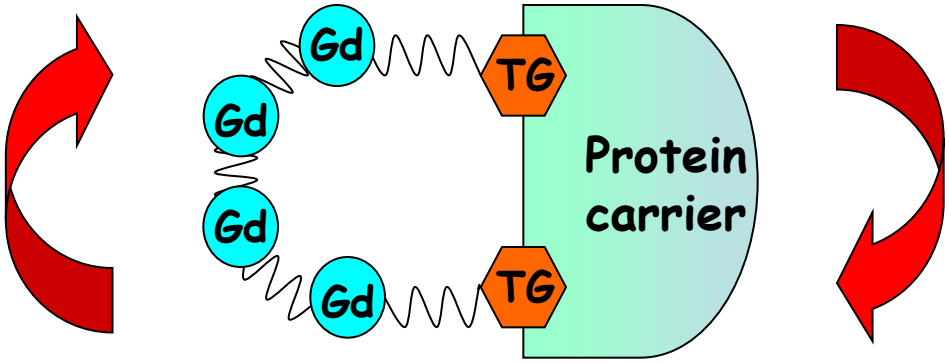
Relaxivity of macromolecular contrast agents

1. Small sized compounds
2. Fullerenes
3. Small dendrimers (ex.Gadomer-17)
4. Protein carriers
5. Dendrimers (ex.PAMAM-G5)
6. Micelles
7. Liposomes



The problem of internal rotation

Approaches to solve the problem (1)



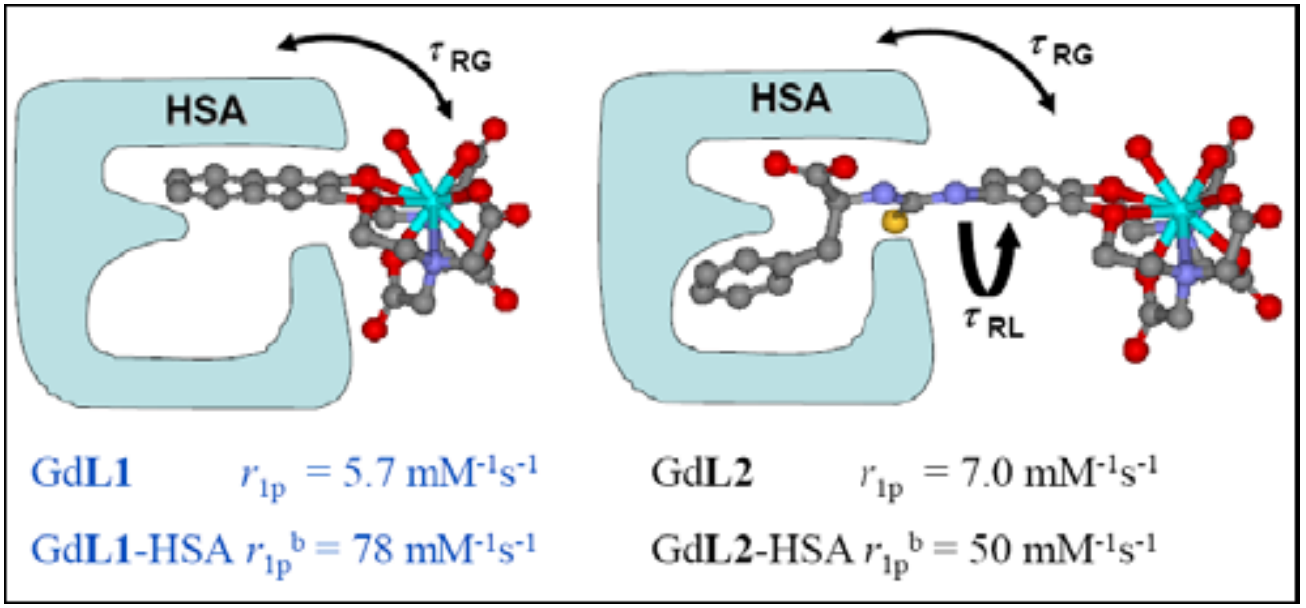
GdDTPA tetramer non targeted
r_{1p} per Gd = 24

→

GdDTPA tetramer twice targeted to HSA
$r_{1p}{}^{b}$ per Gd = 41

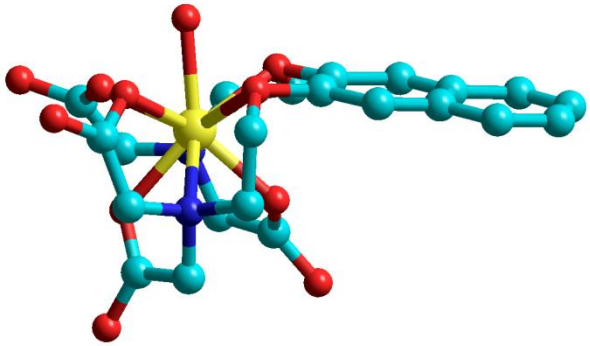
Z. Zhang, M. T. Greenfield, M. Spiller, T. J. McMurry, R. B. Lauffer and P. Caravan, *Angew.Chem.Int.Ed.* **2005**, *44, 6766-6769*

Approaches to solve the problem (2)

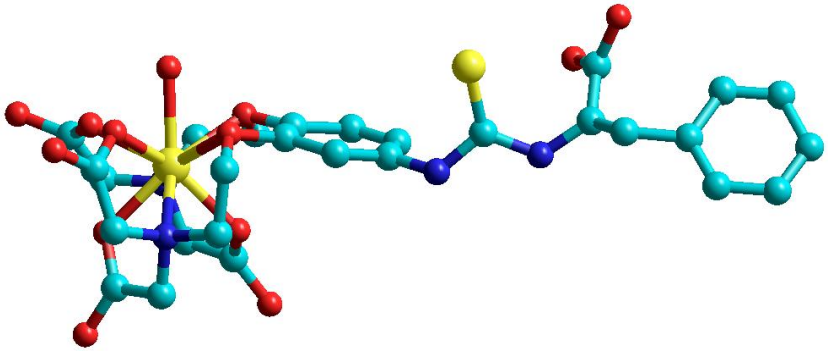


Maximizing the relaxivity of HSA-bound gadolinium complexes
by simultaneous optimization of rotation and water exchange
Chem. Commun., **2007**, 4044-4046

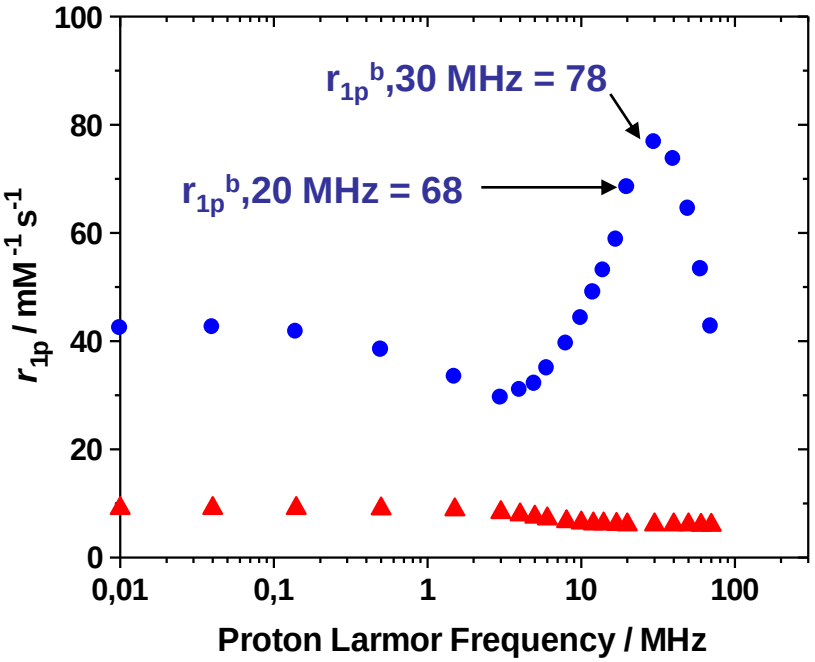
Binding to HSA: ^{1}H NMRD

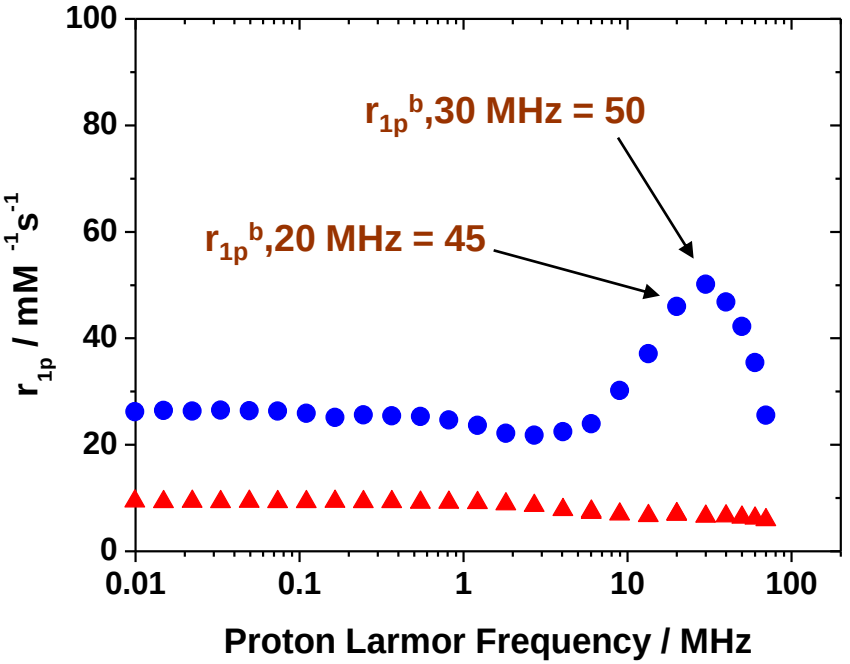


GdL1



GdL2



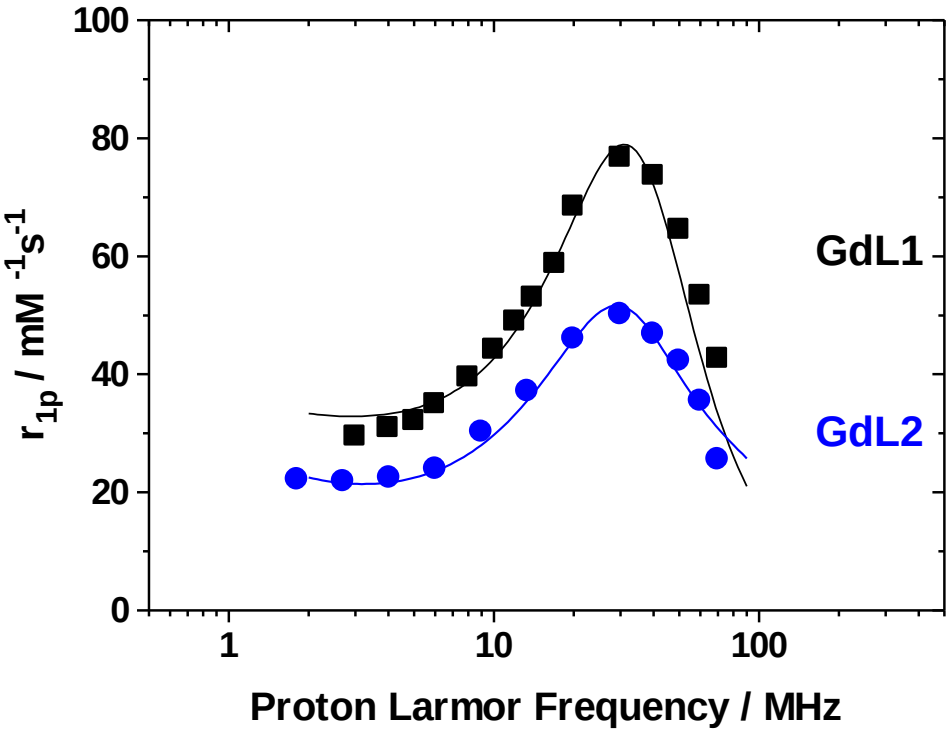


$$r_{1p}^{IS} = \frac{q}{55.6} \times \frac{1}{T_{1M} + \tau_M}$$

Lipari-Szabo model free approach:

$$\frac{1}{T_{1M}} = \frac{2}{15} \frac{\gamma_H^2 g^2 S(S+1)\beta^2}{r_{Gd-H}^6} \left[\frac{3S^2 \tau_{C1g}}{1+\omega_H^2 \tau_{C1g}^2} + \frac{3(1-S^2)\tau_{C1}}{1+\omega_S^2 \tau_{C1}^2} \right]$$

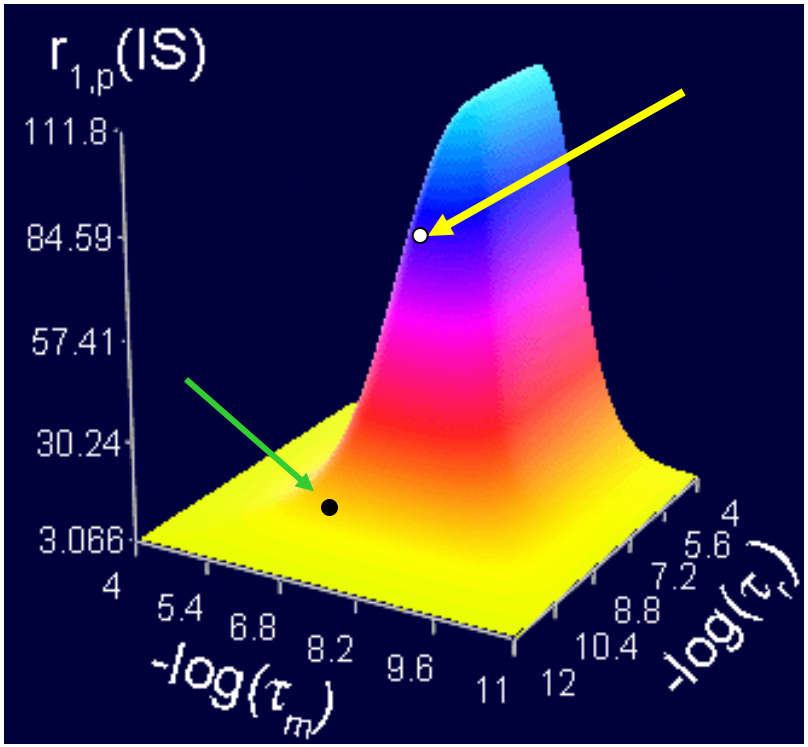
$$\frac{1}{\tau_{C1}} = \frac{1}{\tau_M} + \frac{1}{\tau} + \frac{1}{T_{1e}} \quad \Rightarrow \quad \frac{1}{\tau} = \frac{1}{\tau_{Rg}} + \frac{1}{\tau_{Rl}}$$

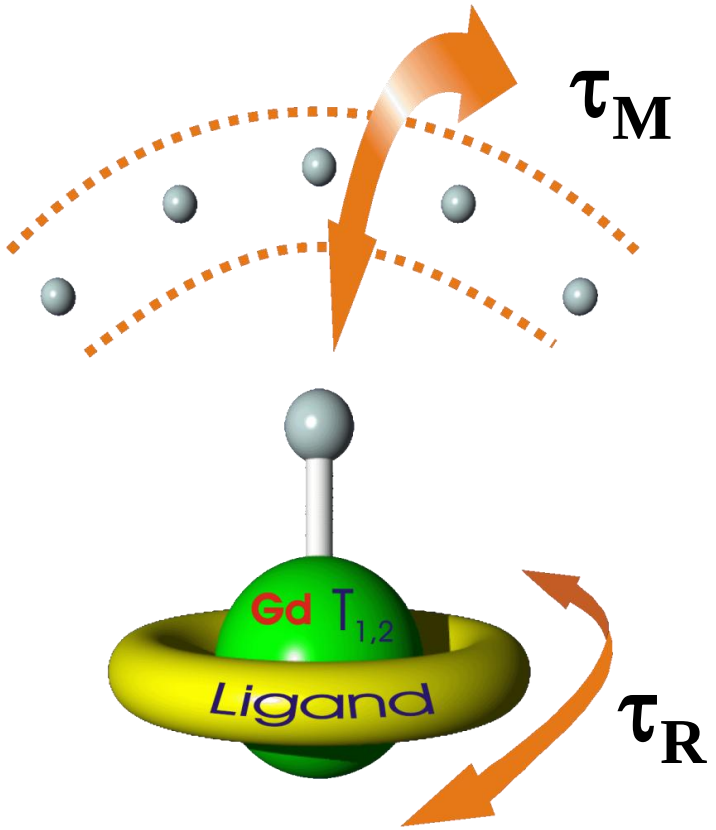


	GdL1	GdL2
τ_{Rg}(ns)	20	20
τ_{Rl}(ns)	9.0	1.1
S^2	0.64	0.31

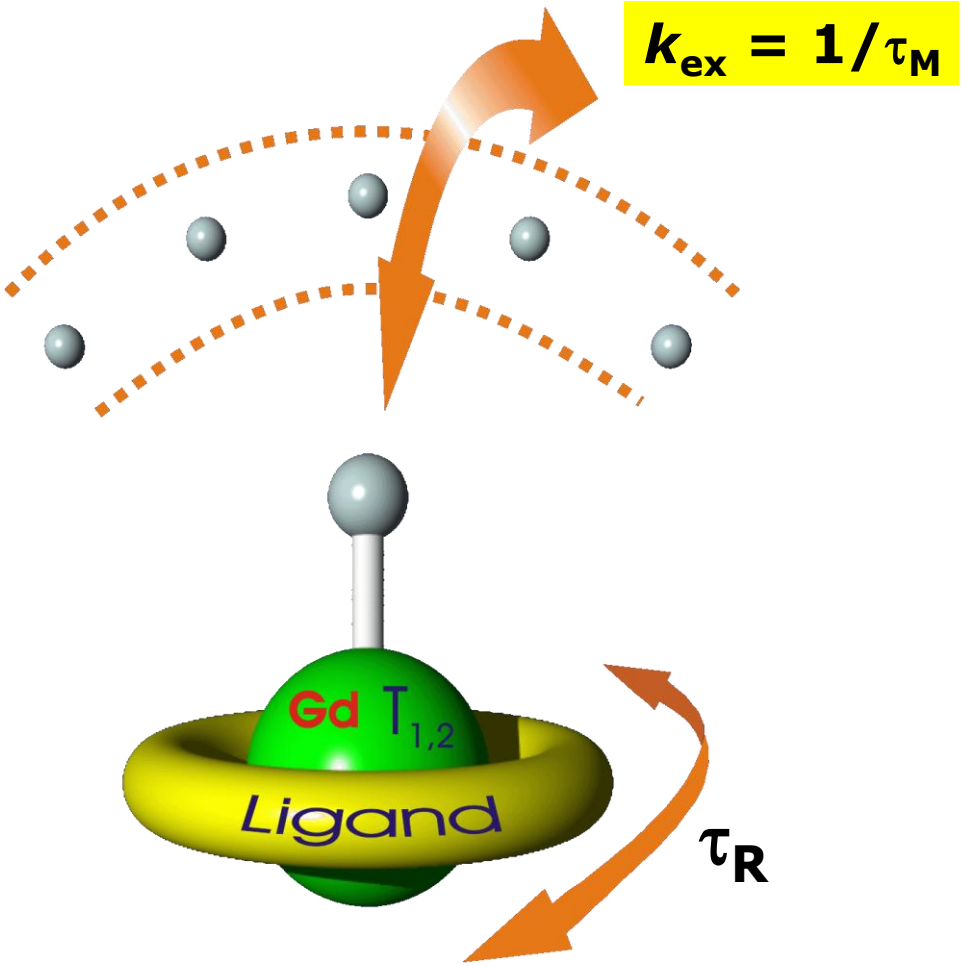
Conclusions

By optimizing both the rotational dynamics and the rate of water exchange for the first time the high relaxivity value predicted by the theory has been obtained .



