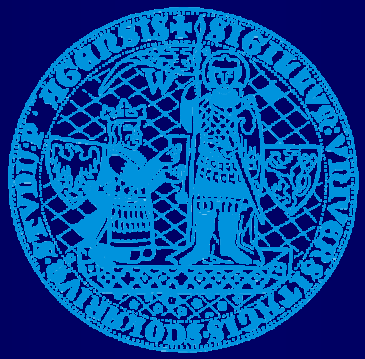
" Relaxometric study of dimeric and dendrimeric Gd(III) complexes of a phosphinated DOTA analogue "

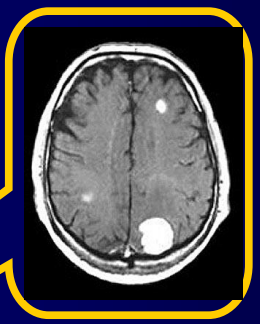
Jakub Rudovský

Charles University in Prague



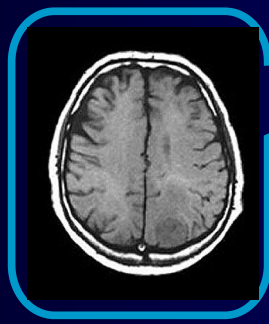
Gd(III) complexes - contrast agents for MRI

With angiographical CA



With extracelular CA

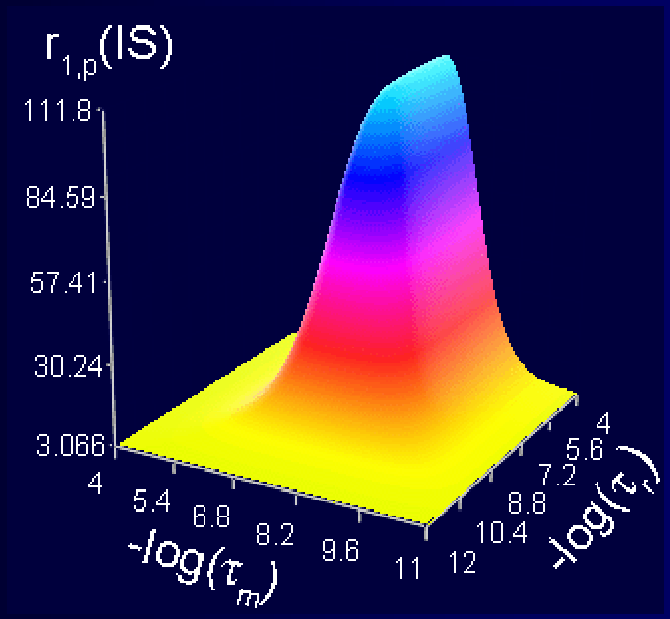
Without CA



Optimizing efficacy

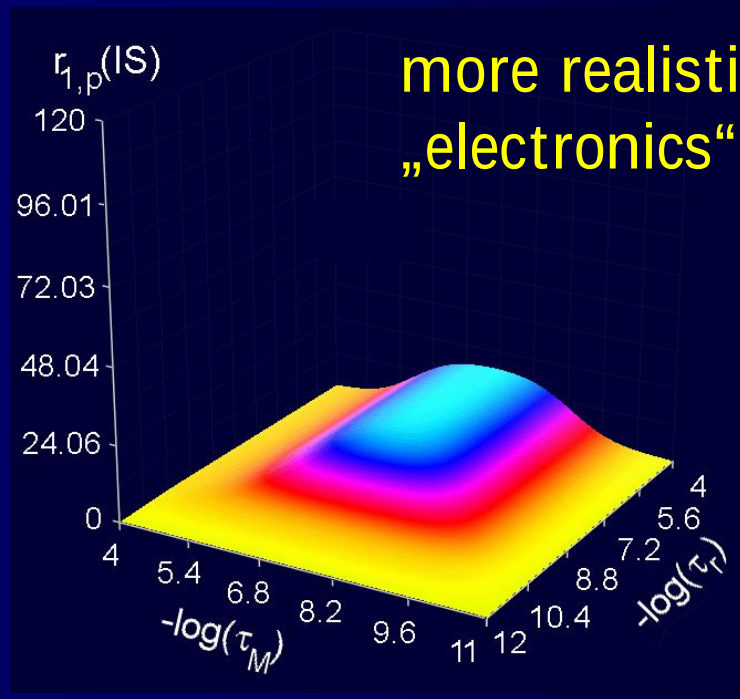
relaxivity – r_1 [$s^{-1}mM^{-1}$] ⟺ f (B , T , q , t_r , t_M , $T_{e1,2}$)

BSM model - optimal „electronics“



D^2 = 0.05 x 10^{20} s^{-2}

more realistic „electronics“

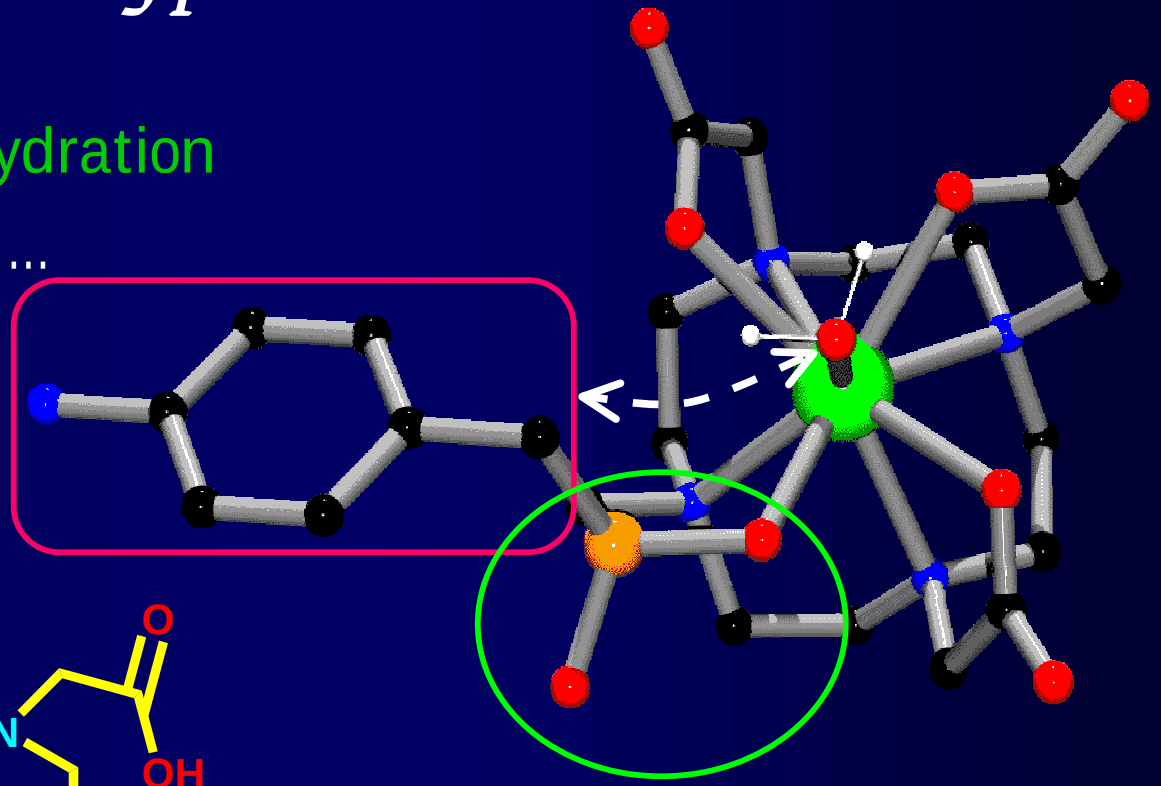


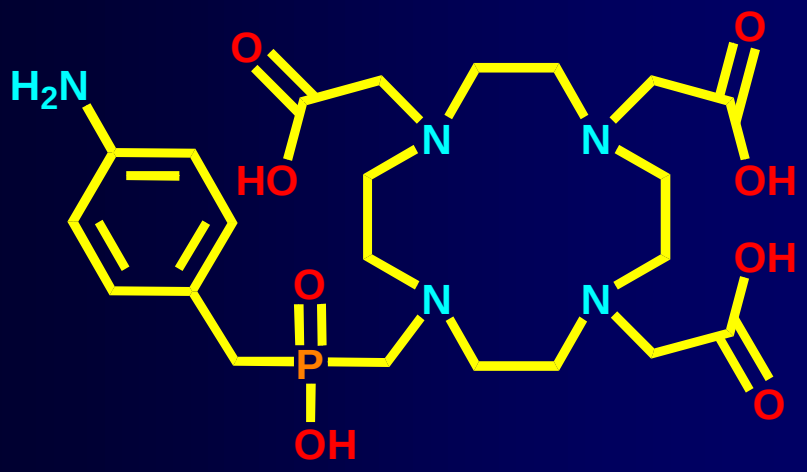
D^2 = 0.5 x 10^{20} s^{-2}

20 MHz, 37 °C, τ_v = 10 ps

Why phoshinates ?

- bifunctionality
- second sphere hydration
- steric hindrance ...



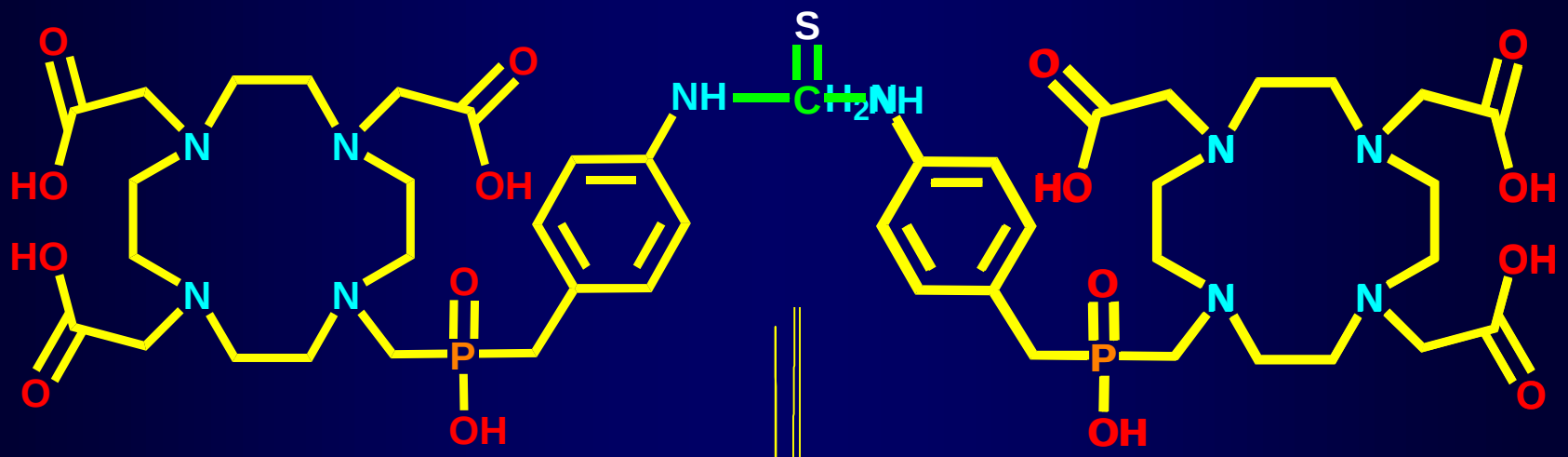


D03A-P^{ABn}

... faster water exchange rate

Rudovsky at al.: Org. Biomol. Chem. 2005, 3, 112-117

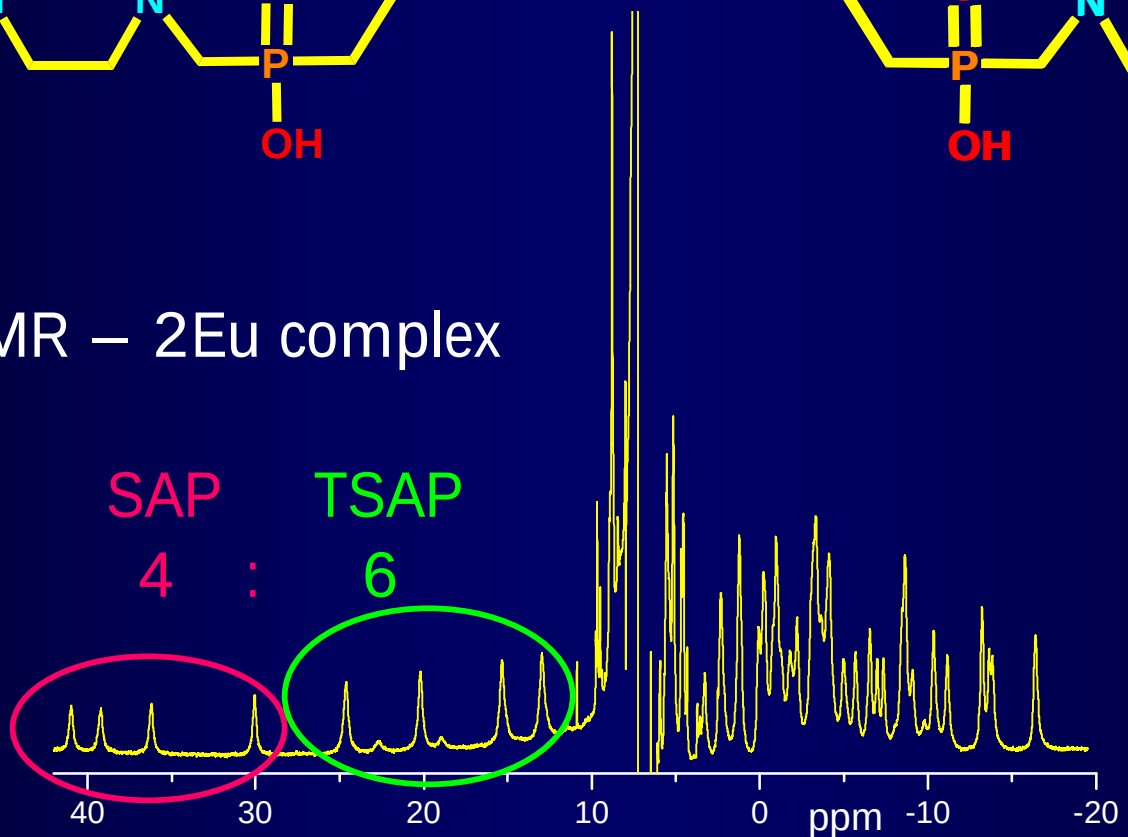
Dimer



^{1}H NMR – 2Eu complex

SAP : TSAP

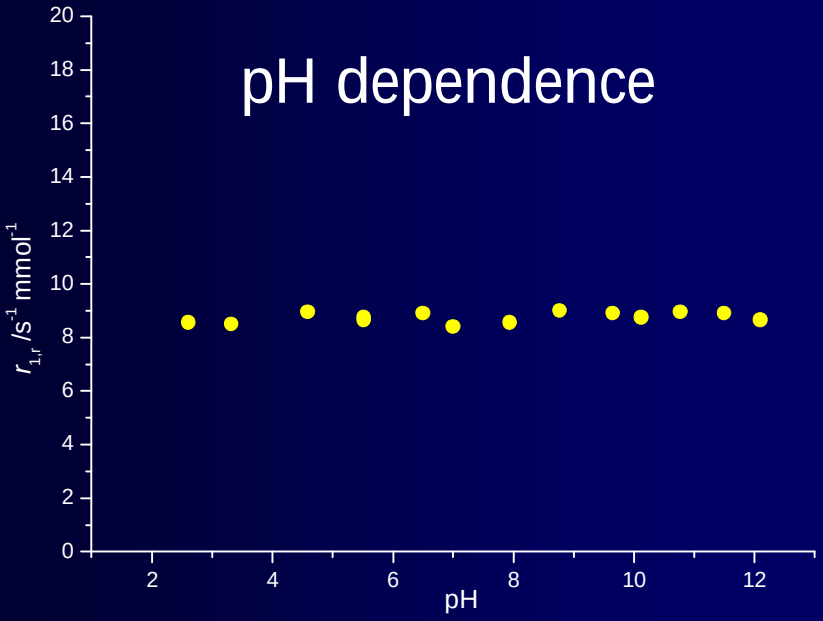
4 : 6



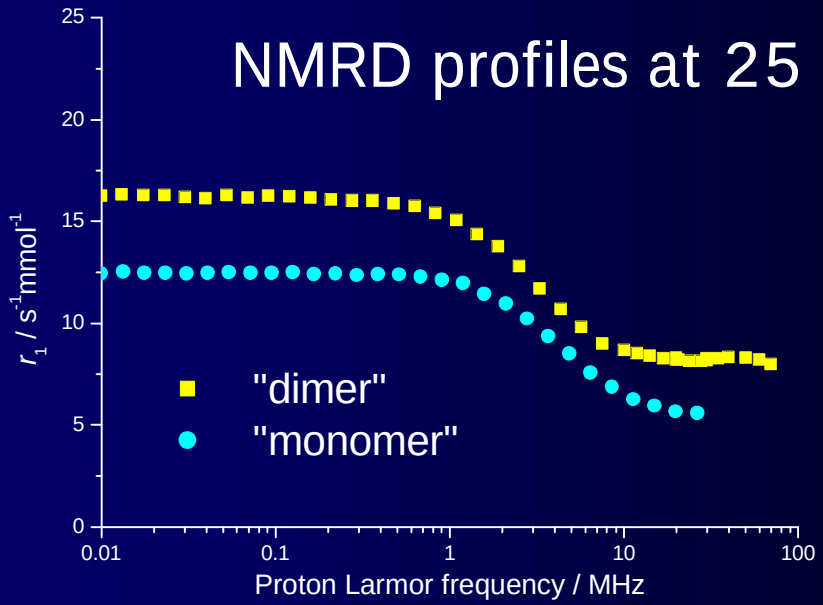
	„dimer“	„monomer“
r_1	6.1	4.2
q	1	1
t_M	53	16
t_r	180	88
q_{ss}	1	1

(pH 7, 37 °C)