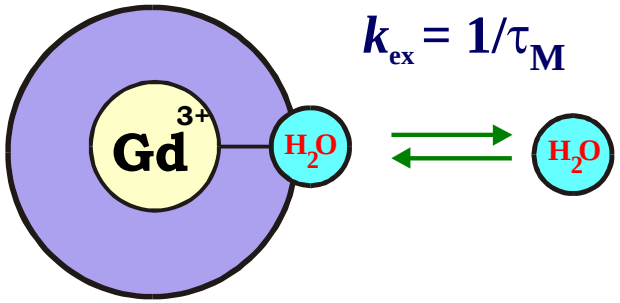


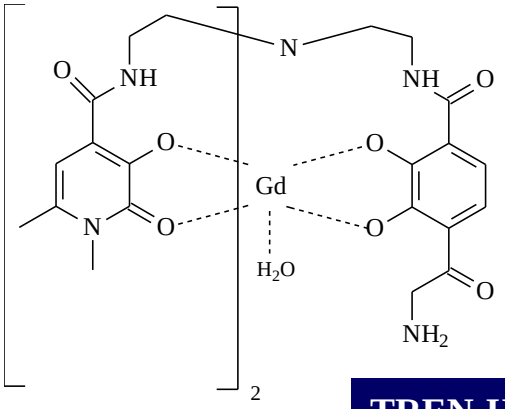
the limiting factors: rotation and exchange…



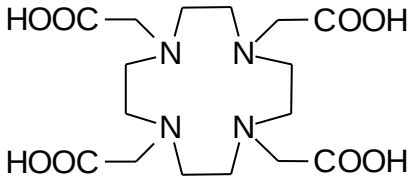
water exchange rate

the reorientational exchange lifetime τ_M

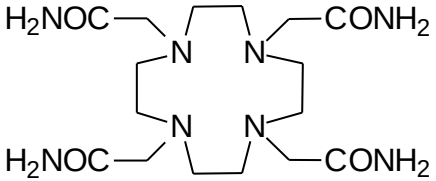




TREN-HOPO



DOTA-MA



PDTA

DOTA

DTPA-BA

aquoion

EGTA

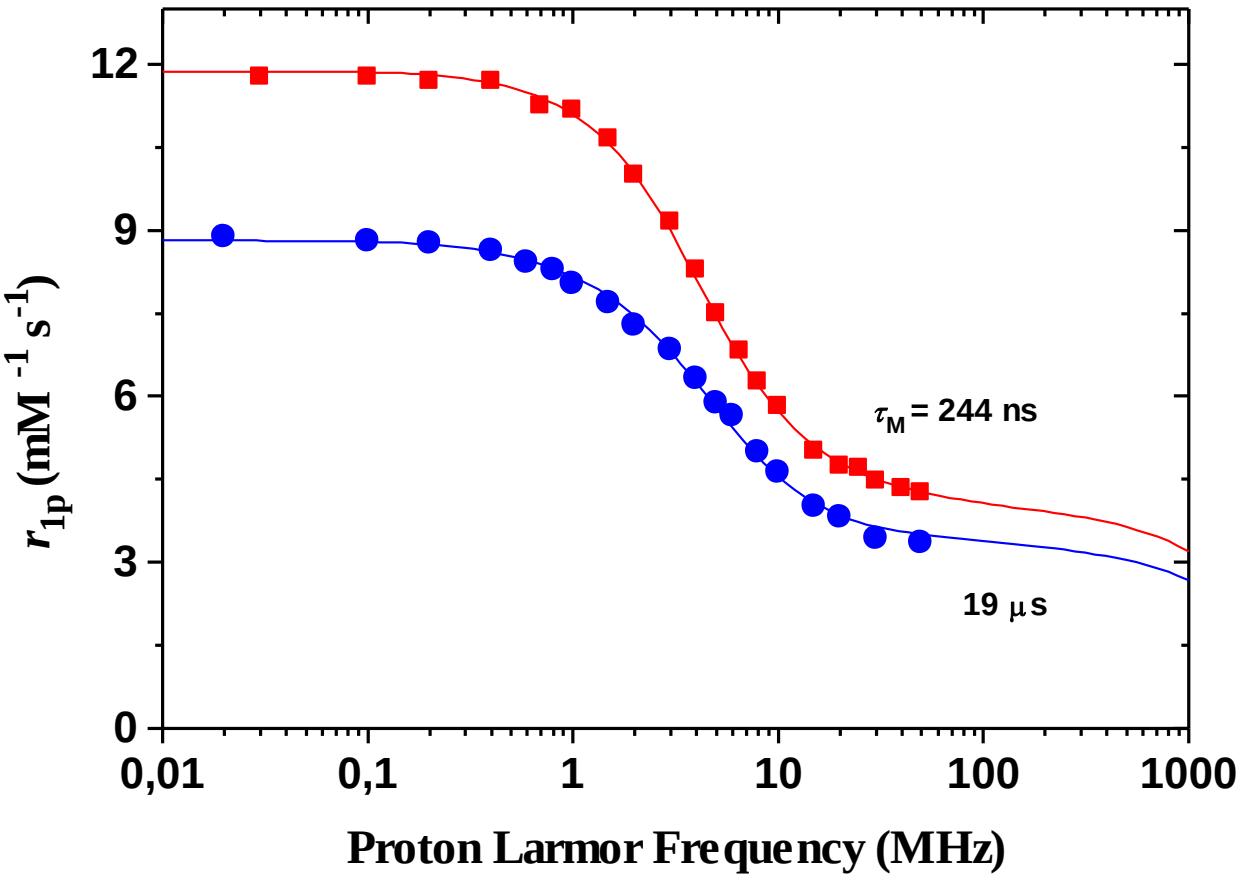
DTPA

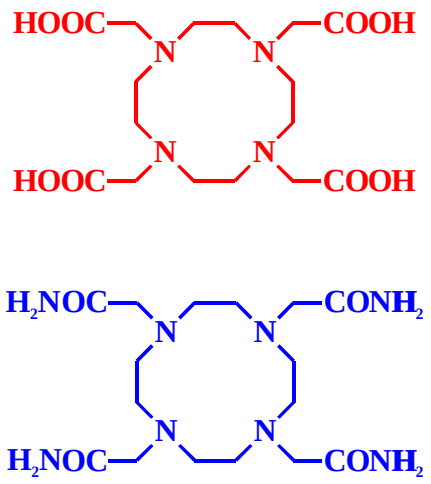
DOTA-TA

10^{-9} 10^{-8} 10^{-7} 10^{-6} 10^{-5} 10^{-4} 10^{-3}

τ_M (s)

the effect of slowing down water exchange…



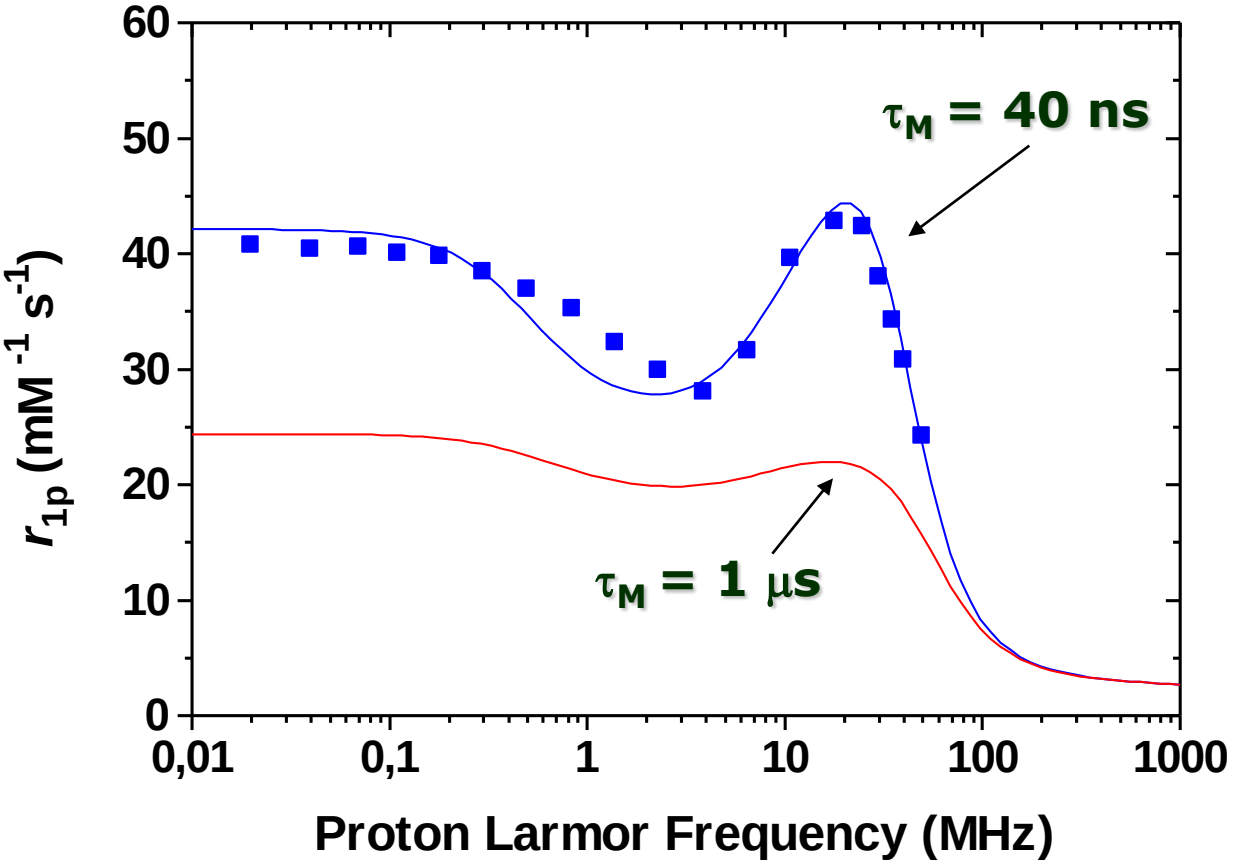


$$r_{1p}^{IS} = \frac{[CA]q}{55.6} \frac{1}{T_{1M} + \tau_M}$$

^{1}H NMRD profile (25°C) of [Gd(DOTA)]$^-$ (squares) and [Gd(DOTAM)]$^{3+}$ (circles) showing the effect on relaxivity due to a slow rate of water exchange

the effect of slowing down water exchange…

…on a macromolecular system: HSA-bound Gd complex



$$r_{1p}^{IS} = \frac{[CA]q}{55.6} \frac{1}{T_{1M} + \tau_M}$$

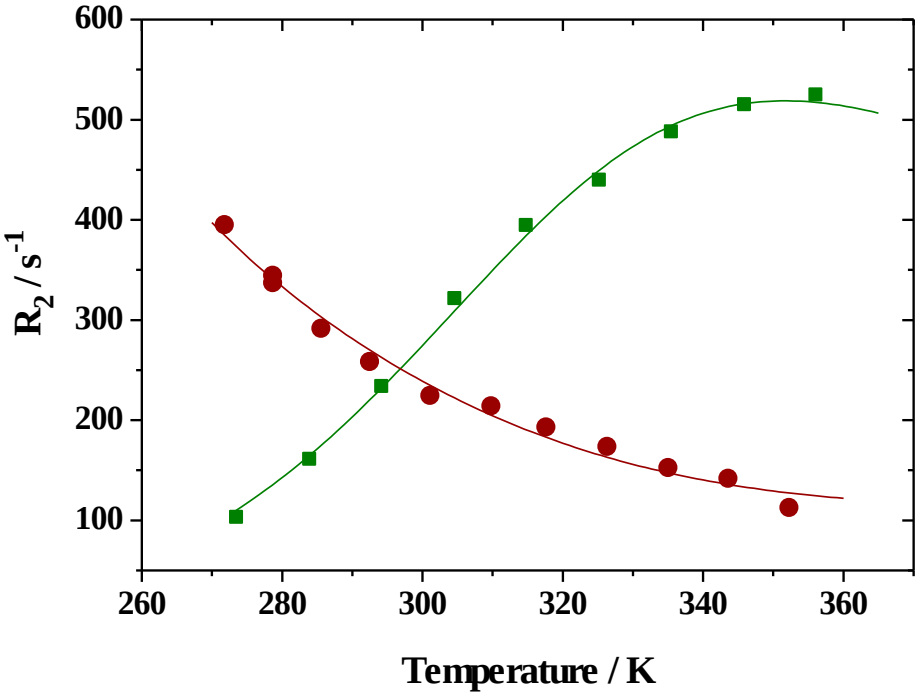
Techniques: ^{17}O NMR

$$R_{2p}^{O} = \frac{[C]q}{55.6}(\tau_M^O)^{-1}\frac{R_{2M}^{O\,2} + (\tau_M^O)^{-1}R_{2M}^O + \Delta\omega_M^{O\,2}}{\left(R_{2M}^O + (\tau_M^O)^{-1}\right)^2 + \Delta\omega_M^{O\,2}}$$

Swift-Connick Equations

$$R_{2M}^{O} = \frac{1}{3}\left(\frac{A}{\hbar}\right)^2 S(S+1)\left(\tau_{E1} + \frac{\tau_{E2}}{1+\omega_s^2\tau_{E2}^2}\right)$$