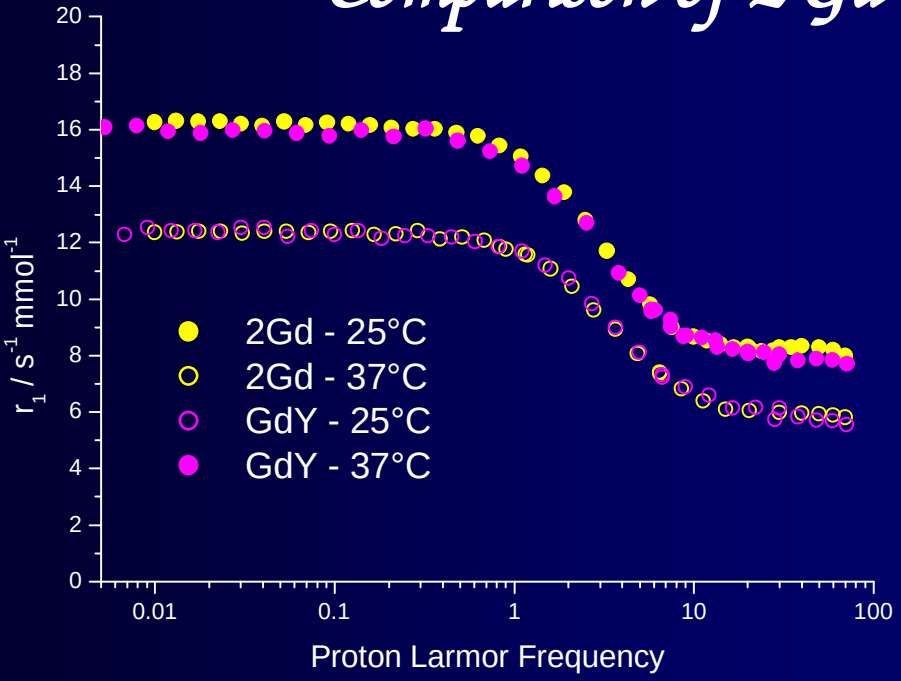
pH dependence

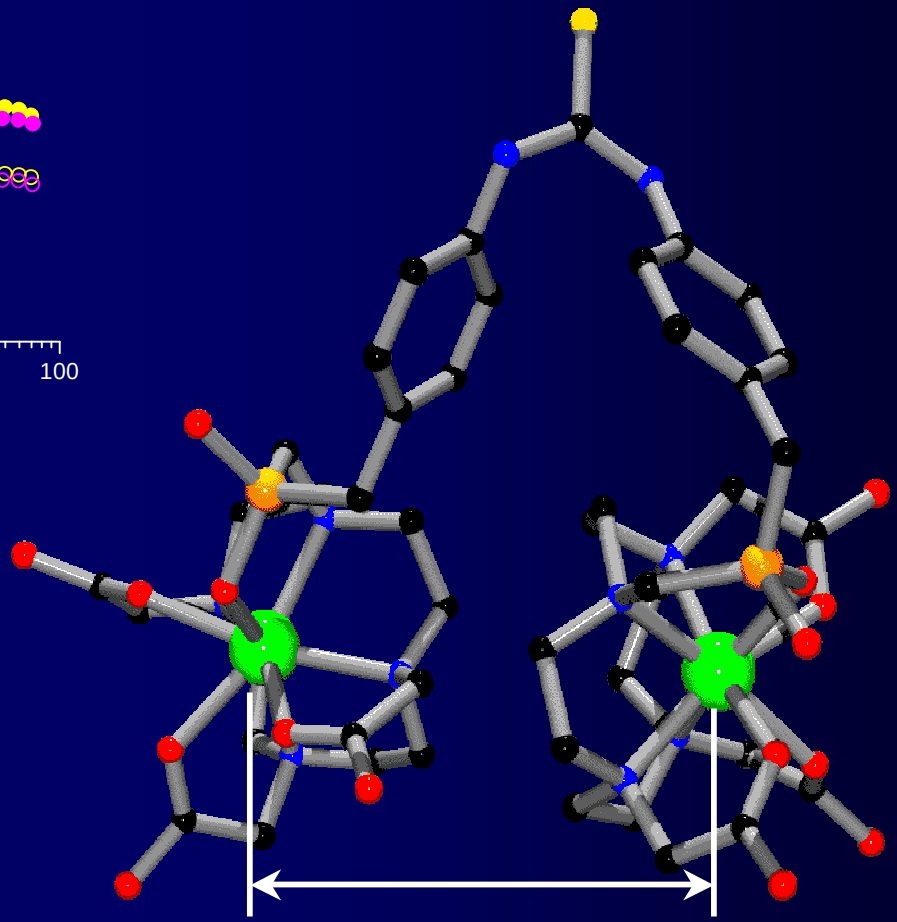


NMRD profiles at 25 °C



Comparison of 2 Gd- and GdY- complex

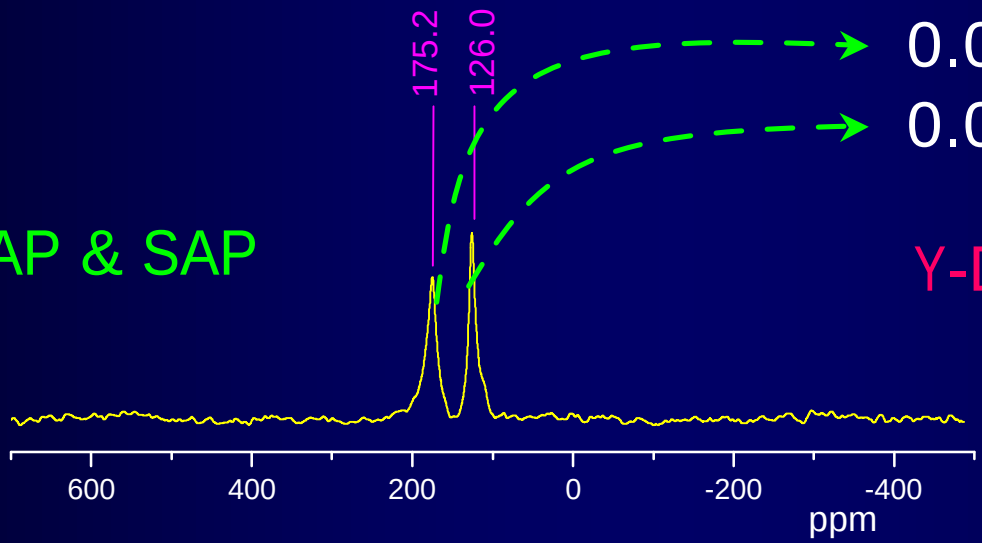




8 *Å* (from MM)