$$\tau_{Ei}^{-1} = \tau_M^{O\,-1} + T_{iE}^{-1}$$

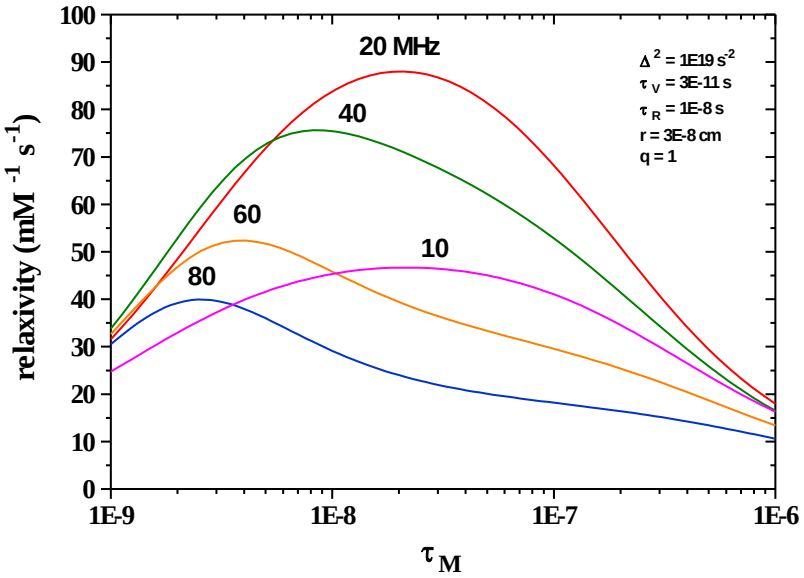


slow exchange

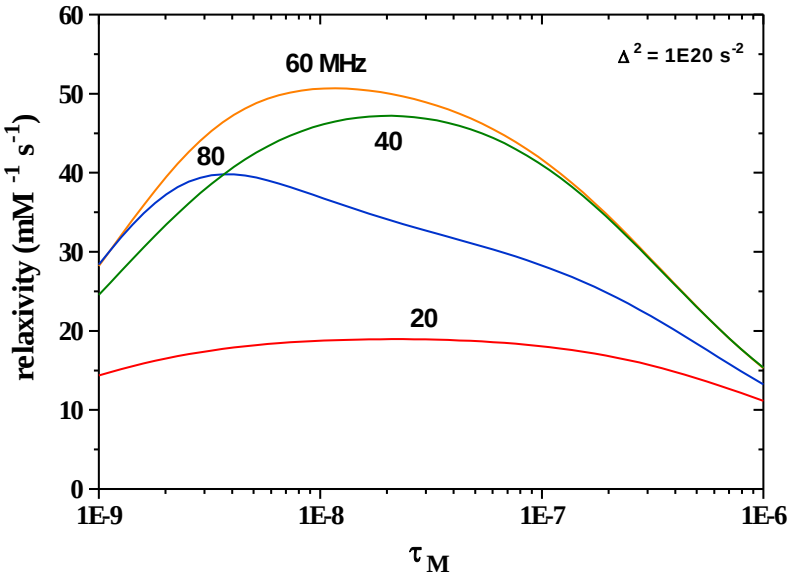
fast exchange

the reorientational exchange lifetime τ_M

⇨ **the optimal τ_M value depends on B_0**



DOTA-like complexes



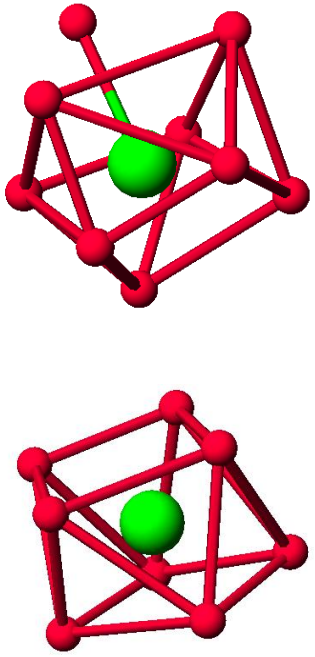
DTPA-like complexes

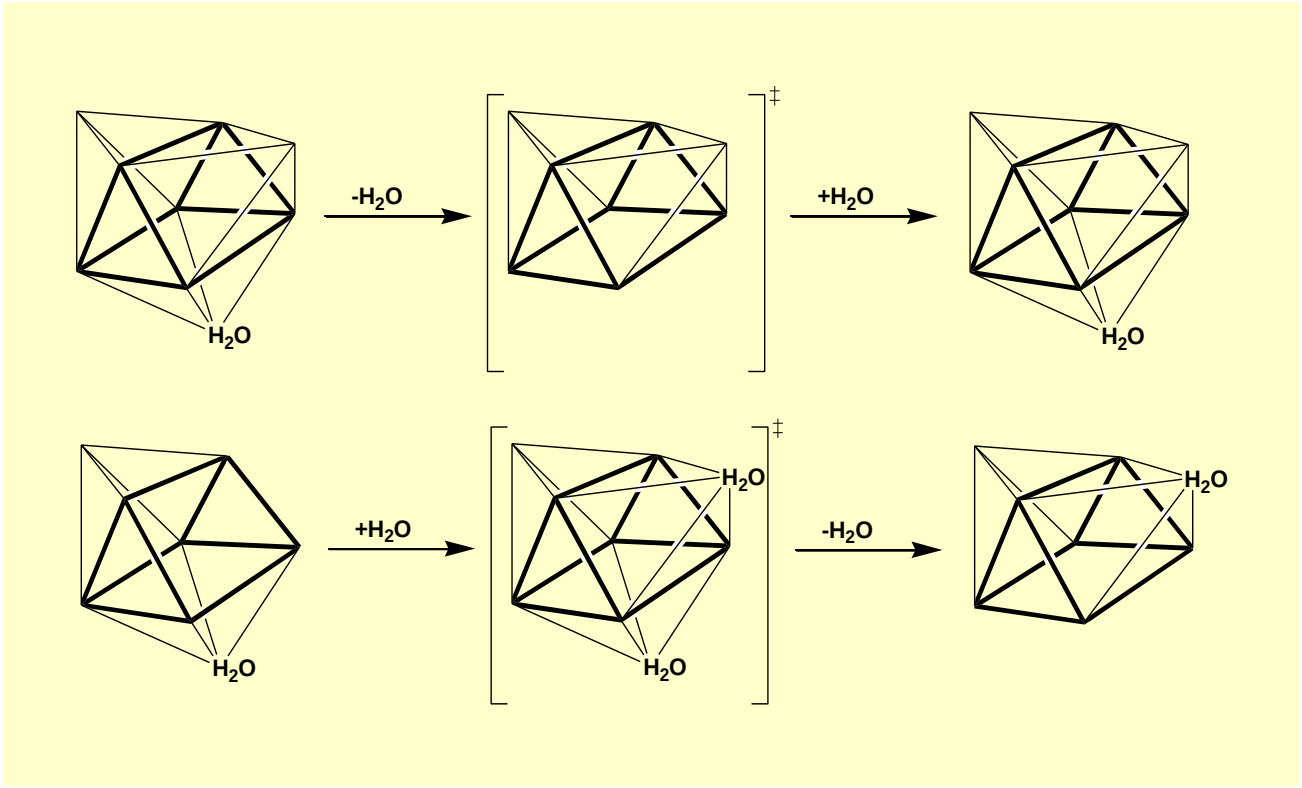
The Factors That Control Water Exchange

- **8- or 9-coordinate ground state (mechanism of the exchange process)**
- **charge of the complex**
- **molecular geometry**
- **steric interactions at the H_2O binding site**
- **electronic effects**
- **(assistance of 2nd sphere H_2O molecules and nature of the counterion)**

k_{ex} and mechanism of the exchange process

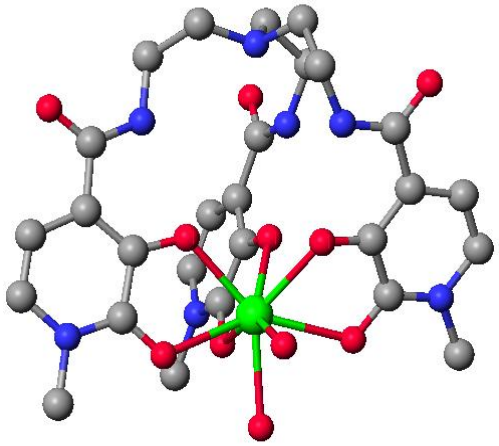
water exchange mechanisms



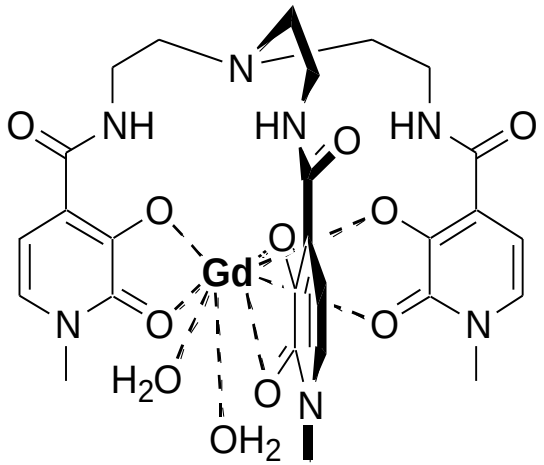


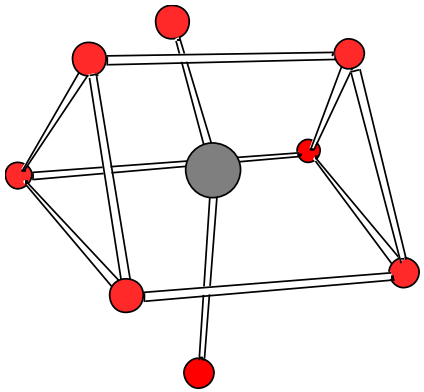
Dissociative (top) and associative (bottom) mechanisms of water exchange at an idealized tricapped trigonal prismatic Gd^{3+} metal center. The dissociative mechanism operates through a coordinatively unsaturated 8-coordinate intermediate, while in the associative mechanism a 9-coordinate intermediate is formed.

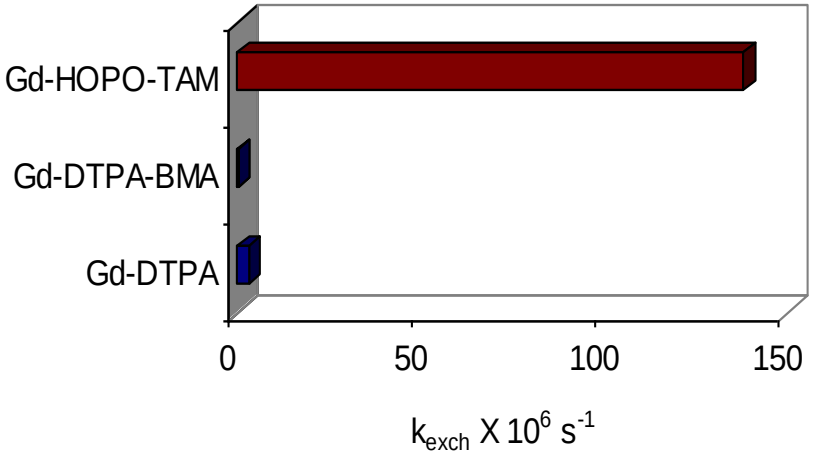
k_{ex} and mechanism of the exchange process



Gd(TREN-trisHOPO)(H_2O)$_2$
X-Ray structure





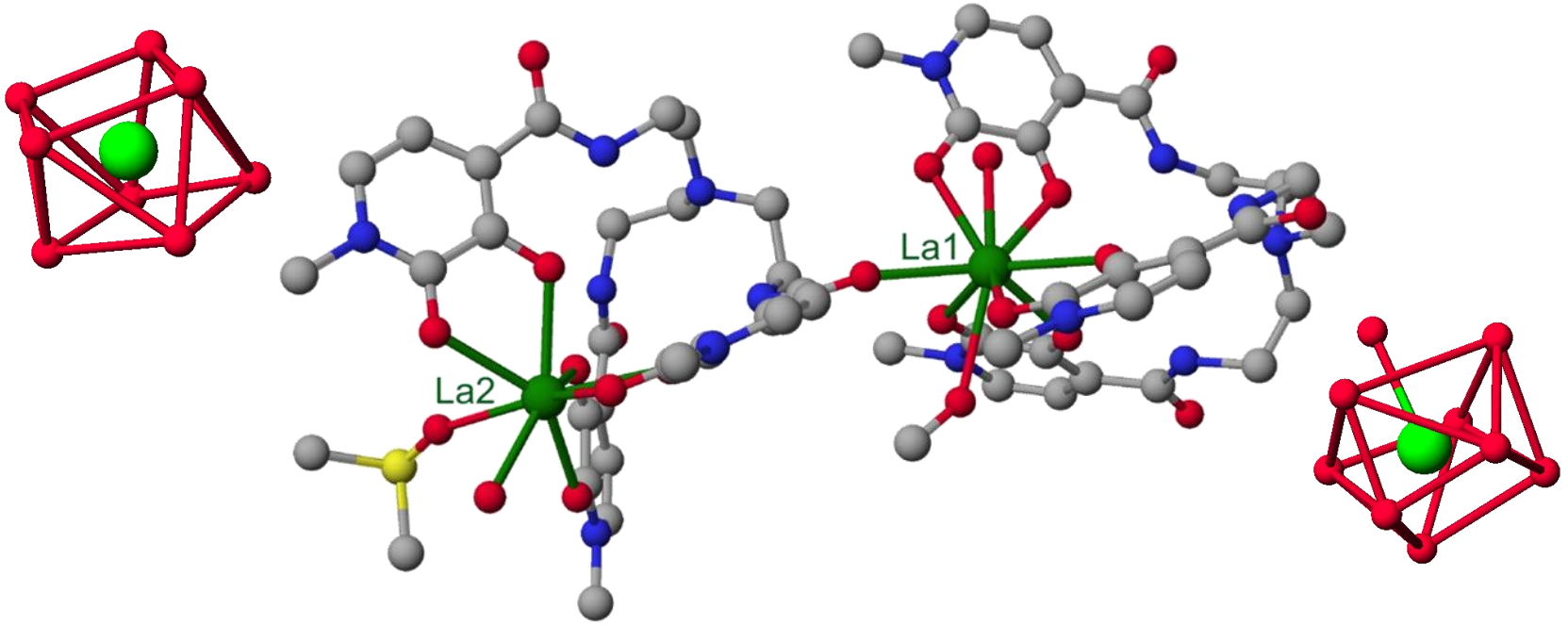


Xu, J.; Franklin, S. J.; Whisenhunt, D. W.; Raymond, K. N. *J. Am. Chem. Soc.* 1995, *117*, 7245.

Cohen, S. M.; Xu, J.; Radkov, E.; Raymond, K. N.; Botta, M.; Barge, A.; Aime, S. *Inorg. Chem.* 2000, *39*, 5747.

k_{ex} and mechanism of the exchange process

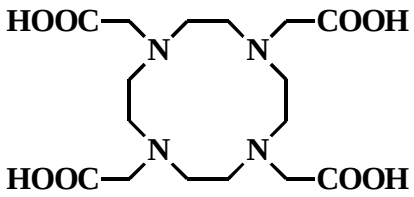
Crystal structure of La-TREN-1-Me-3,2-HOPO dimer of an 8 and 9 coordinate complex



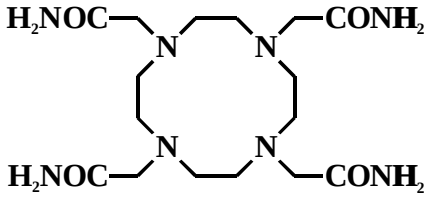
Molecule assembles as a dimer, La1: 9-coordinate; La2: 8-coordinate
La1: monocapped square antiprismatic geometry; La2: square antiprismatic geometry
Water molecules replaced by DMSO and methanol in the solid state

Inorg. Chem. **2000**, *39*, 5747.
J. Am. Chem. Soc. **2003,** *125*, 14274.

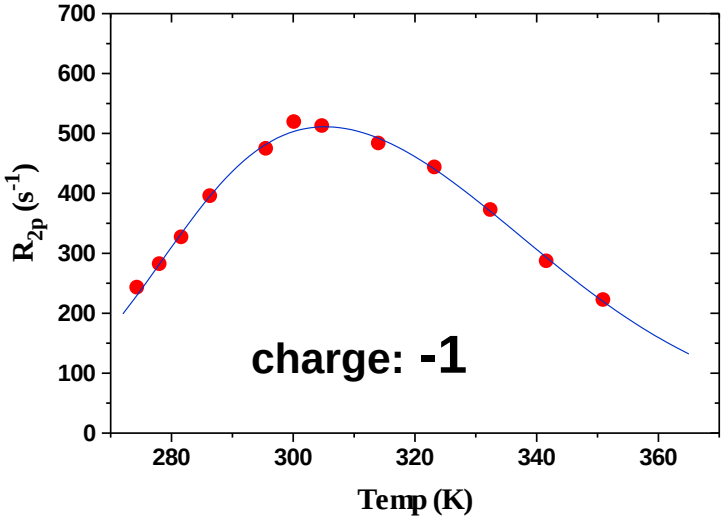
k_{ex} and charge of the complex

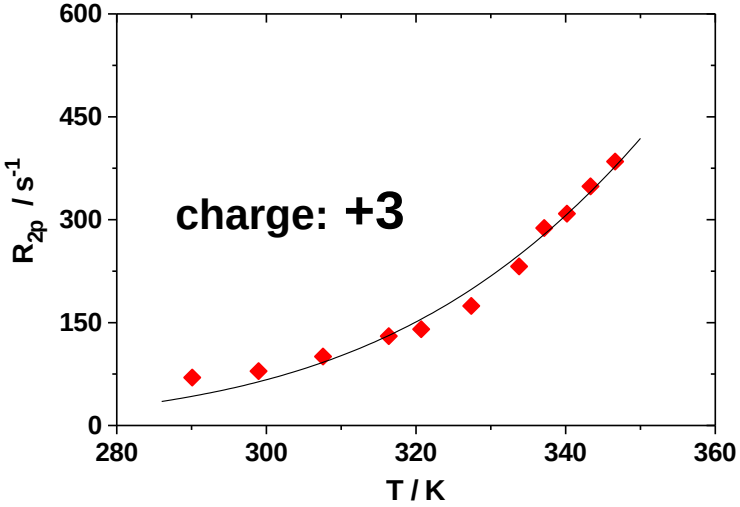


DOTA



DOTAM



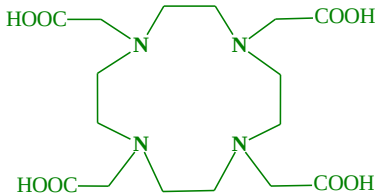


τ_M = 300 ns

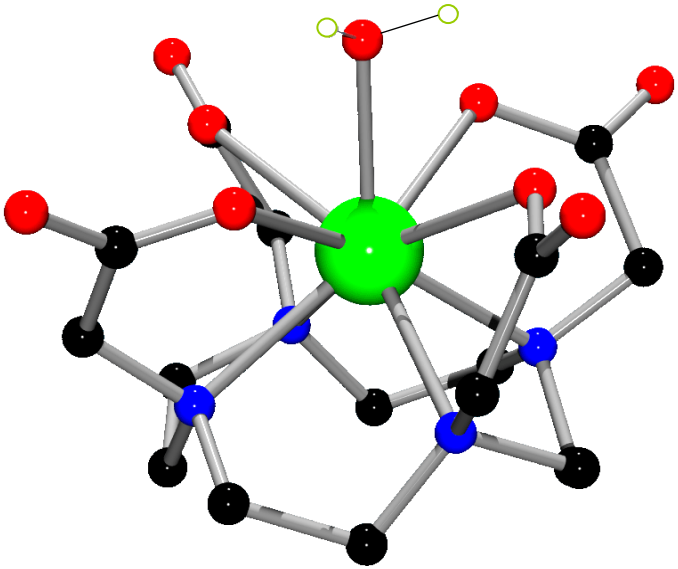
τ_M = 14 μs

k_{ex} and molecular geometry

DOTA



…and derivatives



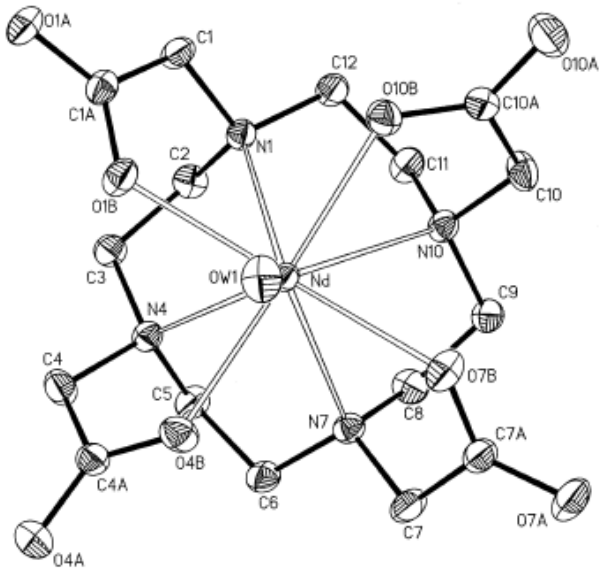


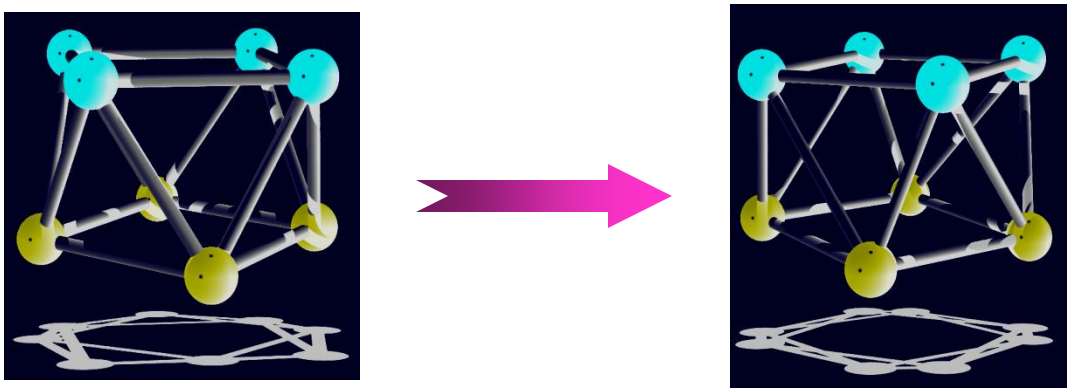
Figure 4. SA geometry in $[Nd(DOTA)(H_2O)]^-$, ORTEP view.

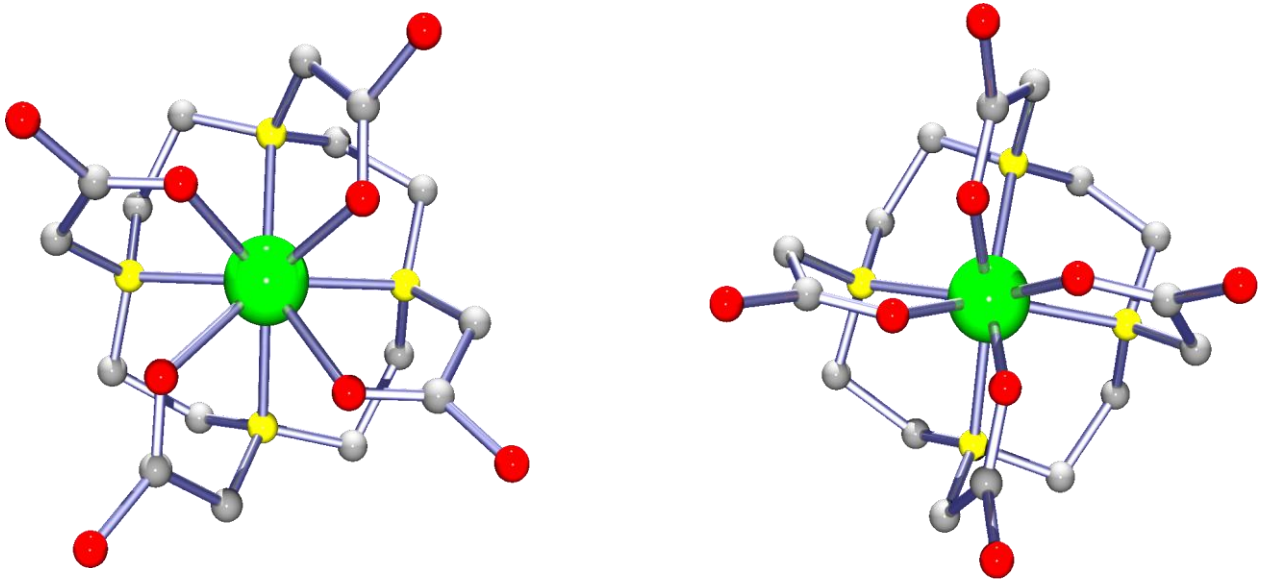
SAP

square antiprismatic geometry

Inorg. Chem. **2003**, *42*, 148–157

k_{ex} and molecular geometry





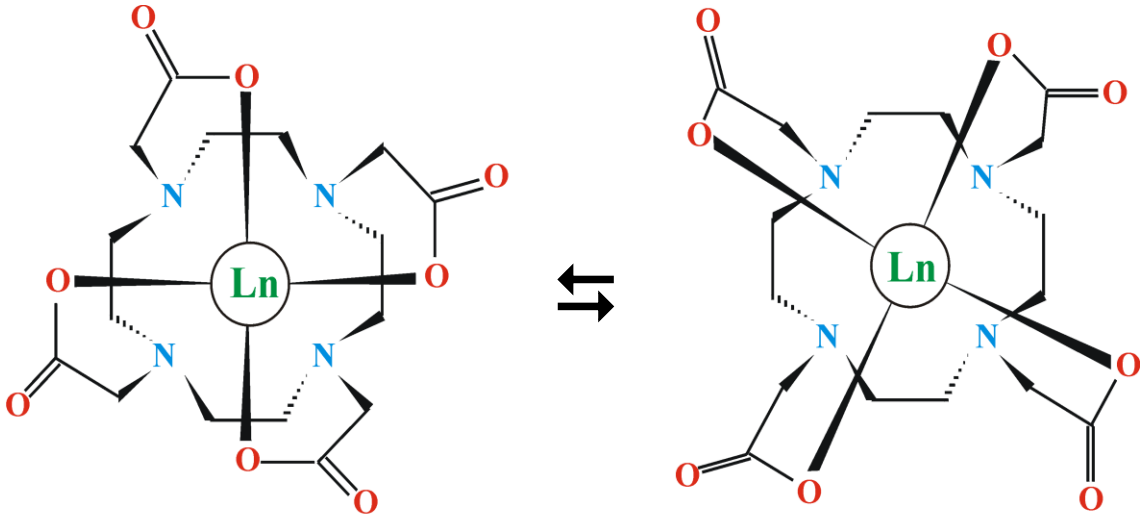
SAP
Pr-Ho

in the solid state

TSAP
La-Ce

k_{ex} and molecular geometry

LnDOTA complexes are present in solution as a mixture of the 2 isomers



SAP (M) ⇆ **TSAP (m)**

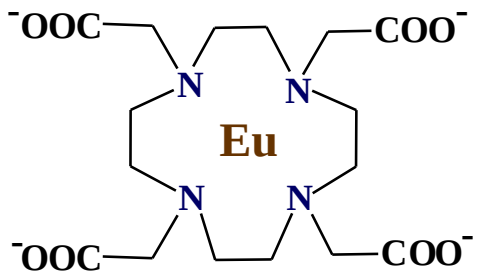
k_{ex} (m) >> k_{ex} (M)

for Eu complexes of tetraamide DOTA derivatives

Angew. Chem. Int. Ed., **1998**, *37*, 2673

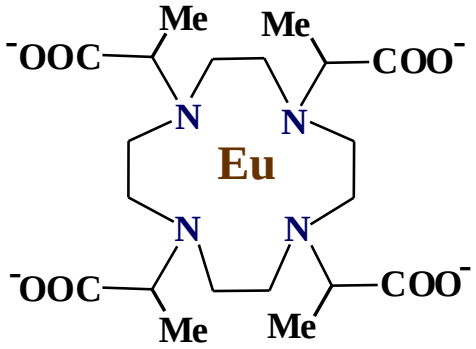
J. Am. Chem. Soc., **1999**, *121*, 5762

k_{ex} and molecular geometry



DOTA

SAP>>TSAP



DOTMA

SAP<<TSAP

K^{298} = [m]/[M] = 0.21

ΔH° = 3.4 (*k*J/mol)

ΔS° = -1 (J/mol·K)

$$M \underset{}{\overset{K}{\leftrightarrows}} m$$

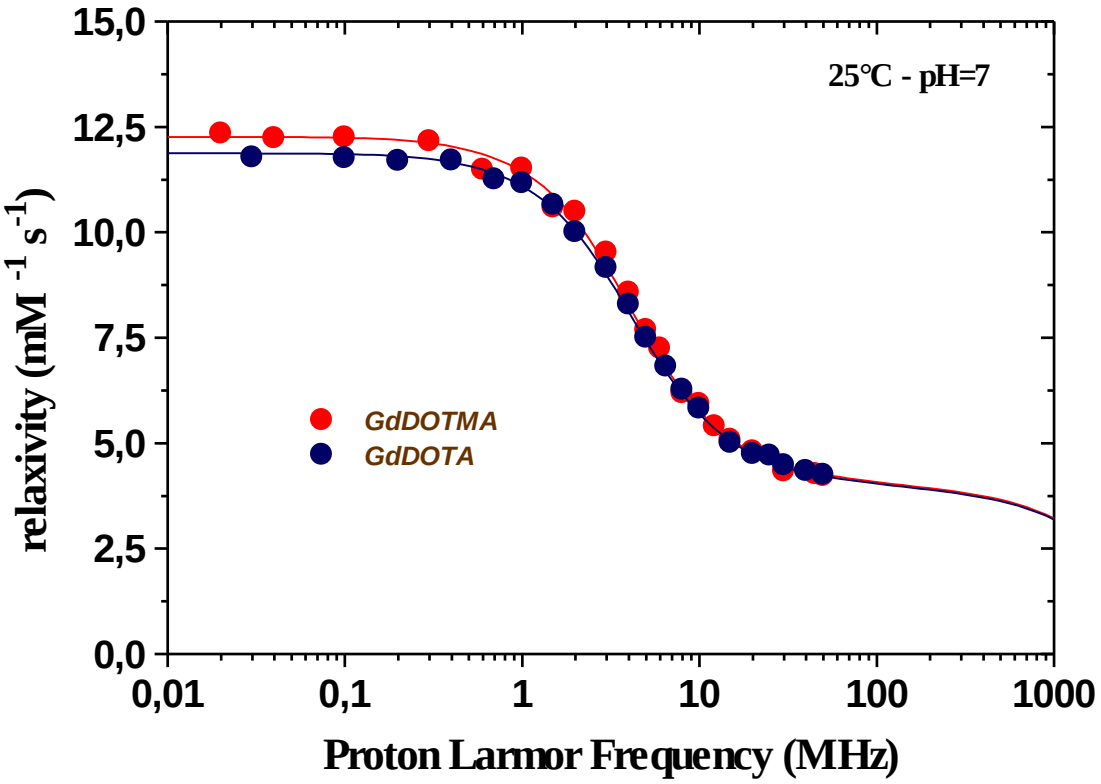
K^{298} = [m]/[M] = 4.5

ΔH° = 6.0 (*k*J/mol)

ΔS° = 33 (J/mol·K)

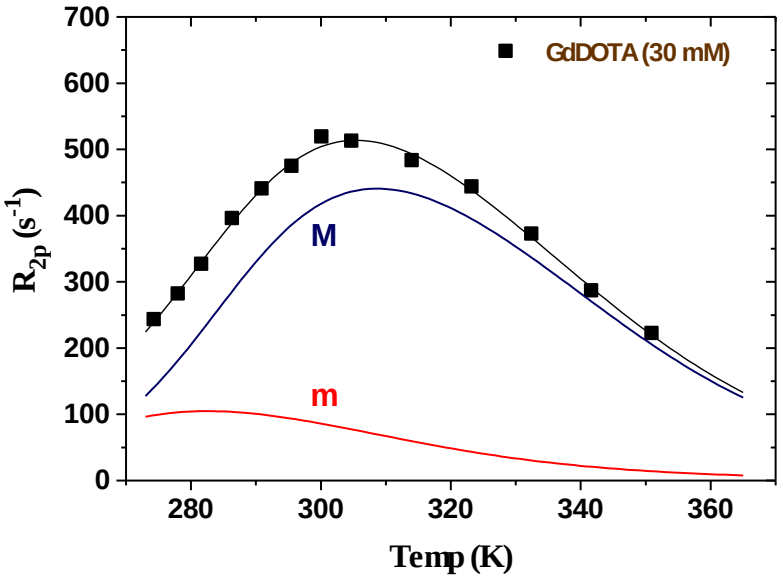
(*Inorg.Chem.*, **1997**, *36*, 2059)

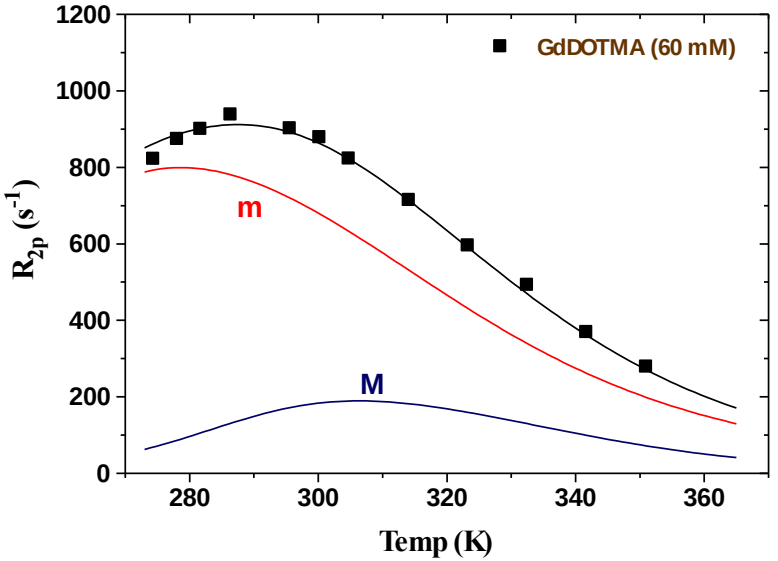
k_{ex} and molecular geometry



- **The electronic relaxation times of the two isomers are very similar**

k_{ex} and molecular geometry

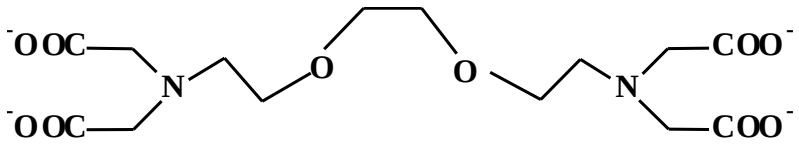




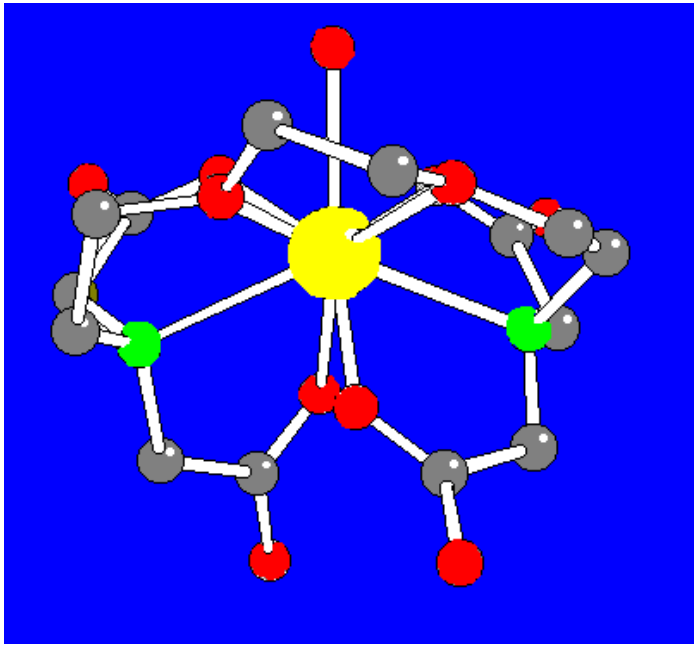
τ_M (M) = 376 ns
τ_M (m) = 41 ns
ΔH_M (M) = 55 kJ/mol
ΔH_M (m) = 48 kJ/mol
$\Delta^2 = 1.2 \times 10^{19}$ s^{-2}
τ_V = 6.4 ps

τ_M (M) = 380 ns
τ_M (m) = 42 ns
ΔH_M (M) = 54 kJ/mol
ΔH_M (m) = 40 kJ/mol
$\Delta^2 = 1.1 \times 10^{19}$ s^{-2}
τ_V = 6.0 ps

k_{ex} and steric interactions



EGTA



The high water exchange rate of $[Gd(EGTA)(H_2O)]^-$ is explained in terms of a limiting dissociative exchange mechanism favoured by the steric constraints on the water binding site

$k_{ex} = 3.1 \times 10^7\ s^{-1}$

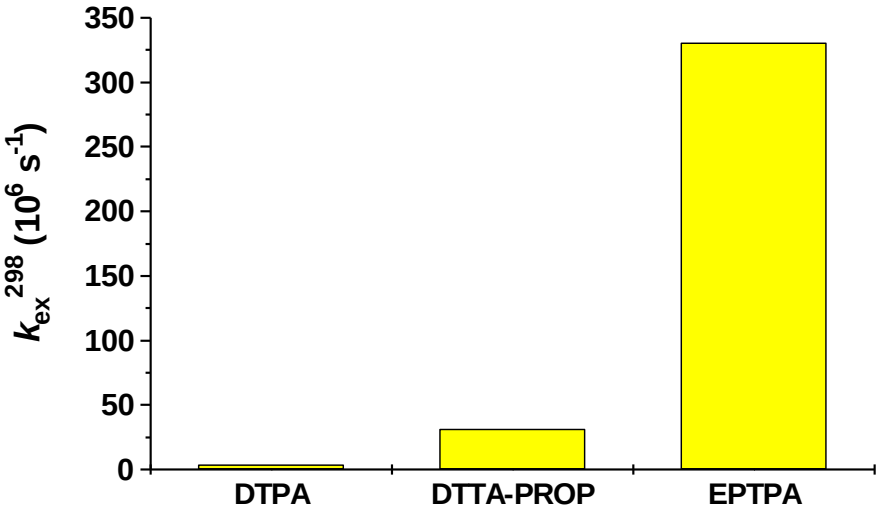
Inorg. Chem., **1997,** *36*, 5104

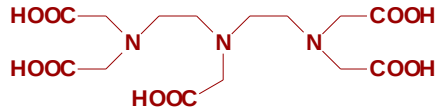
k_{ex} and steric interactions

acceleration of water exchange by inducing steric compression at the water binding site