^{89}Y NMR – dimer-GdY

T_1 relaxation times



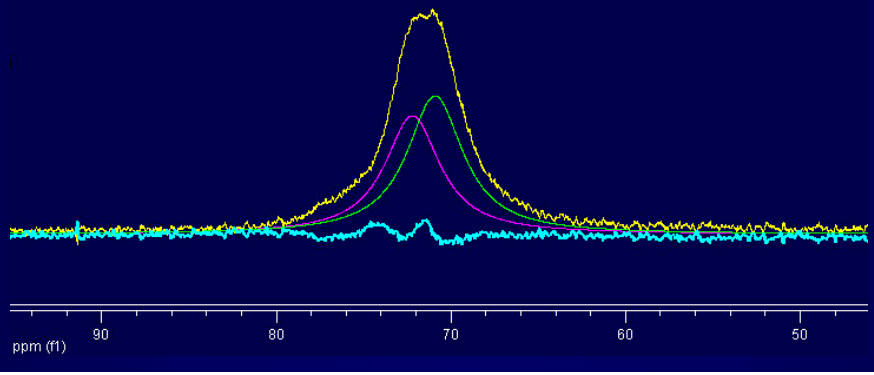
0.076 s
0.088 s

> 9.9 Å
> 10.2 Å

TSAP & SAP

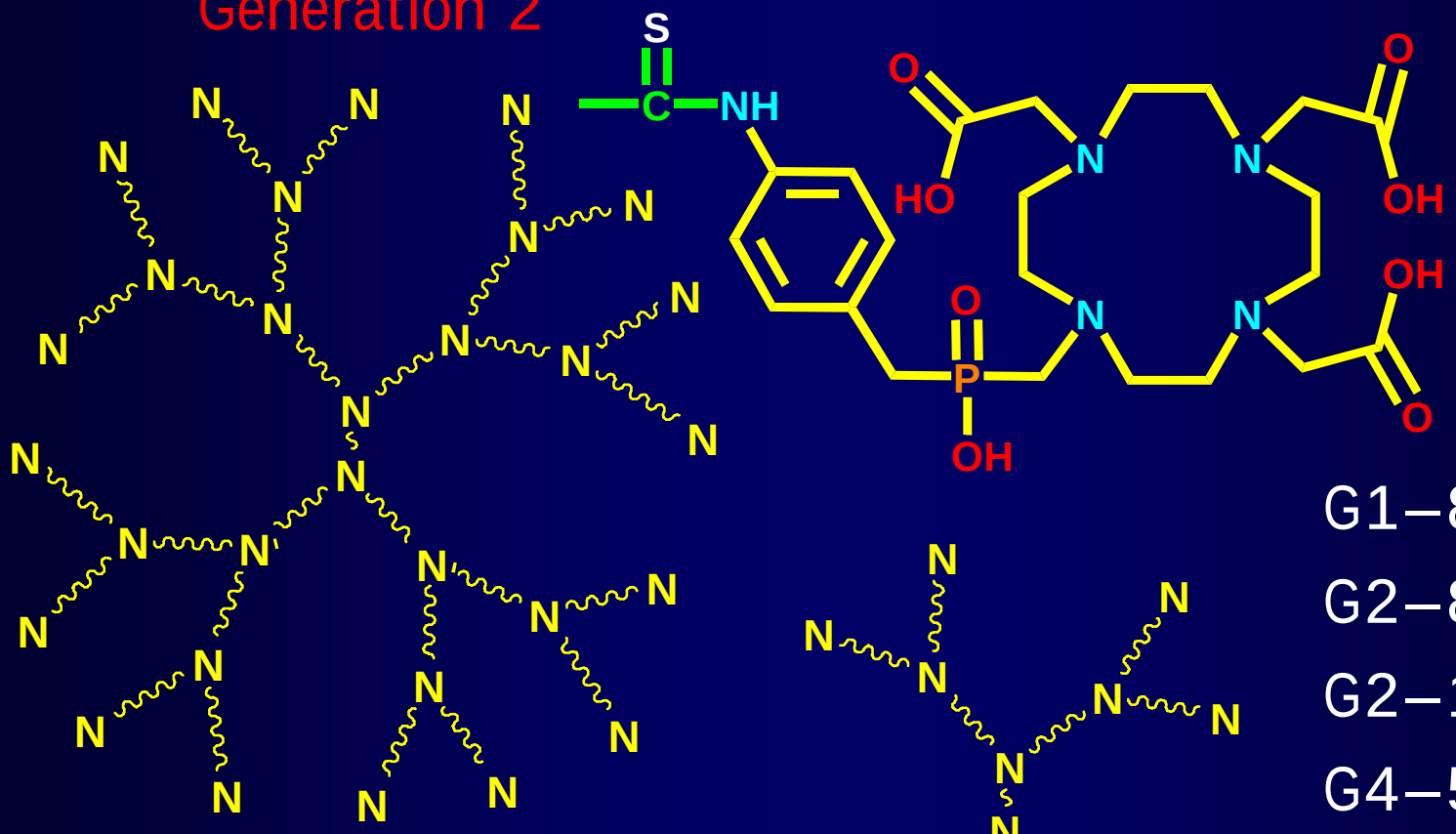
Y-DOTA – 183 s

^{31}P NMR – dimer-GdY



Conjugation of DO3A-P ABn

Generation 2



Poly(amidoamine) – PAMAM family

Generation 1

G1–8 Gd

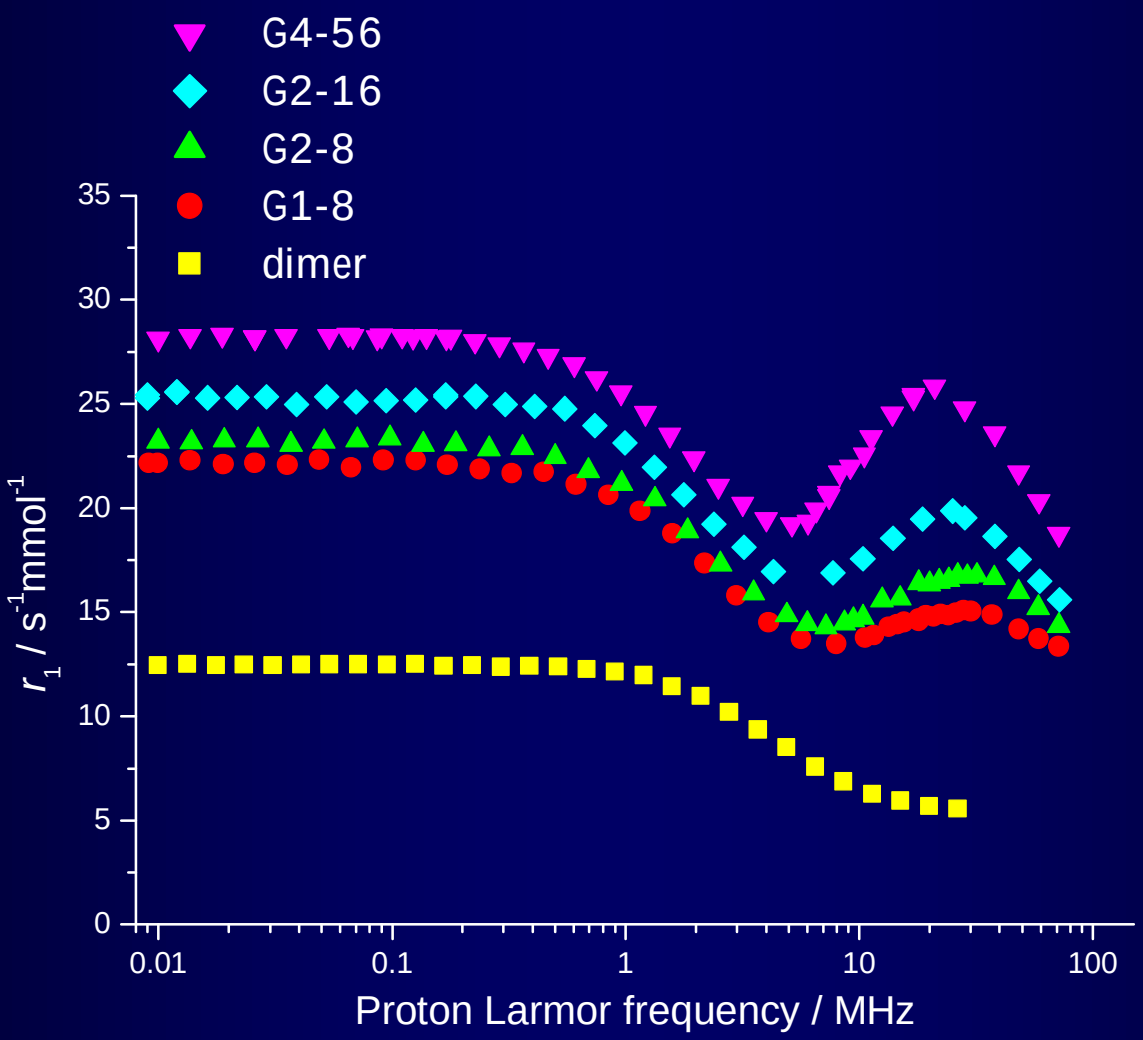
G2–8 Gd

G2–16 Gd

G4–56 Gd

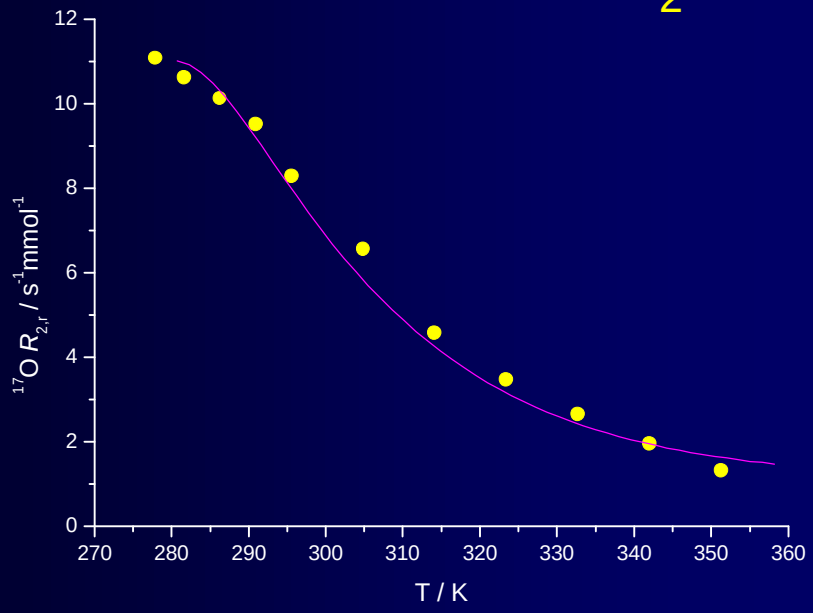
G2–16 Gd/Y

^1H NMRD profiles

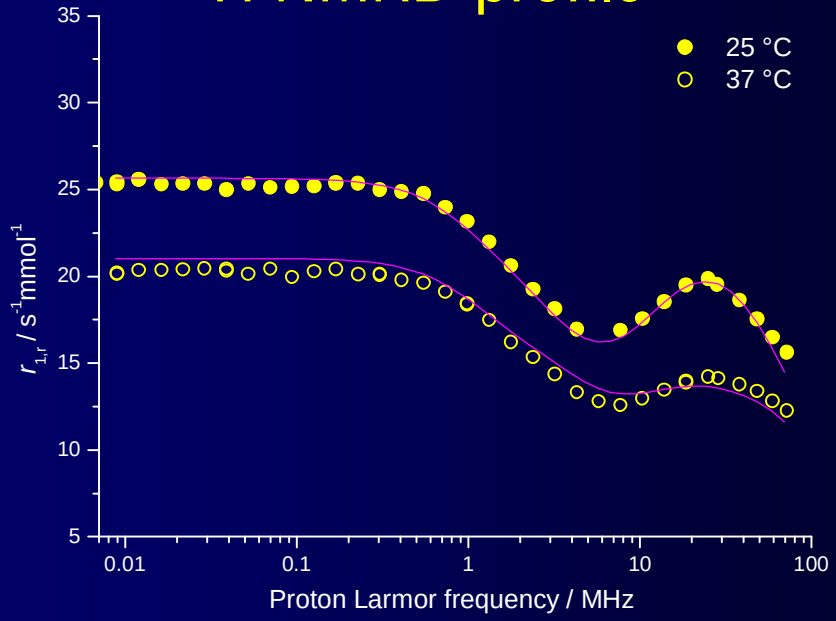


at pH = 7, 25 ℃

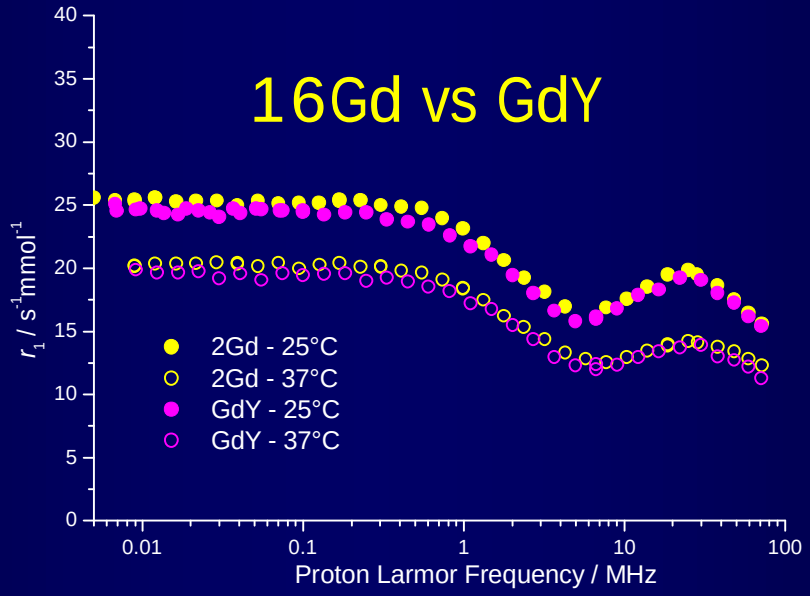
VT - ^{17}O NMR – T_2



^{1}H NMRD profile



16Gd vs GdY

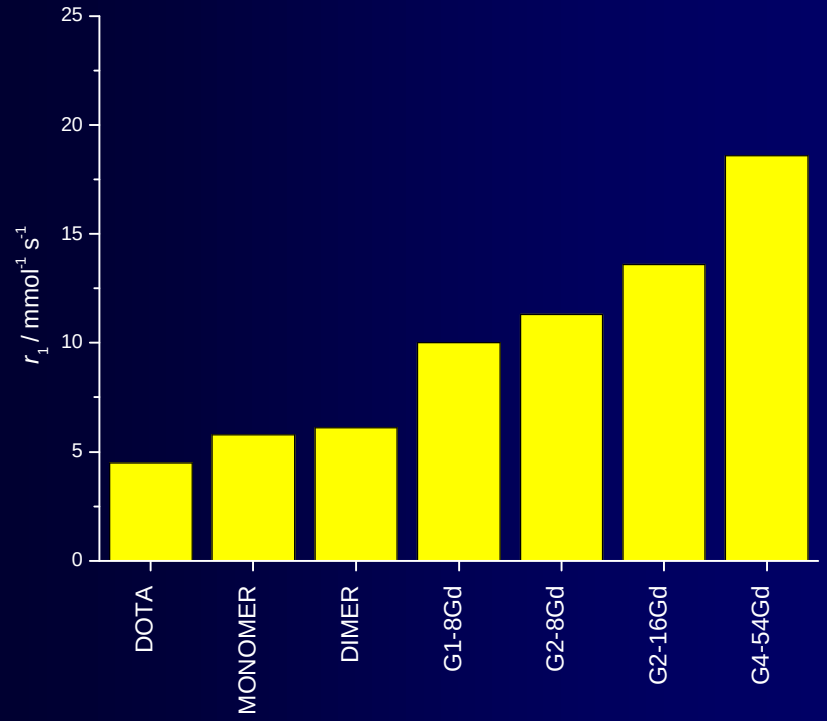


Results – Lipari-Szabo fit

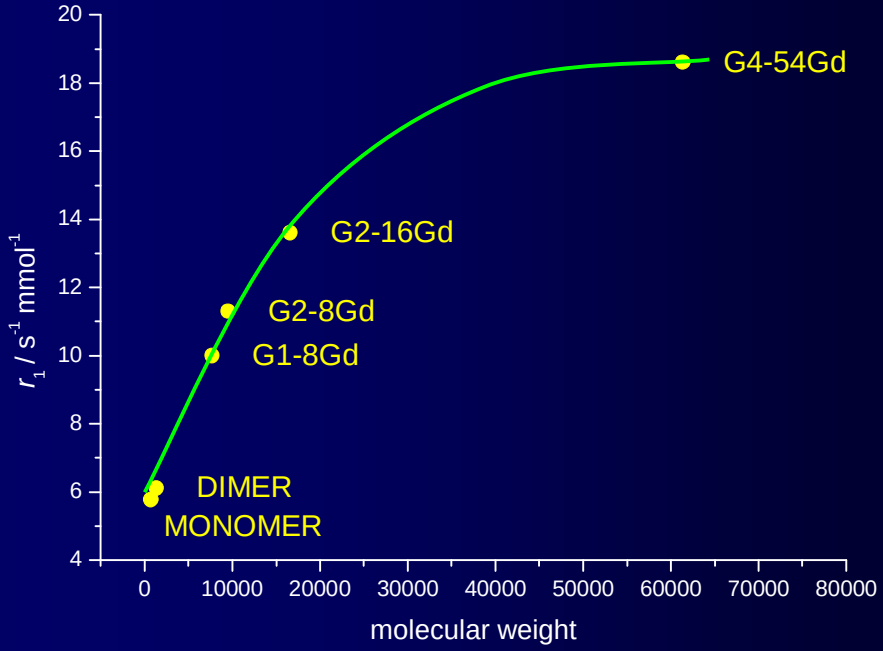
	G1–8 Gd	G2–8 Gd	G2–16 Gd	G4–56 Gd	
r_1	10	11.3	13.6	18.6	(pH 7, 37°C)
t_M	48	80	50	88	ns
$t_{r,\ l}$	115	117	100	131	ps
$t_{r,\ g}$	1560	1770	2520	3120	ps
S^2	0.25	0.28	0.25	0.3	
q_{ss}	2	2	2	2	

G. Lipari, S. Szabo, J. Am. Chem. Soc. 1982, 104, 4546 –4559

Attained relaxivities per 1mM Gd

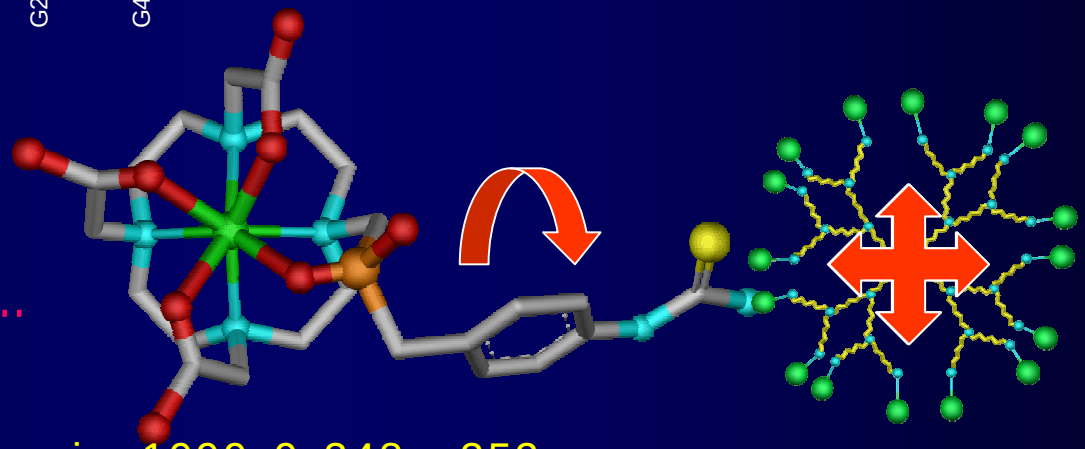


Attained relaxivities per molecular weight



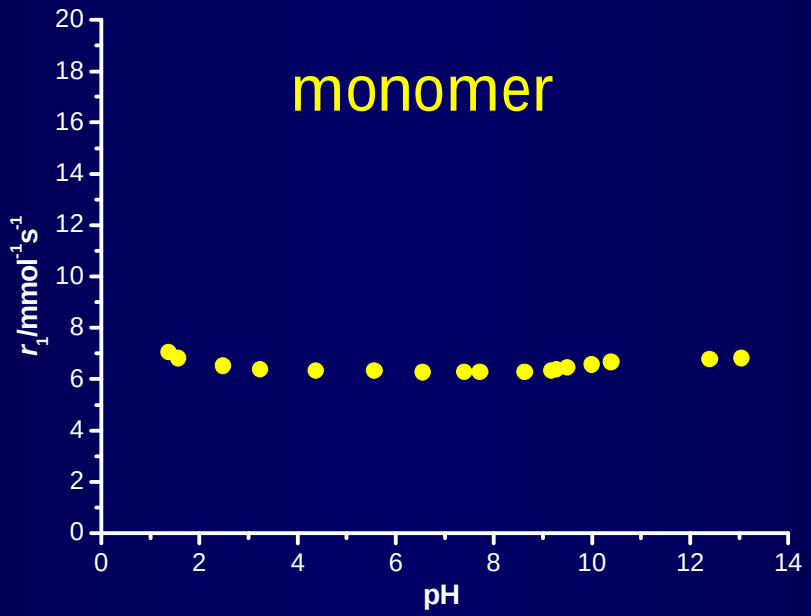
pH 7, 37 °C

...internal mobility...

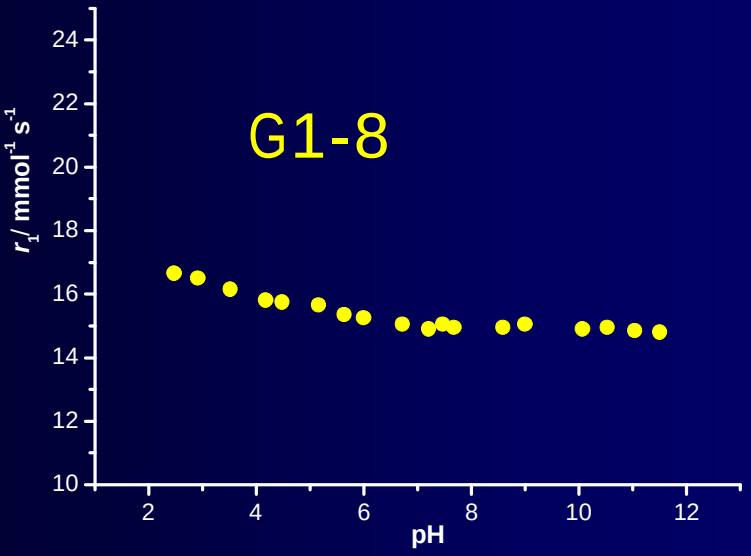


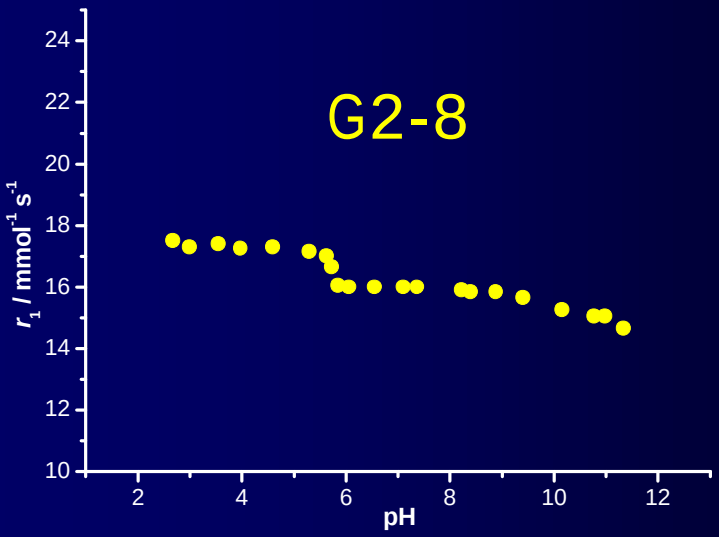
L. H. Bryant at al.: Magn. Reson. Imaging 1999, 9, 348 – 352.