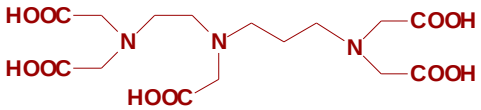
E. Ruloff, É. Tóth, R. Scopelliti, R. Tripier, H. Handel, A. E. Merbach, *Chem. Commun.*, **2002**, 2630
S. Laus, R. Ruloff, É. Tóth, A. E. Merbach, *Chem. Eur. J.*, **2003**, *9*, 3555

k_{ex} and steric effects

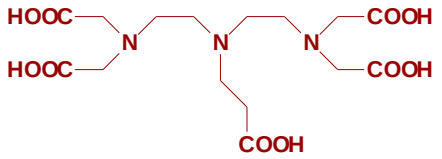




DTPA

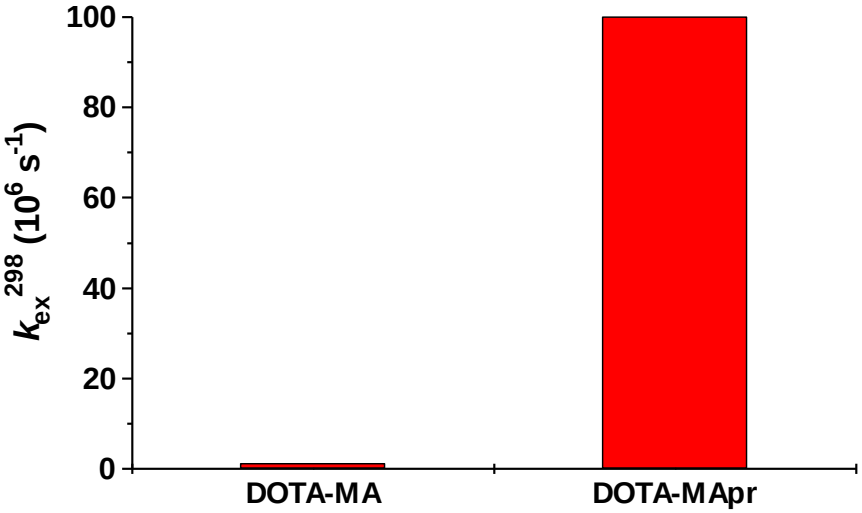


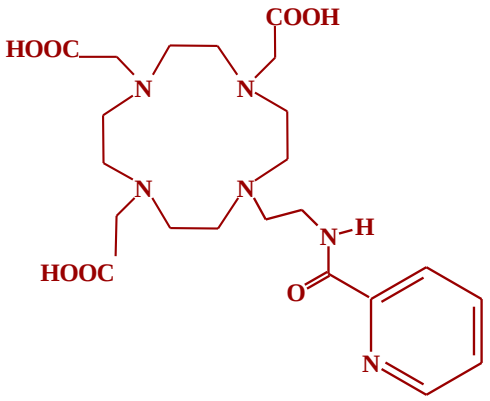
EPTPA



DTTA-PROP

Merbach, Toth et al. *Chem. Eur. J.*, **2003**, 3555

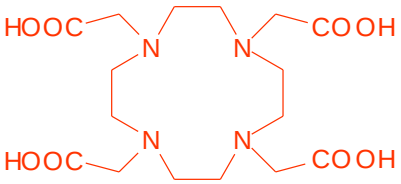


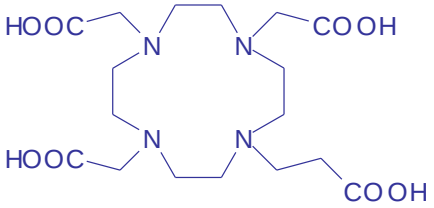


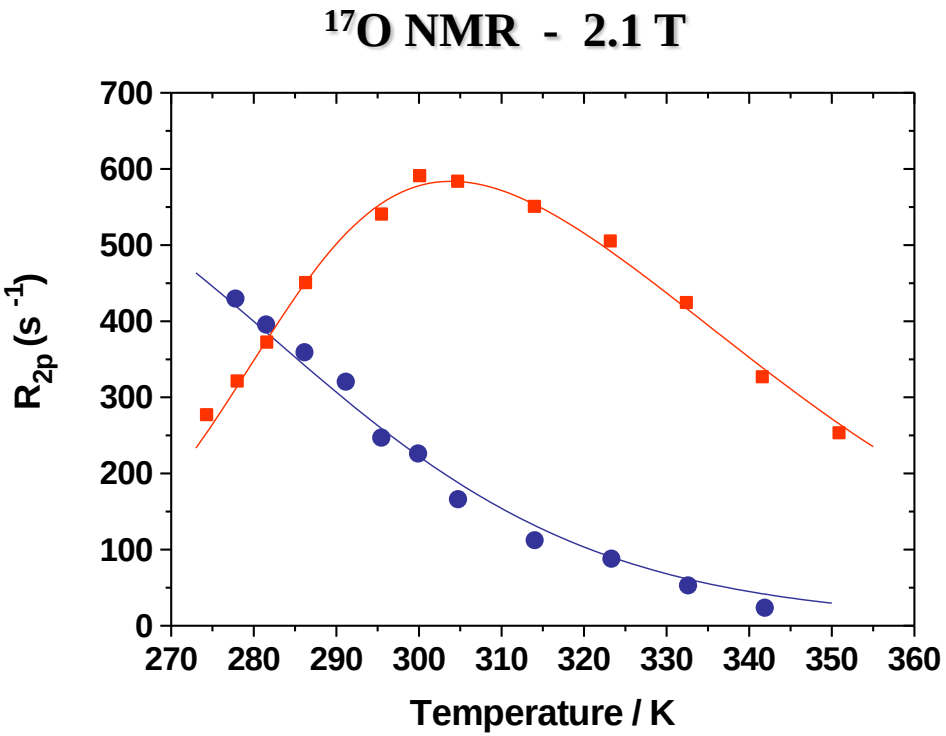
DOTA-MApr

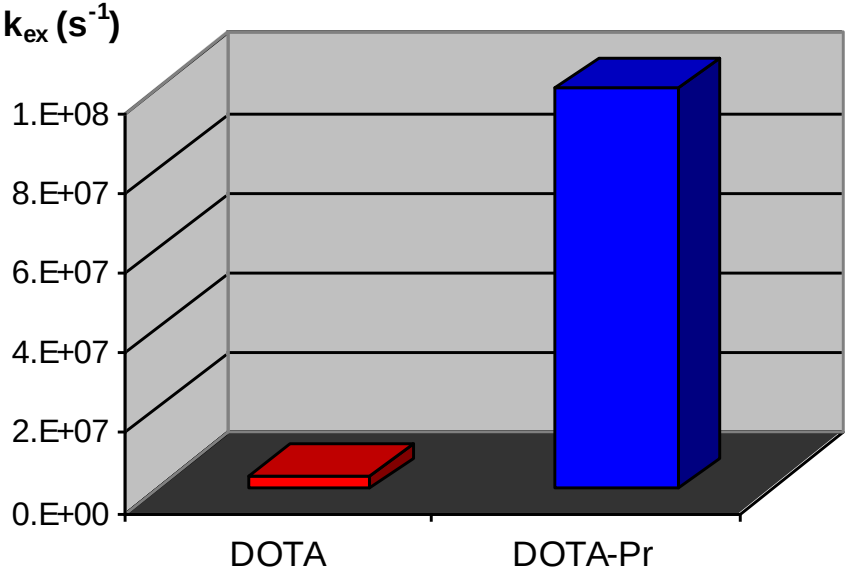
Parker, Botta et al. *Dalton Trans.*, **2004**, 1441

k_{ex} and steric effects

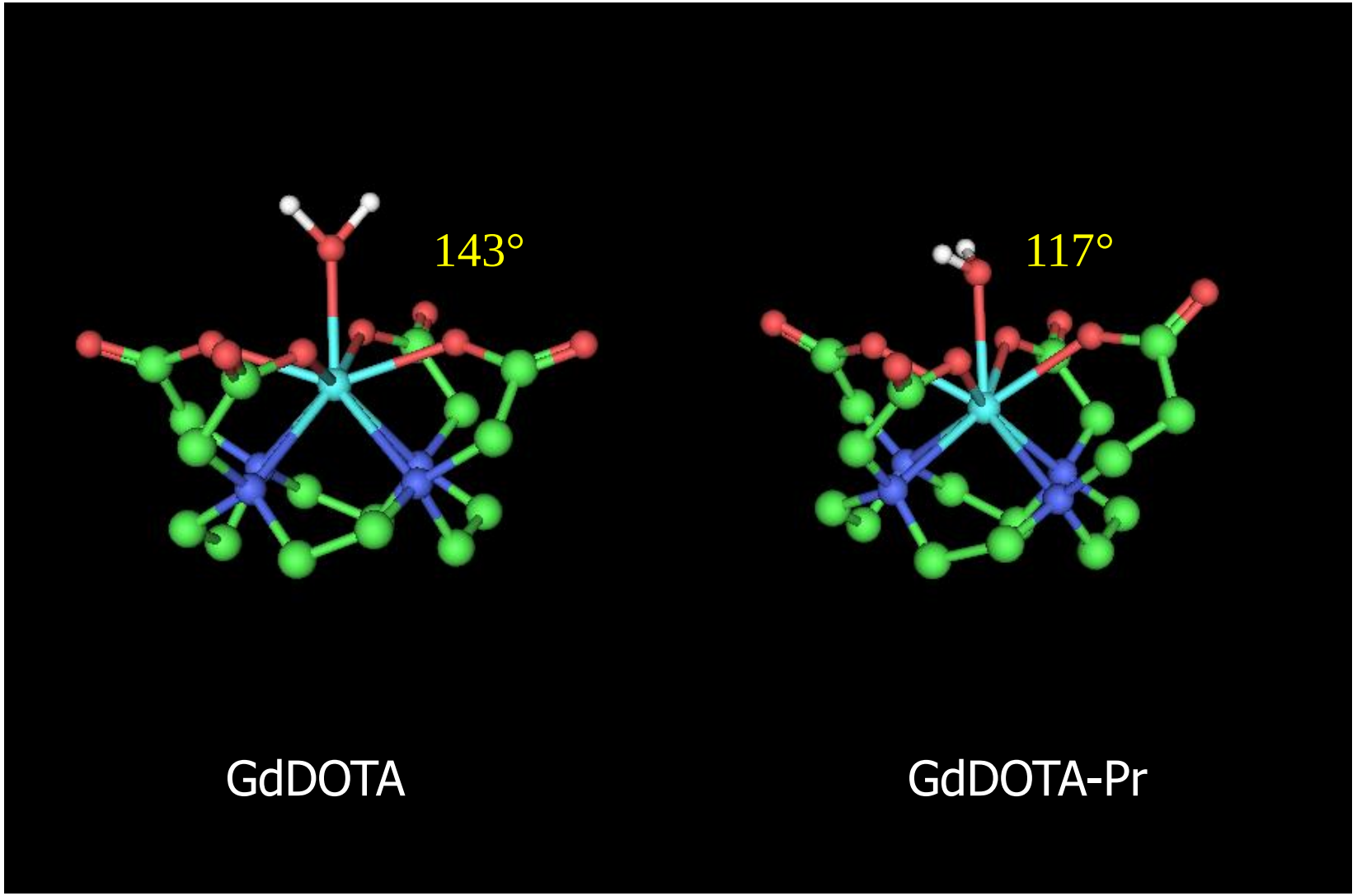




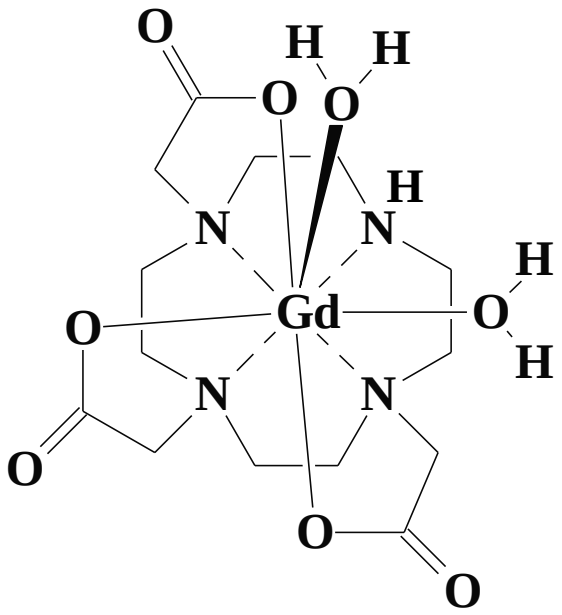




k_{ex} and steric effects



k_{ex} and electronic effects



GdDO3A

q = 1.88

τ_M = 91 ns (25°C)

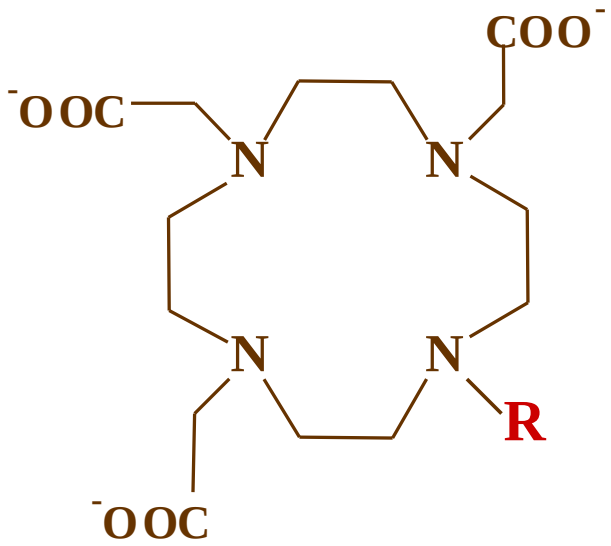
$\Delta^2 = 3\times10^{19}\ s^{-2}$

τ_V = 16 ps

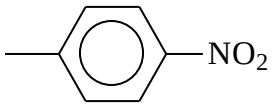
*Merbach, Toth, Helm,.. *Magn. Reson. Chem.*, **1999**, *37*, 701

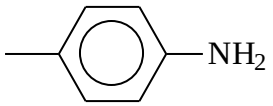
k_{ex} and electronic effects

Can τ_M be modulated by introducing a substituent at the secondary nitrogen atom ?