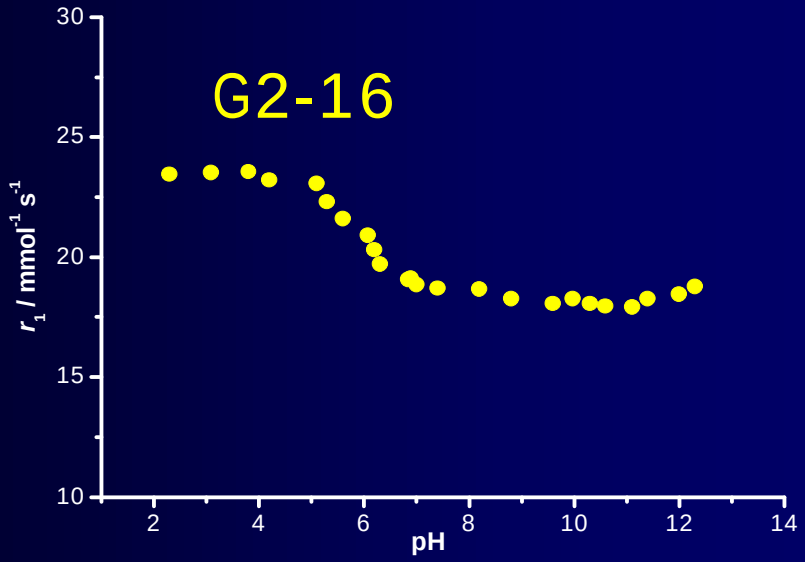
pH dependence of relaxivity

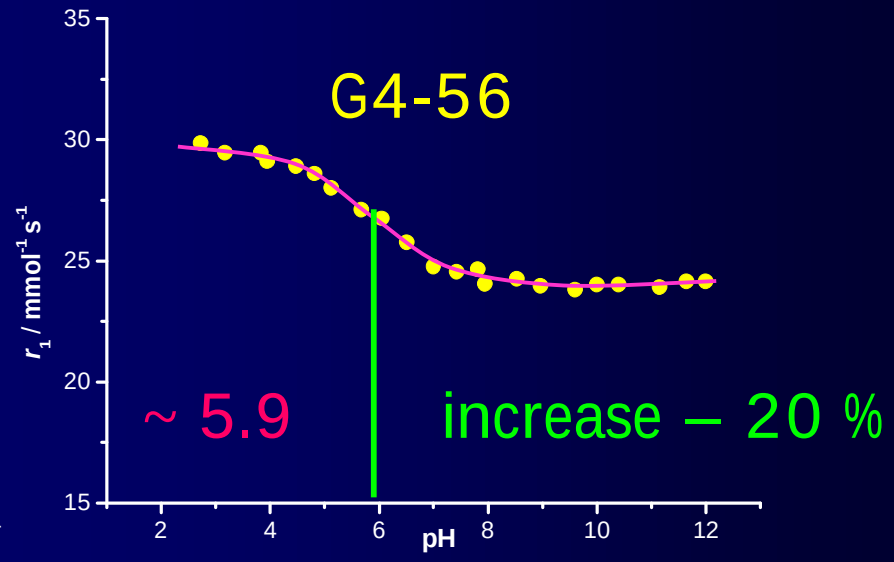


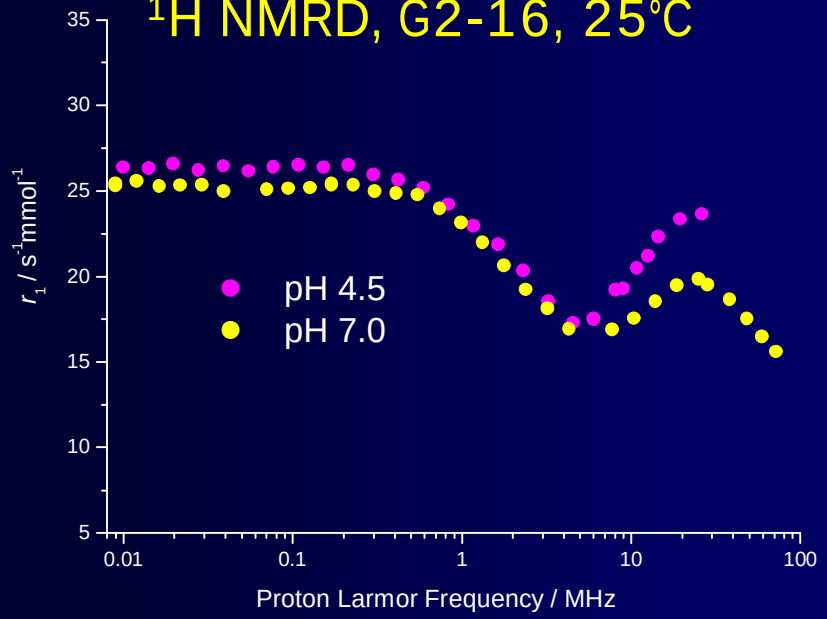
pH dependence of relaxivity

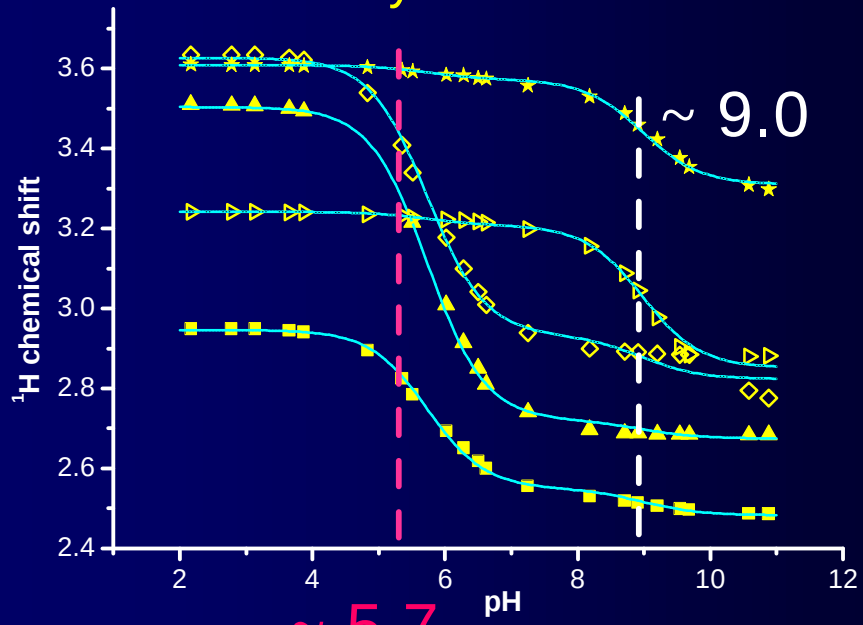


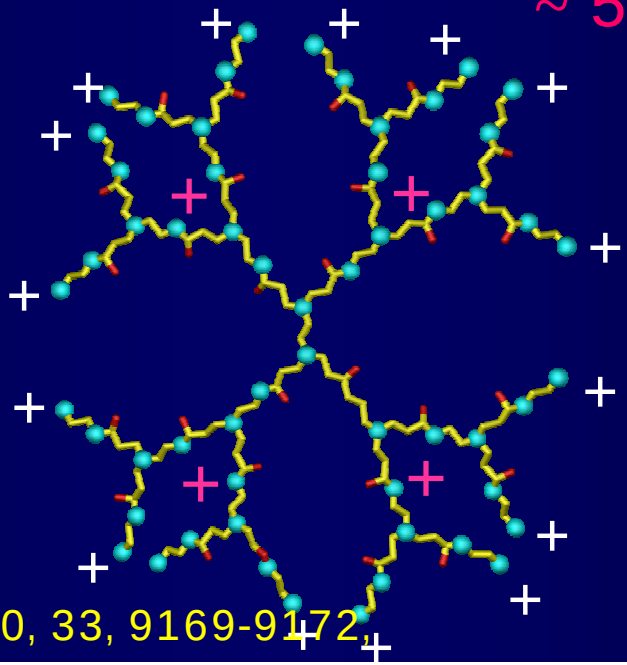








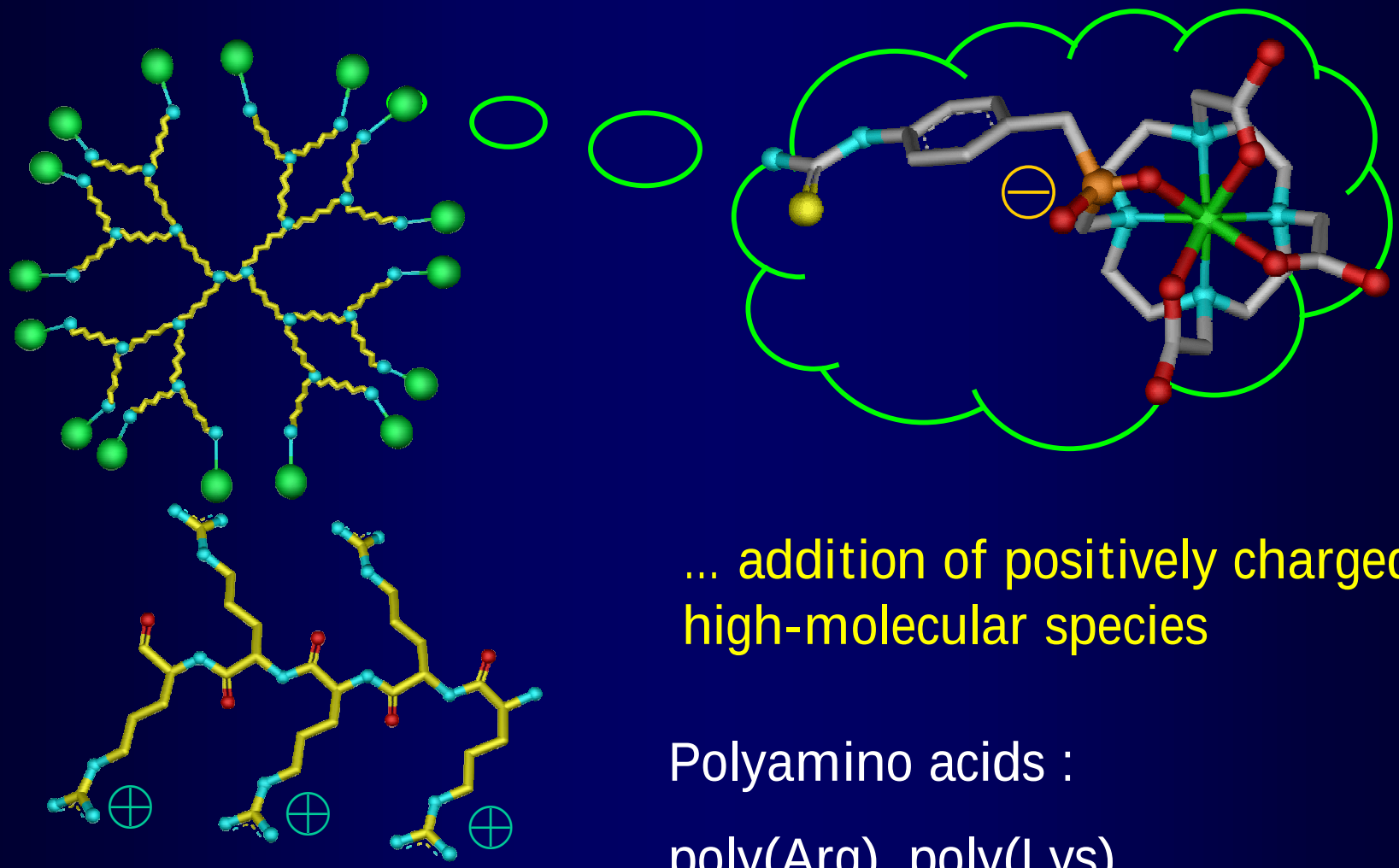




S. Laus at al.:, Chem. Eur. J. 2005

Tomalia at al.: Macromolecules. 2000, 33, 9169-9172,

Interaction with polyaminoacides

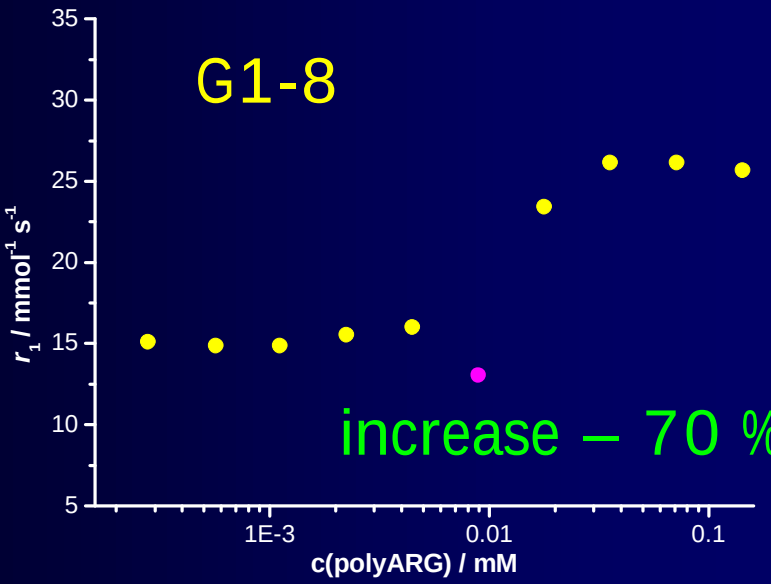


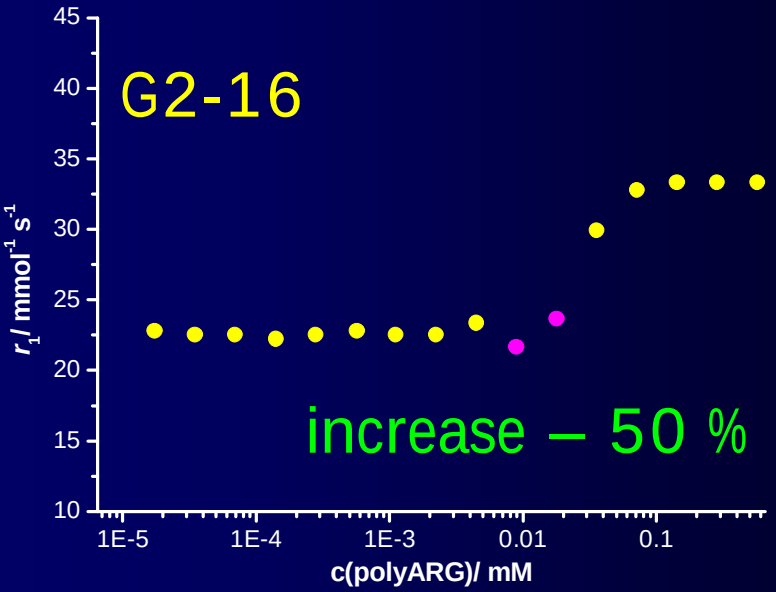
... addition of positively charged high-molecular species

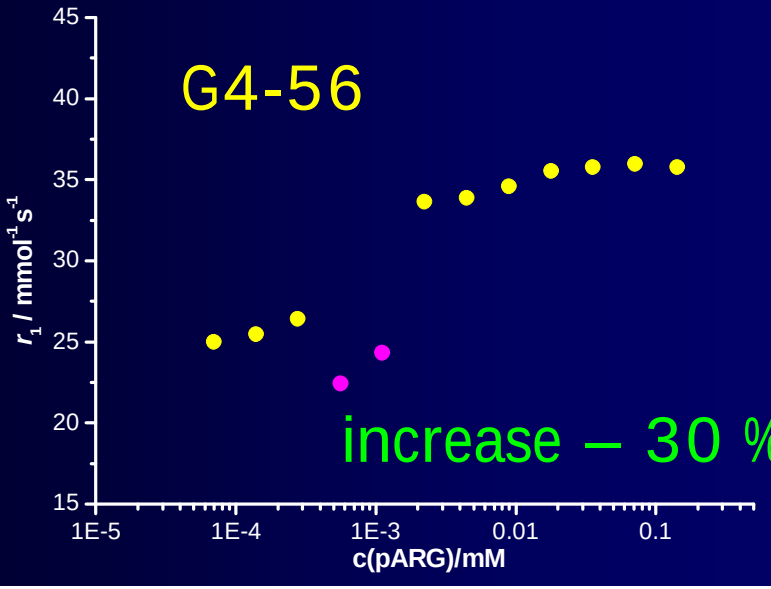
Polyamino acids :

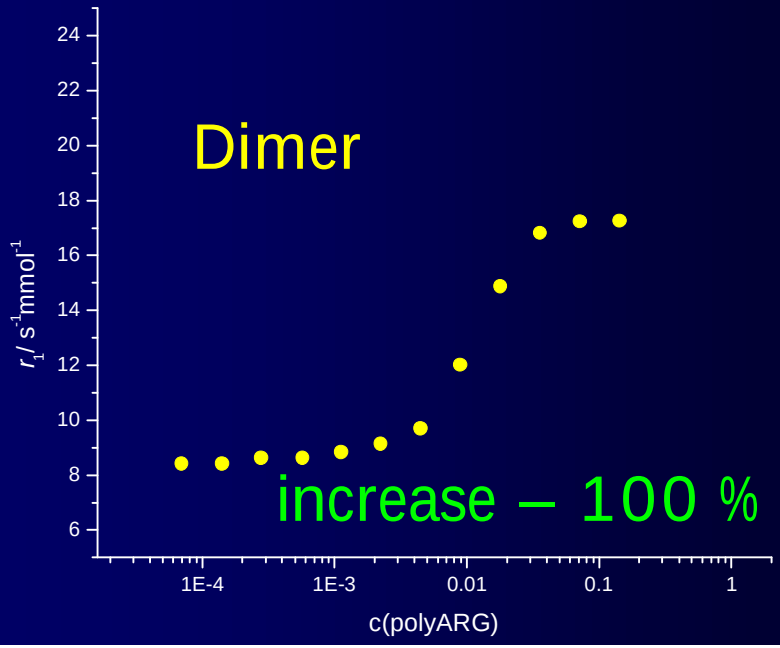
poly(Arg), poly(Lys)