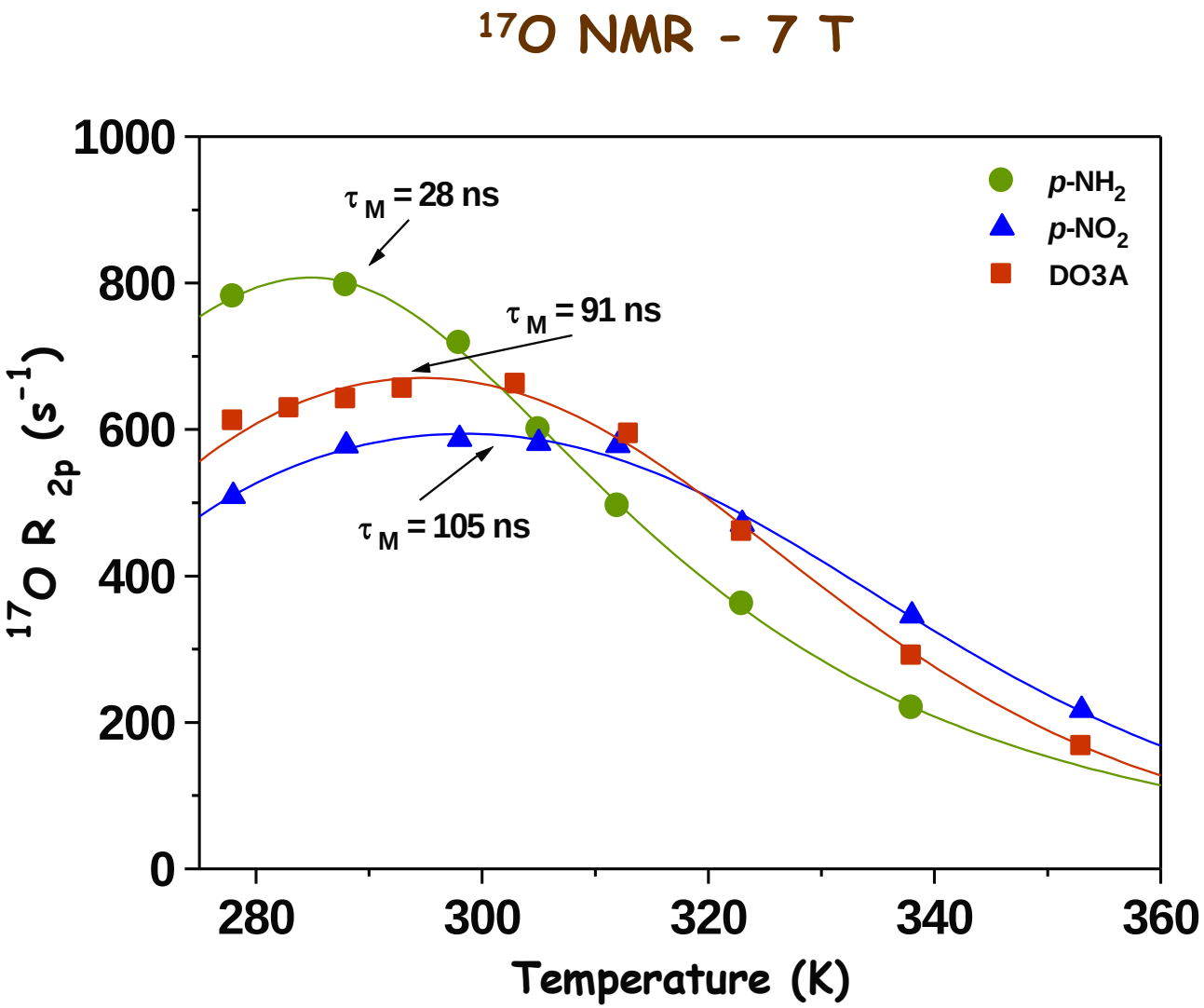


R =



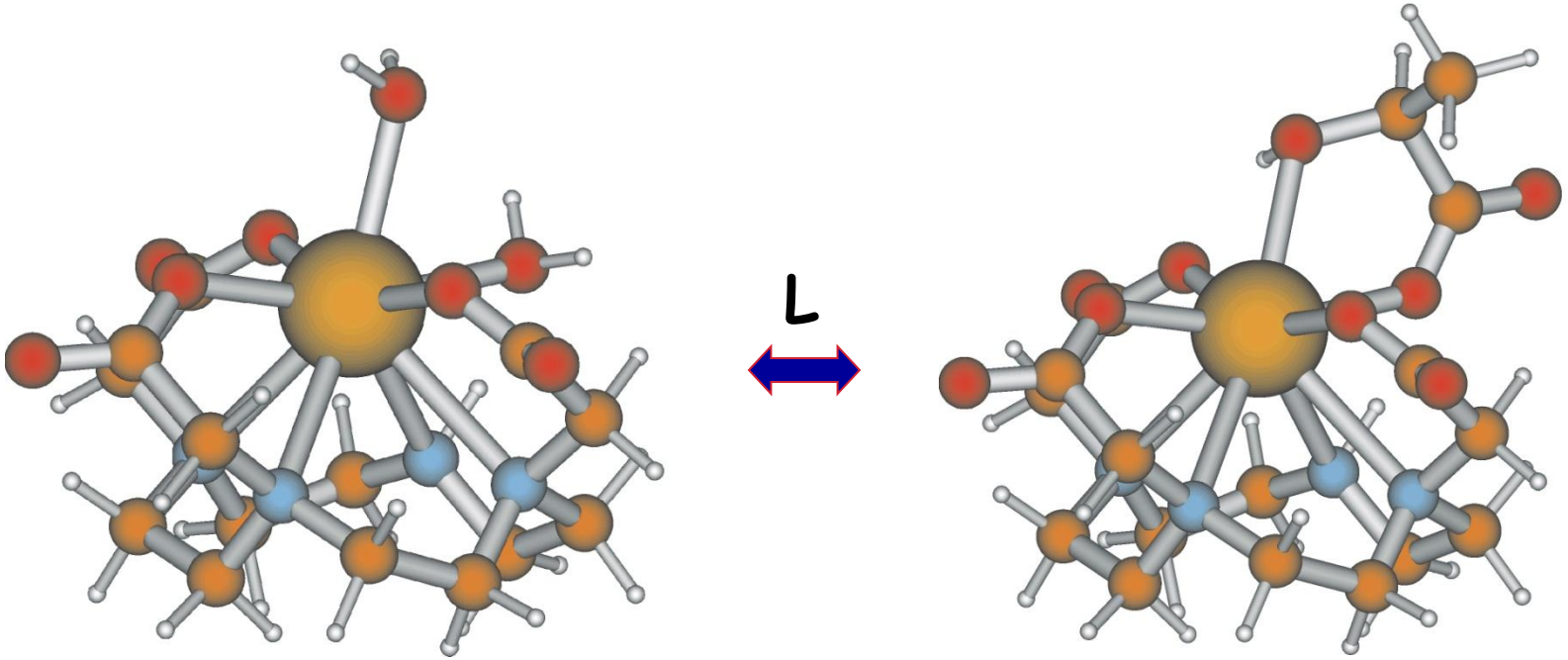


k_{ex} and electronic effects



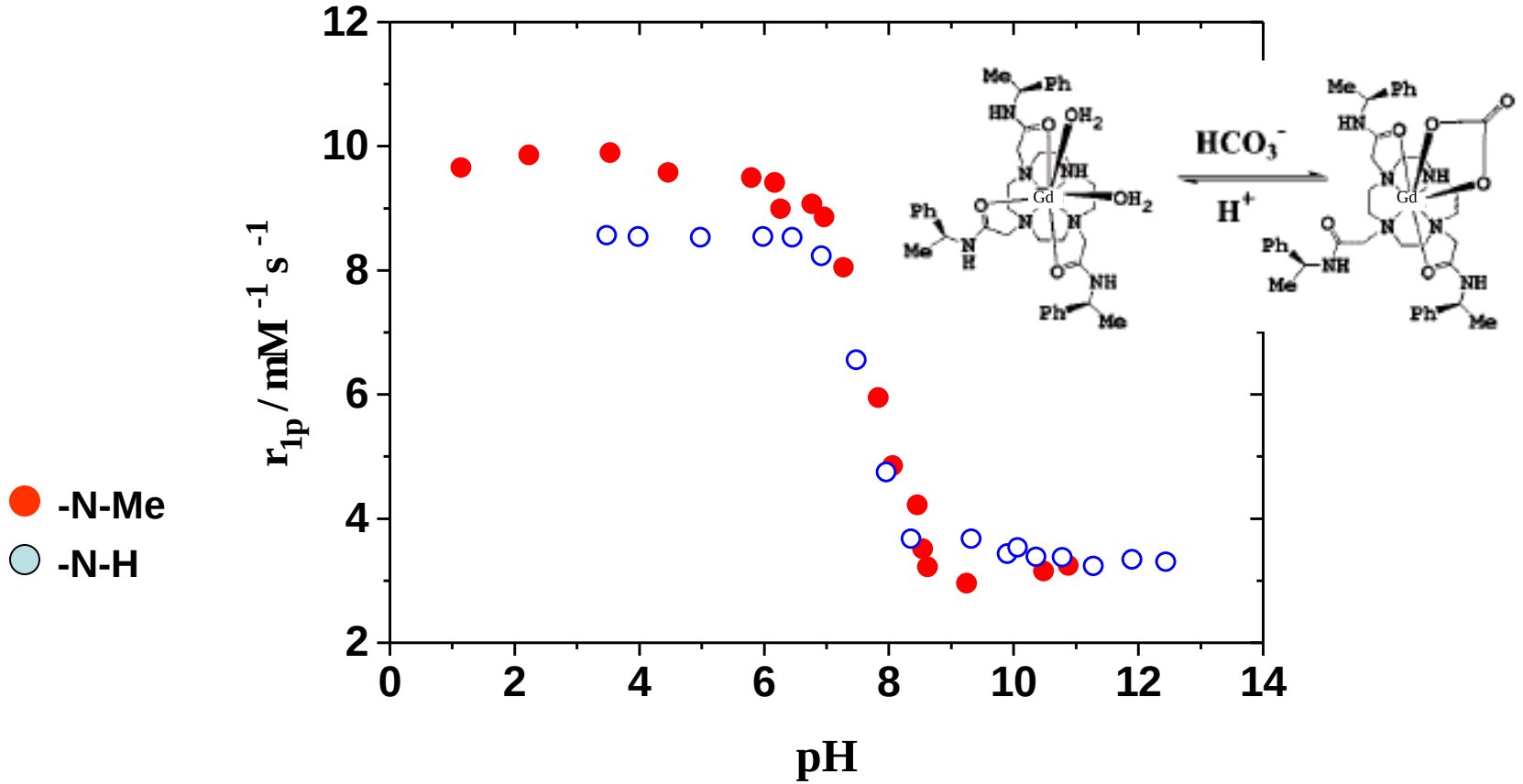
Eur. J. Inorg. Chem. 2003, 3530–3533

q=2 complexes: possible formation of ternary systems!



Ternary complexes with carbonate

20 MHz - 25°C



Ternary complexes with carbonate

$$[GdL(H_2O)_2]^{3+} + CO_3^{2-} \overset{K}{\rightleftharpoons} [GdL(CO_3)]^{+} + 2\,H_2O$$

$$H_2CO_3 + 2H_2O \overset{\beta_2}{\rightleftharpoons} CO_3^{2-} + 2H_3O^{+}$$

$$K_A = K \times \beta_2 = \frac{[GdL(CO_3)]^{+}\ [H_3O]^{+}}{[GdL(H_2O)_2]\ [H_2CO_3]}$$

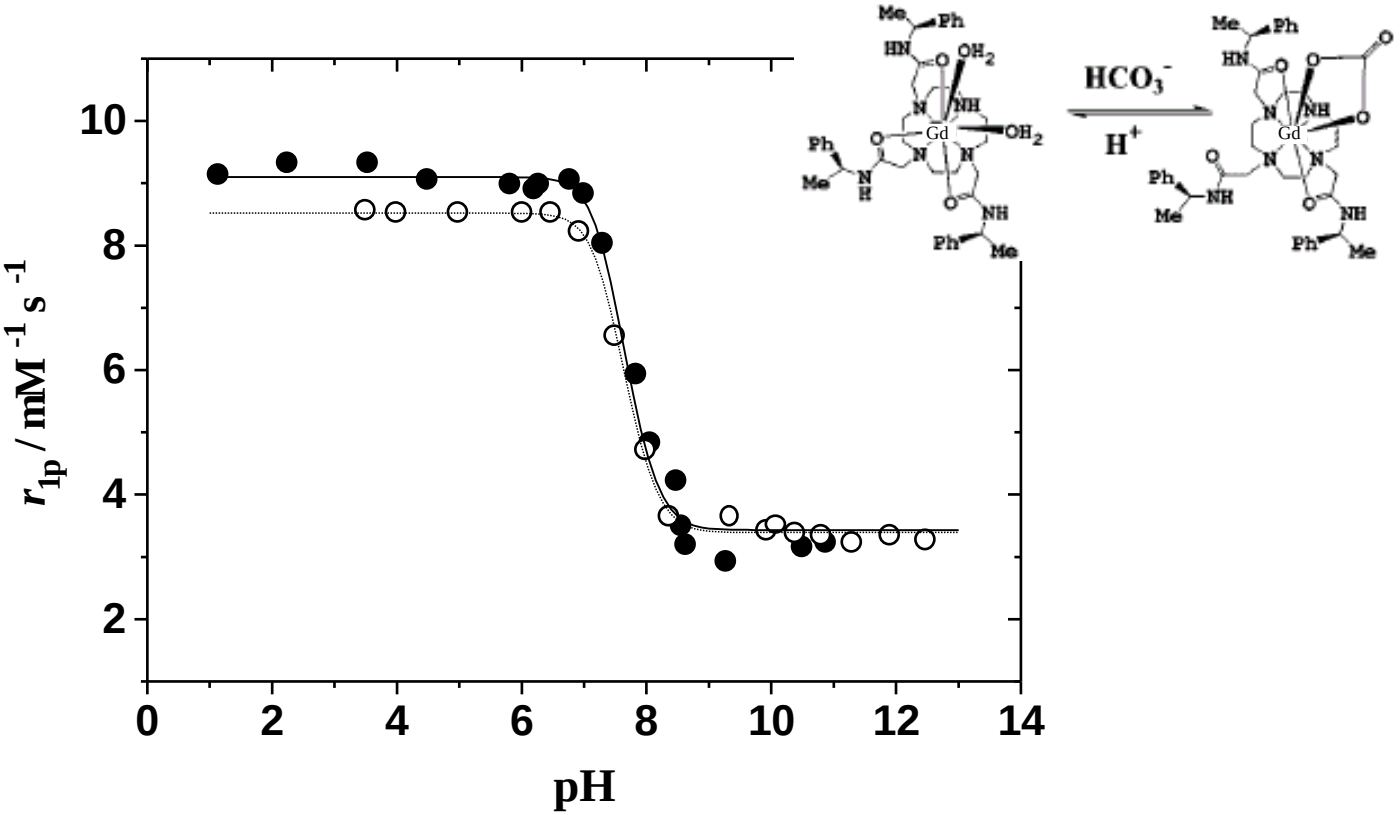
$$R_{1p} = ([C_F]r_{1p}^{F} + [C_B]r_{1p}^{B}) \cdot 1000$$

$$[C_B] = \frac{\left(K\beta_2 L_T + K\beta_2 C_T + [H^+]^2 + \beta_2\right) - \sqrt{\left(K\beta_2 L_T + K\beta_2 C_T + [H^+]^2 + \beta_2\right)^2 - 4K\beta_2{}^2 L_T C_T}}{2K\beta_2}$$

Ternary complexes with carbonate

K= 1.9 x 10^6 M ● -N-Me

1.1 x 10^6 M ○ -N-H

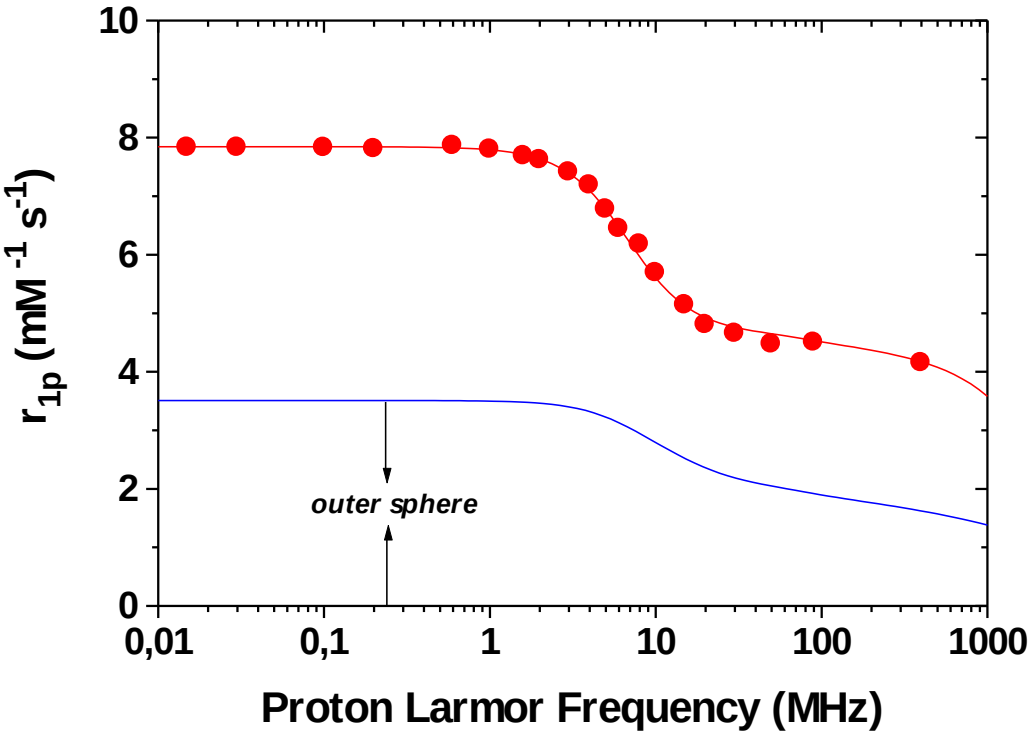


Chem. Eur. J., **2003**, *9*, 2102

“second sphere” relaxivity

second sphere contribution to relaxivity

$[Gd(DTPA)(H_2O)]^{2-}$: nature of the hydration spheres



q = 1

r = 3 Å

τ_R = 74 ps

τ_M = 330 ns

a = 3.5 Å

D = 2.24×10^{-5} $cm^2 s^{-1}$

second sphere contribution to relaxivity

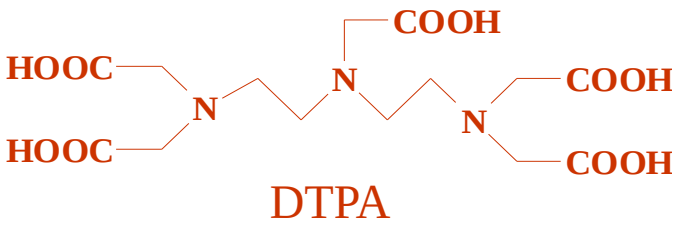
three well-defined hydration shells can be observed consisting of:

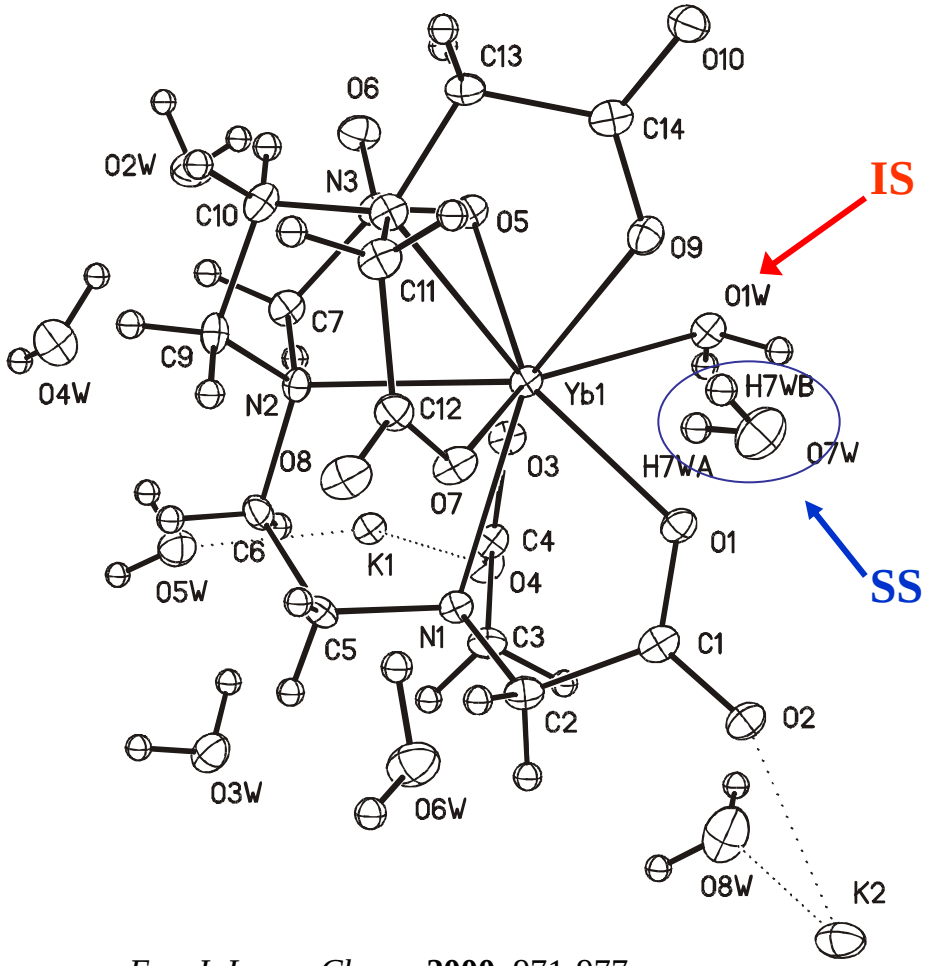
i) one coordinated water molecule;

ii) several water molecules in the outer coordination sphere of the Yb^{III} ion and

iii) one water molecule surprisingly close to the Yb and H-bonded to proximate -COOH groups

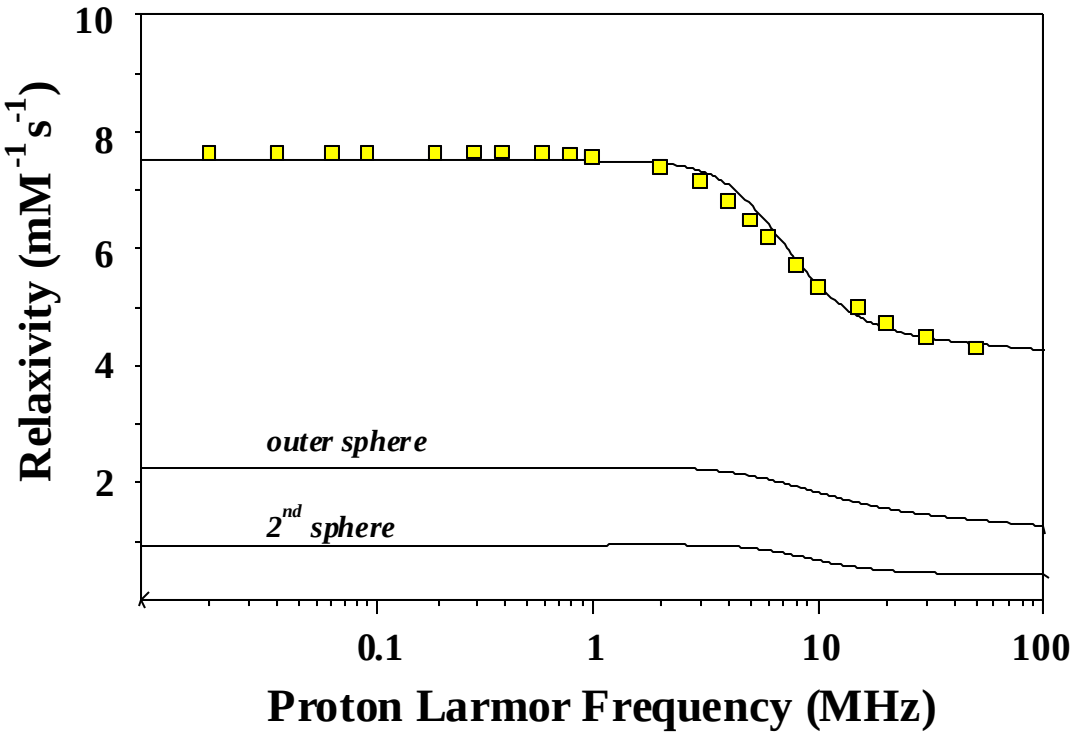
$K[Yb(DTPA)(H_2O)]$





Eur. J. Inorg. Chem., **2000**, 971-977

second sphere contribution to relaxivity



$q = 1$

$r = 2.95$ Å

$\tau_R = 65$ ps

$\tau_M = 330$ ns

$a = 4.5$ Å

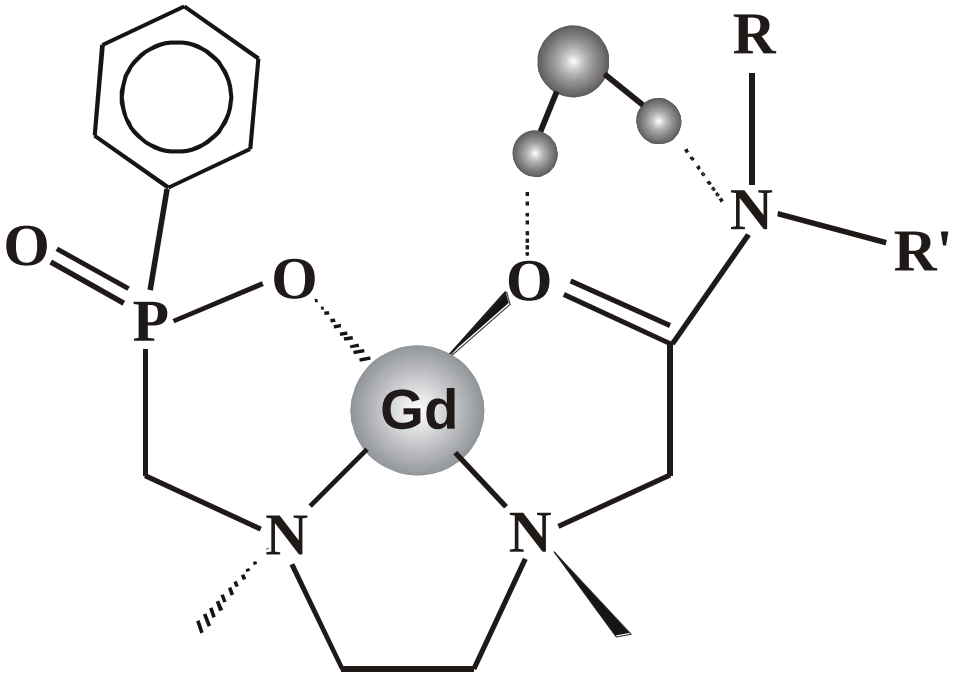
$q' = 1$

$r' = 3.28$ Å

"The contribution of the SS term is about 10% of the total relaxivity but is very important for a correct and more realistic interpretation of the experimental data. Furthermore, its contribution can be optimized and the relaxivity enhanced through a suitable ligand design."

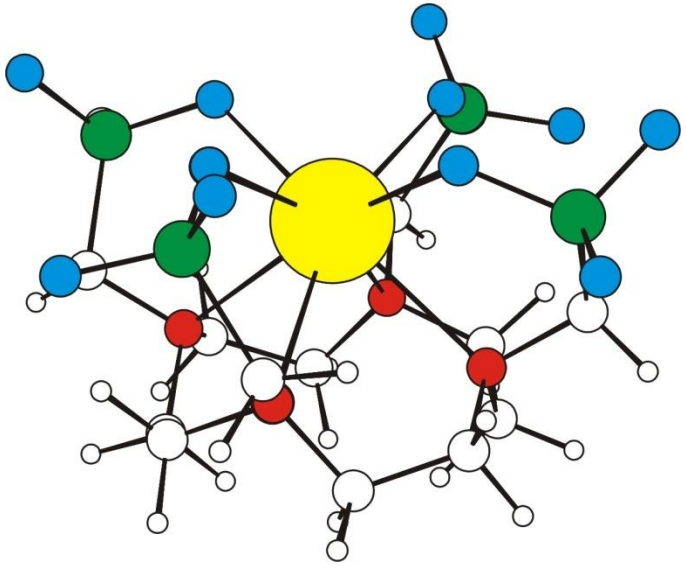
Eur. J. Inorg. Chem., **2000**, 971-977

second sphere contribution to relaxivity



Schematic representation of the *second sphere* water molecule affecting the relaxivity of the complex GdDOTMP-MBu$_2$

second sphere contribution to relaxivity



GdDOTP

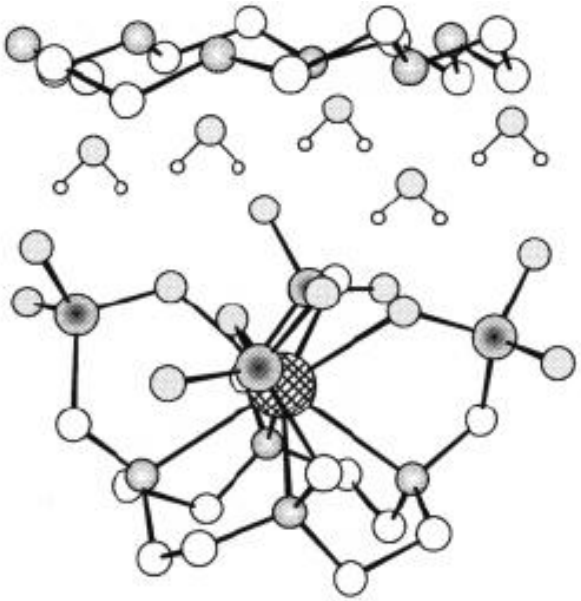
$q = 0$

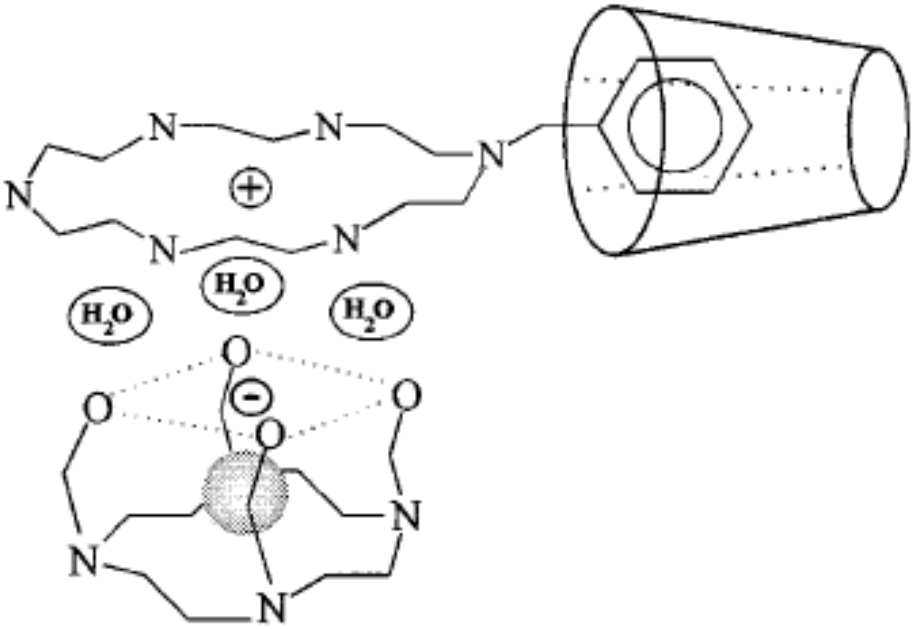
$r_{1p} = 4.58$

strong contribution from water molecules H-bonded to phosphonate groups

second sphere contribution to relaxivity

enhancement of r_{1p} (ss)





$r_{1p} = 7.7$ $r_{1p} = 18.1$

r_{1p} (os) = 2.5

Relaxivity enhancement

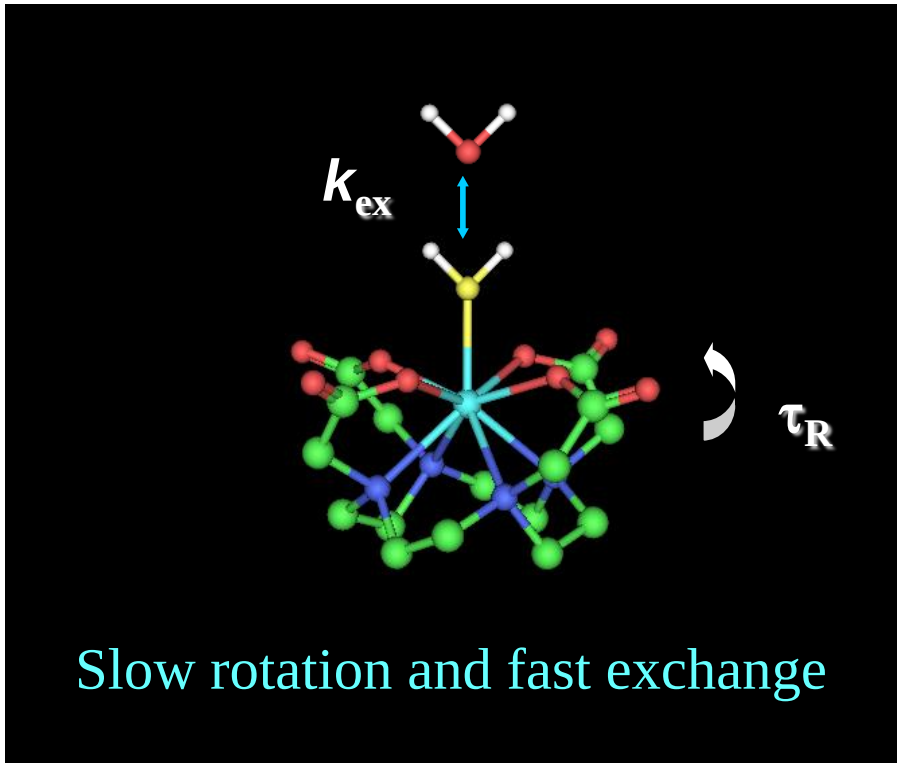
at

high fields (> 1 T)

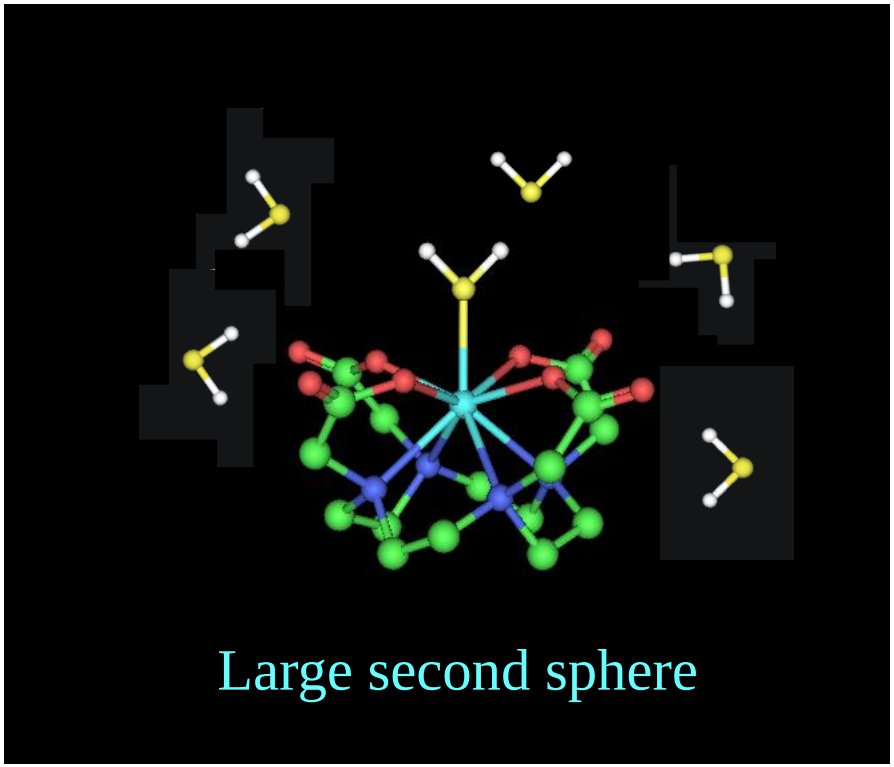
Relaxivity enhancement at high fields

medium molecular weight conjugates

- efficent coupling of the local motion of the Gd-OH_2 vector with the rotational motion of the whole complex
- fast rate of water exchange
- large number second sphere water molecules



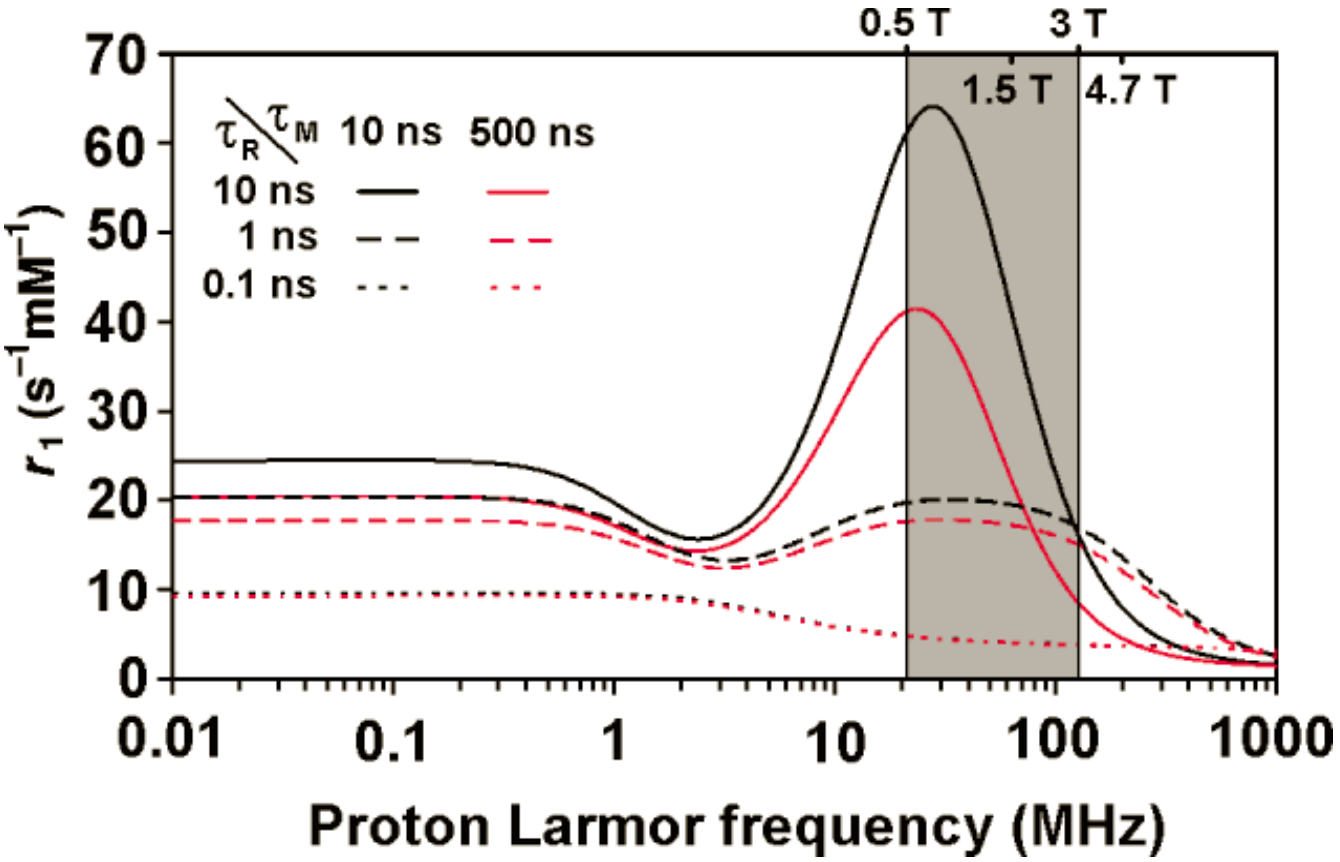
Slow rotation and fast exchange



Large second sphere

Relaxivity enhancement at high fields

medium molecular weight conjugates



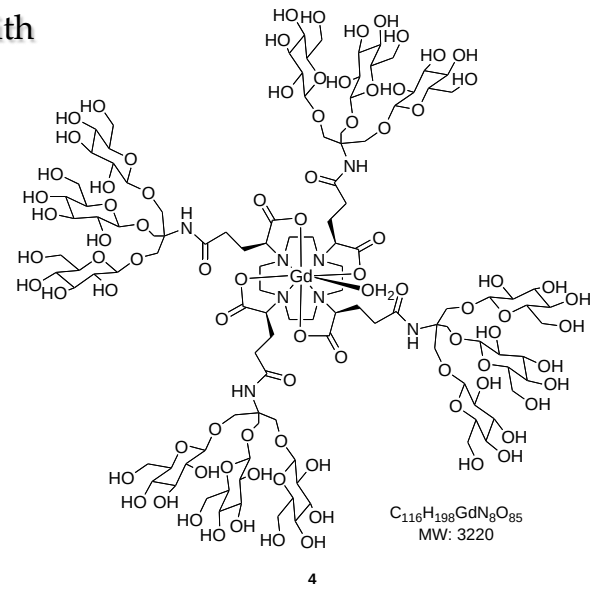
P. Hermann, J. Kotek, V. Kubíček, I. Lukeš, *Dalton Transactions*, **2008**, 3027.

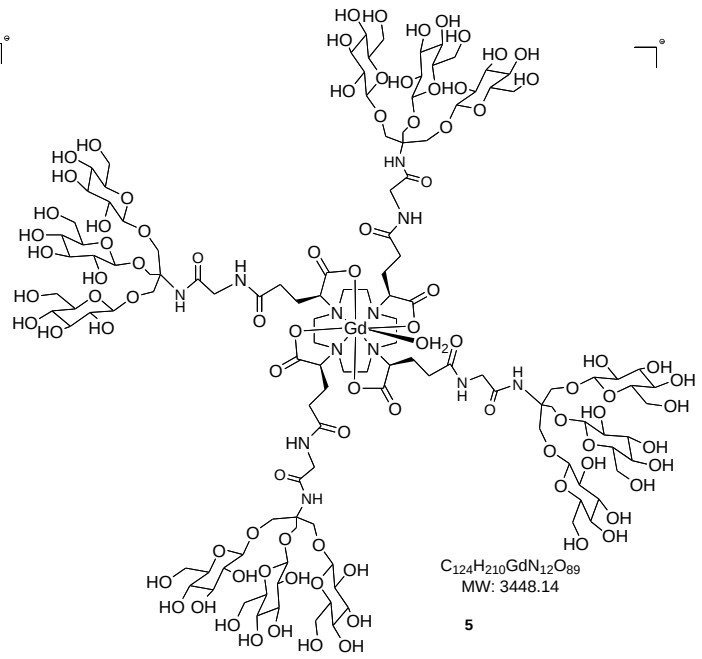
Relaxivity enhancement at high fields

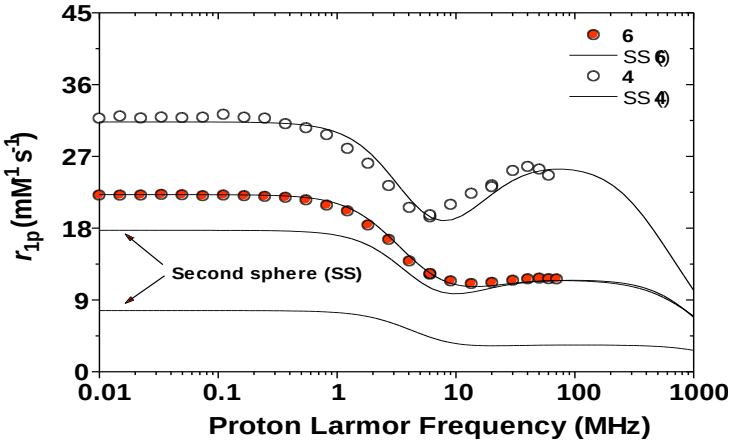
hydrophilic dendritic structure, packed with second sphere H_2O molecules, with the Gd ion at the focal point