Titration with poly(Arg)-56



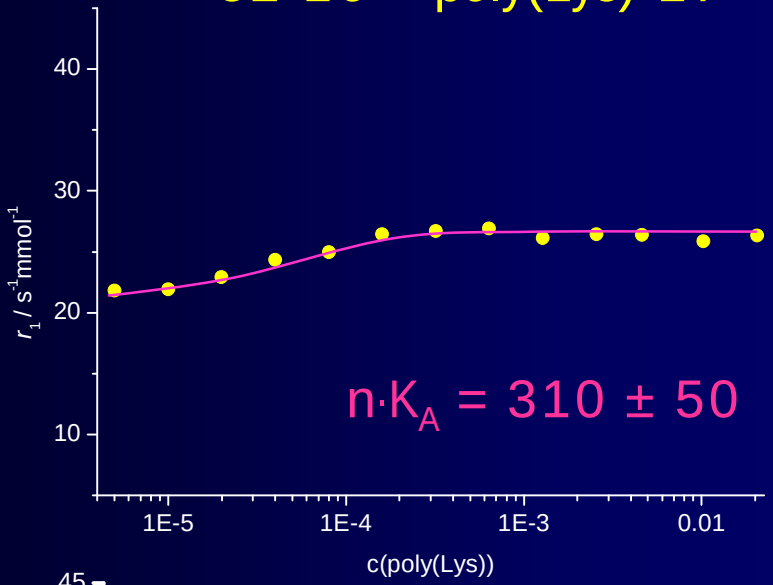






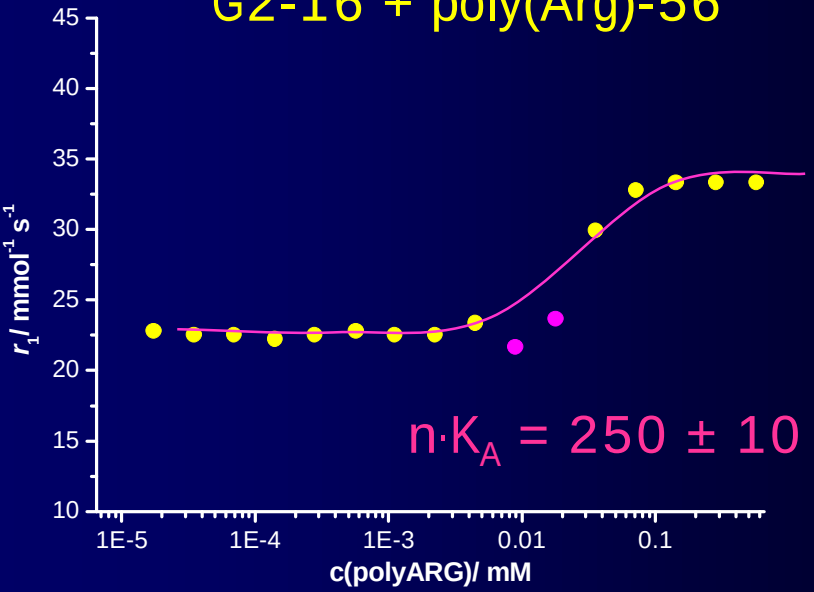
Comparation of polyaminoacides

G2-16 + poly(Lys)-17



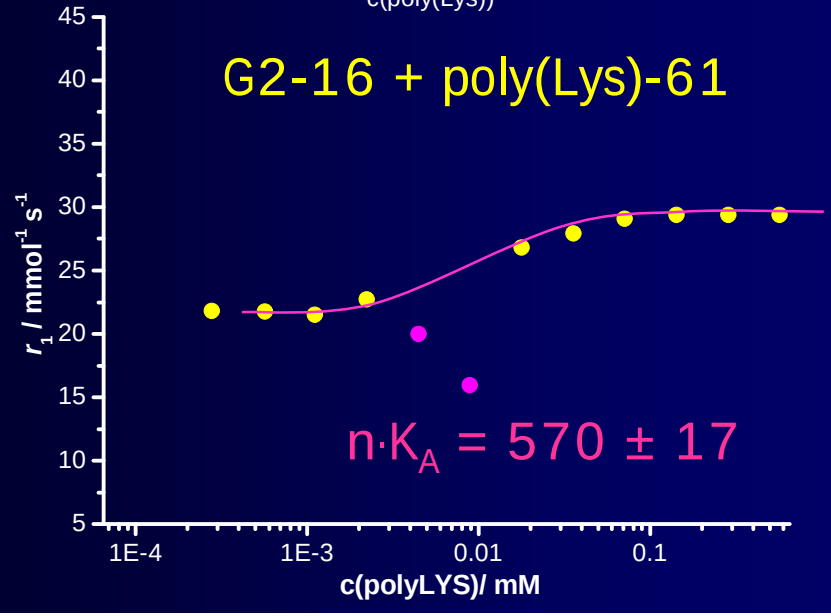
$n \cdot K_A = 310 \pm 50$

G2-16 + poly(Arg)-56



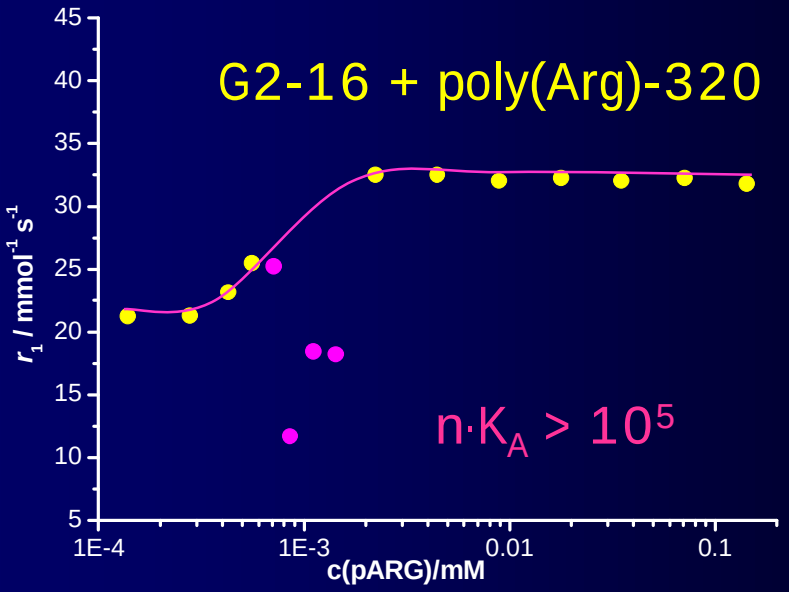
$n \cdot K_A = 250 \pm 10$

G2-16 + poly(Lys)-61

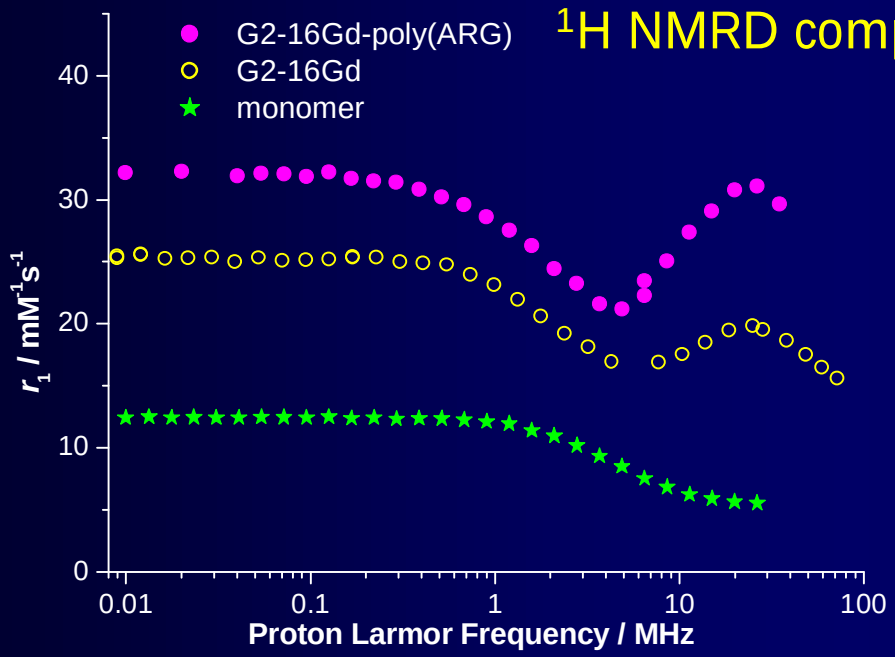


$n \cdot K_A = 570 \pm 17$

G2-16 + poly(Arg)-320

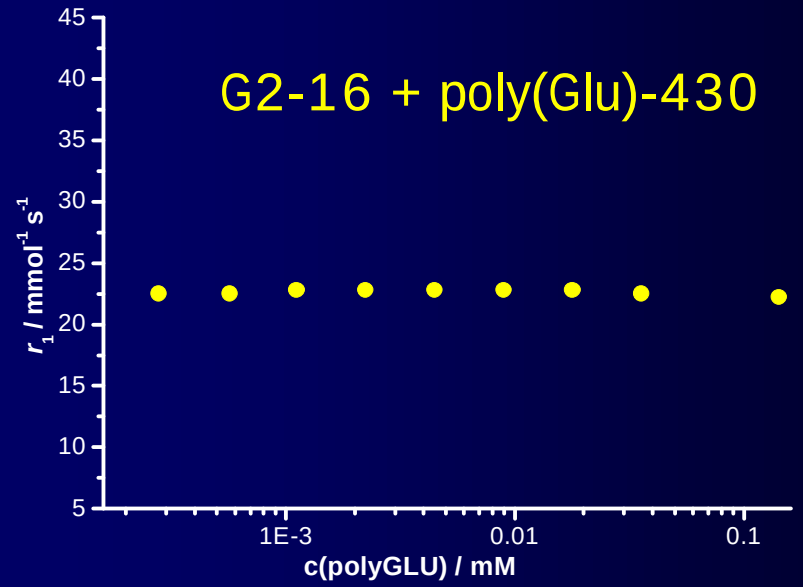


$n \cdot K_A > 10^5$



^{1}H NMRD comparison

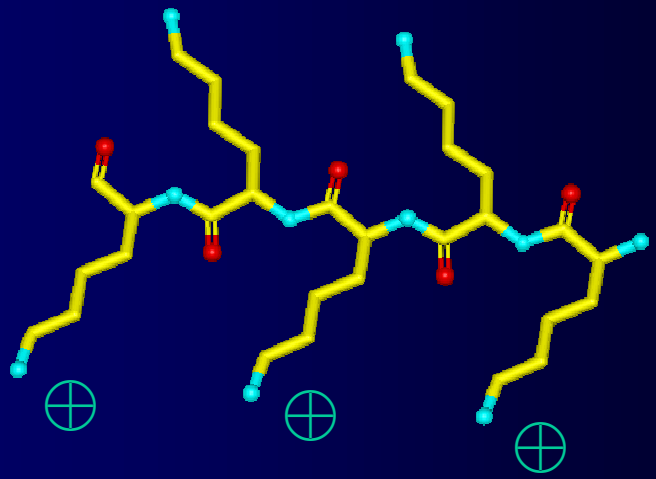
pH 7, 25 ℃



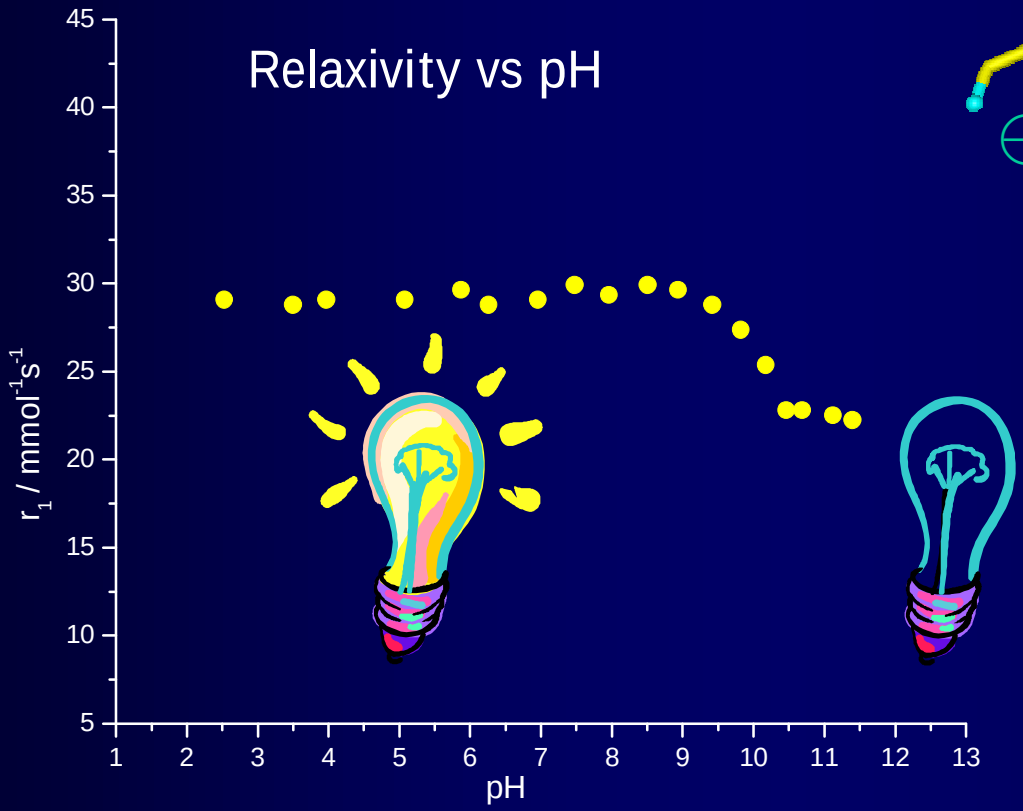
G2-16 + poly(Glu)-430

Switching the relaxivity increase on and off

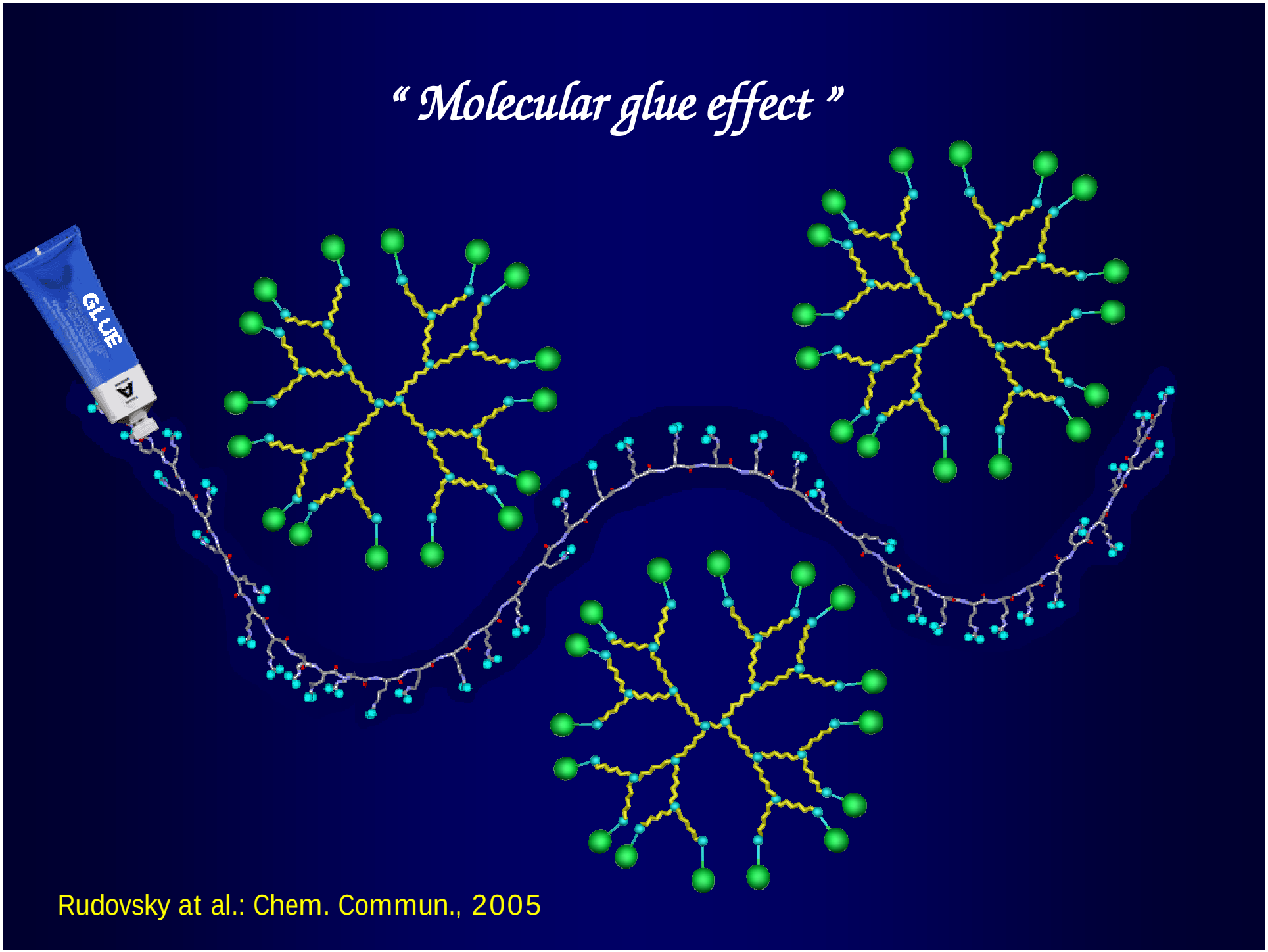
G2-16 + poly(Lys)



Relaxivity vs pH



" Molecular glue effect "



Rudovsky at al.: Chem. Commun., 2005

Summary

- conjugation of phosphinated DOTA-like ligand
- dimer – NMR a relaxometry
- series of low-molecular PAMAM conjugates
- interaction with polyaminoacides – adduct formation

Acknowledgement

Charles University in Prague

Ivan Lukeš

Petr Hermann

Università di Torino

Silvio Aime

Mauro Botta

Honza Kotek

Vojta Kubíček

COST D-18

DIMI

EMIL

NATO

GACR