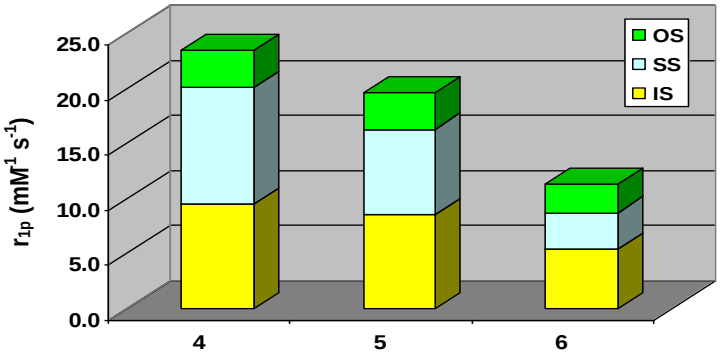
$q=1$

efficient coupling of the local motion of the Gd-OH2 vector with the rotational motion of the whole complex fast rate of water exchange large number second sphere water molecules





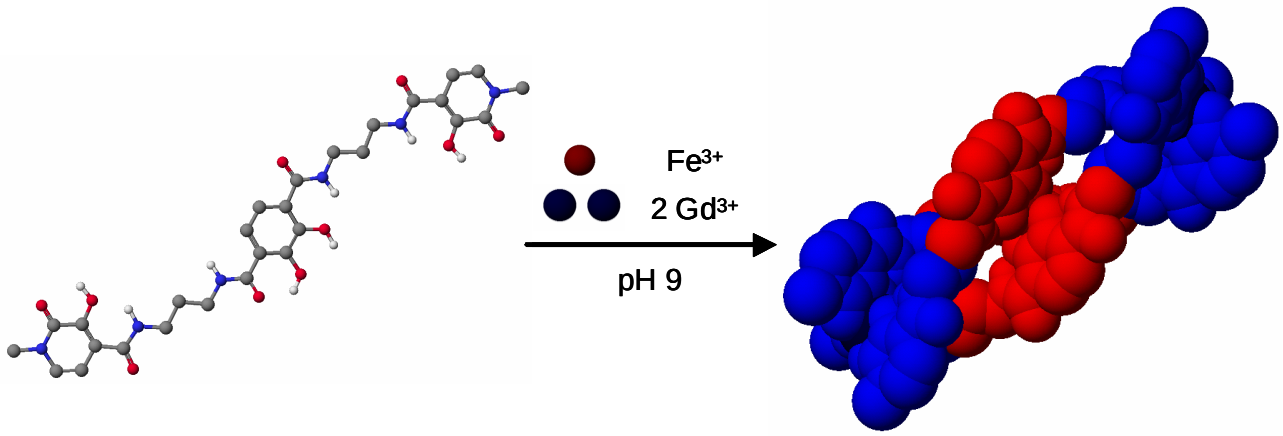


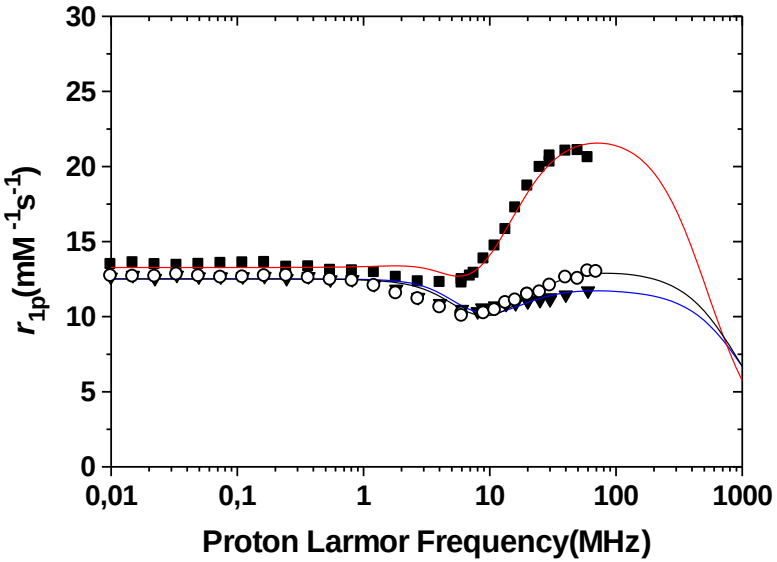


M. Botta, D. Parker et al., *Chem. Commun.*, **2006**, 1064–1066
Chem. Commun., **2005**, 474–476

Relaxivity enhancement at high fields

Fe(III) Templated Gd(III) Self-Assemblies

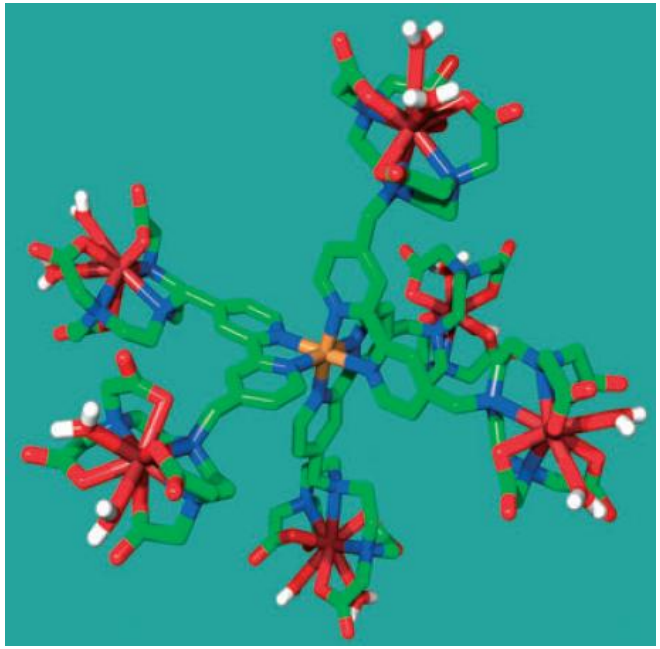


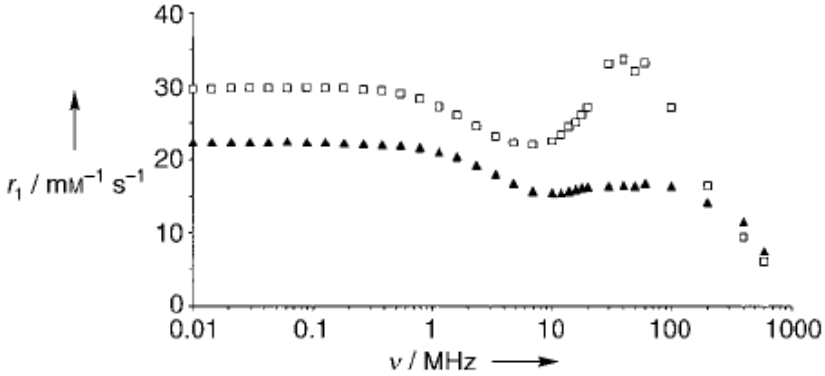


Pierre, V.C., Botta, M. and Raymond, K.N, *J. Am. Chem. Soc.*, **2006**, *128,* 2972

Relaxivity enhancement at high fields

Metallostar → MW = 3744 g mol^{-1}



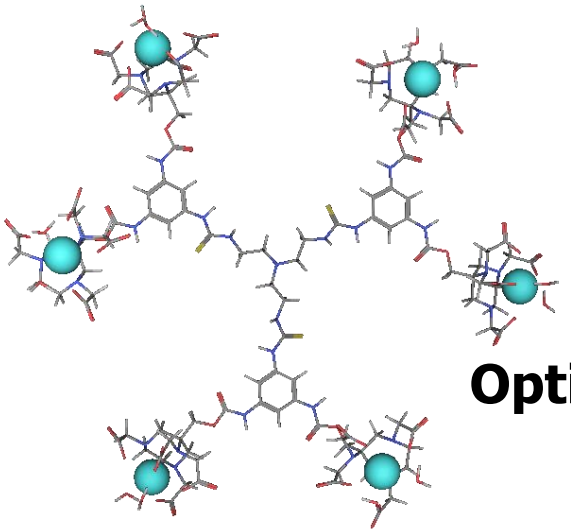


J. B. Livramento, E. Toth, A. Sour, A. Borel, A. E. Merbach, and R. Ruloff, *Angew. Chem. Int. Ed.* **2005**, 44, 1480

The Gd complexes must have high thermodynamic stability and kinetic inertness

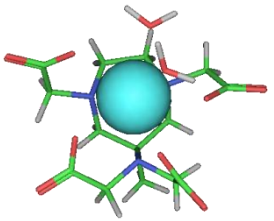
How to increase r_{1p} at high fields?

Multimeric systems



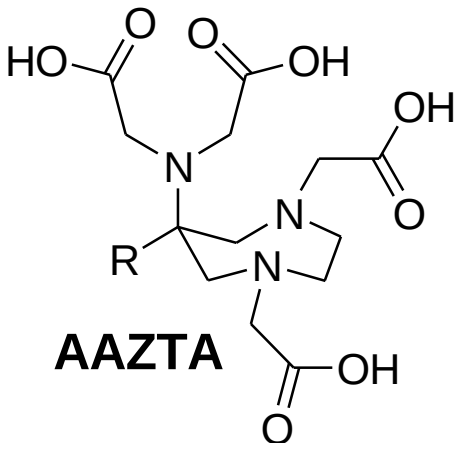
Optimization of

- **the probe**



- **the linker and the scaffold (should be fairly rigid)**
- **the synthesis (as fast and simple as possible)**

How to increase r_{1p} at high fields?



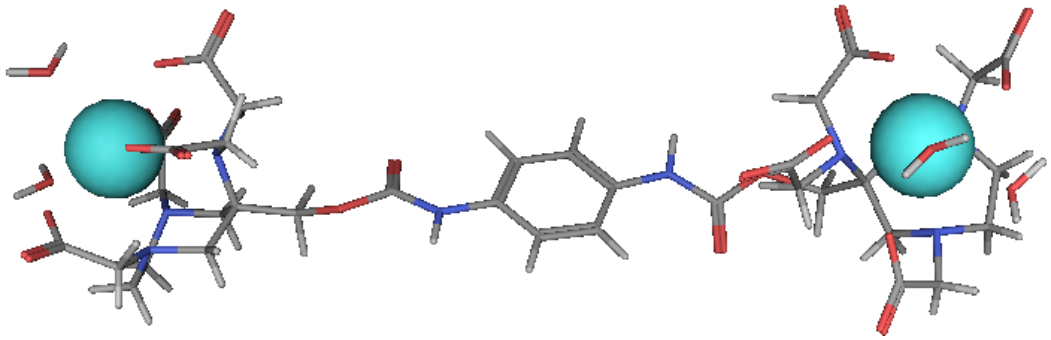
Easily synthesized heptadentate ligand
In 4 steps from cheap starting materials

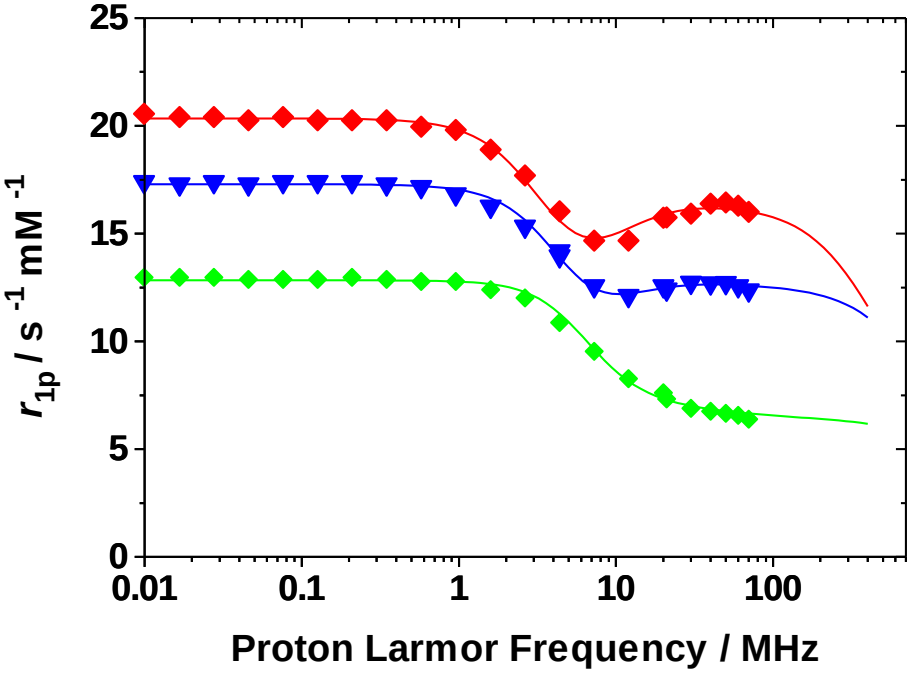
Giovenzana et al. *Inorg. Chem*. **2004**, *43*, 7588.

- **Good thermodynamic stability**
  (Log K_f = 20.24)
- **Unaffected by mono and bidentate anions**
- **Kinetically inert towards trasmetallation**

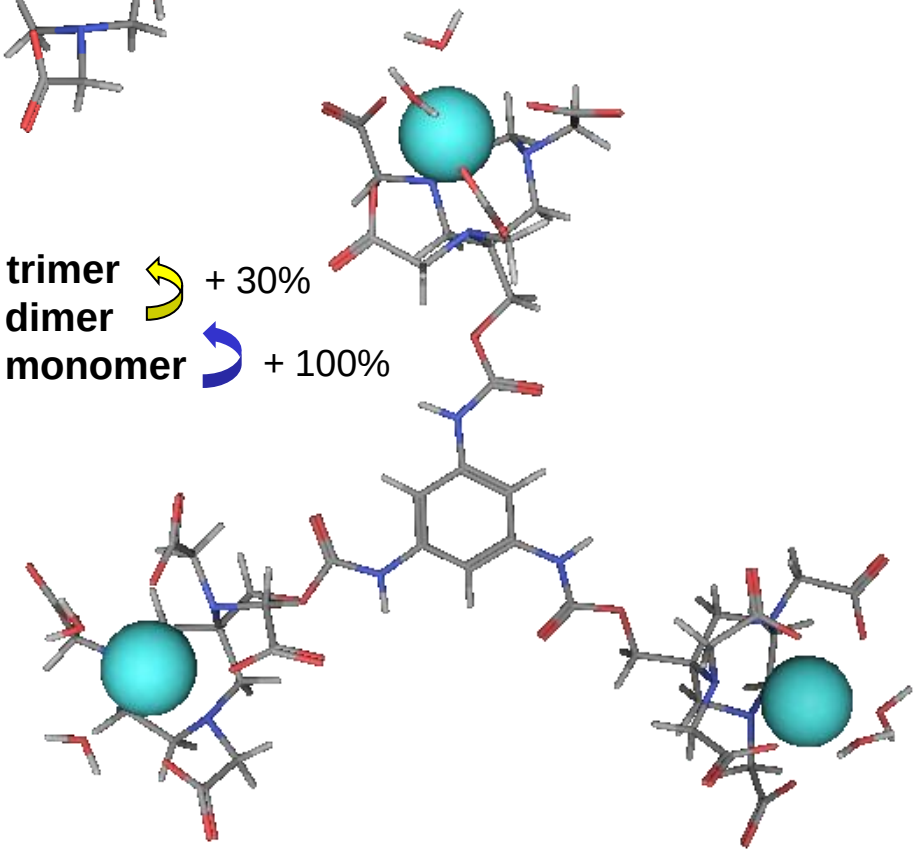
Baranyai, Z.; Uggeri, F.; Giovenzana, G. B.; Benyei, A.; Brucher, E.; Aime S. *Chem. Eur. J.* **2009**, *15*, 1696.

from monomer to trimer

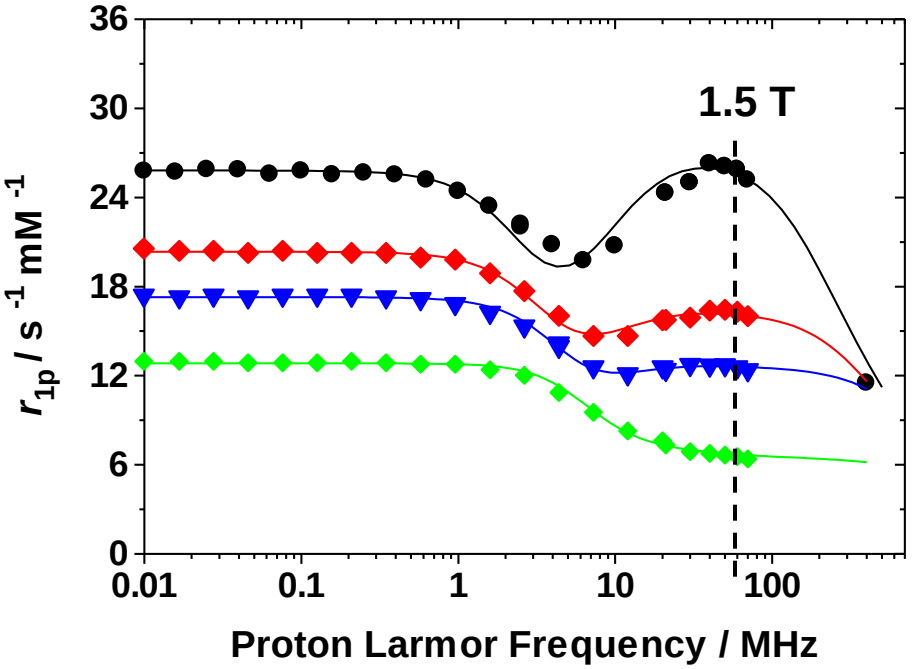


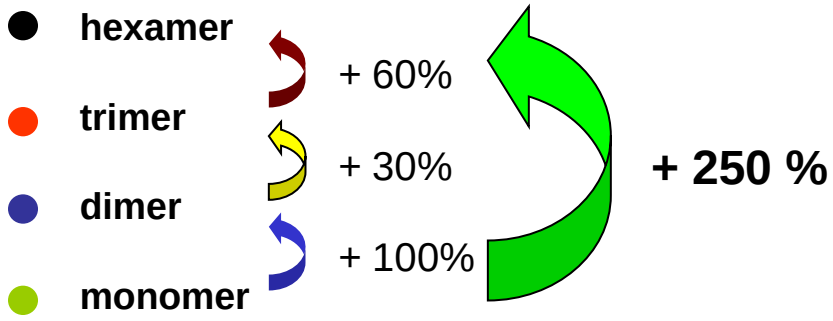


trimer + 30%
dimer
monomer + 100%



How to increase r_{1p} at high fields?





The hexamer presents high relaxivity **per Gd** over a broad range of imaging fields (0.5-3.0 T).

r_{1p} **per molecule** ranges from **138** $mM^{-1}s^{-1}$ at 3.0 T to **156** at 1.5 T (**145** at 0.5 T)

Development

Functionalization of multimers with targeting vectors

References

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