

Supplementary Material

An NMR Relaxometry Approach for Quantitative Investigation of the Transchelation of Gadolinium Ions from GBCAs to a Competing Macromolecular Chelator

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- Figure S1. CaCl_2 -induced transmetallation of Magnevist.
- Figure S2. Deceleration factor as a function of $[\text{Zn}^{2+}]$.
- Figure S3. Comparison of transchelation kinetics in heparin solution.
- Table S1. Relaxivity values of used compounds.
- Table S2. Utilized concentrations for relaxivity determinations.
- Table S3. Utilized concentrations for titration experiments.
- Table S4. Utilized concentrations for transmetallation experiments.

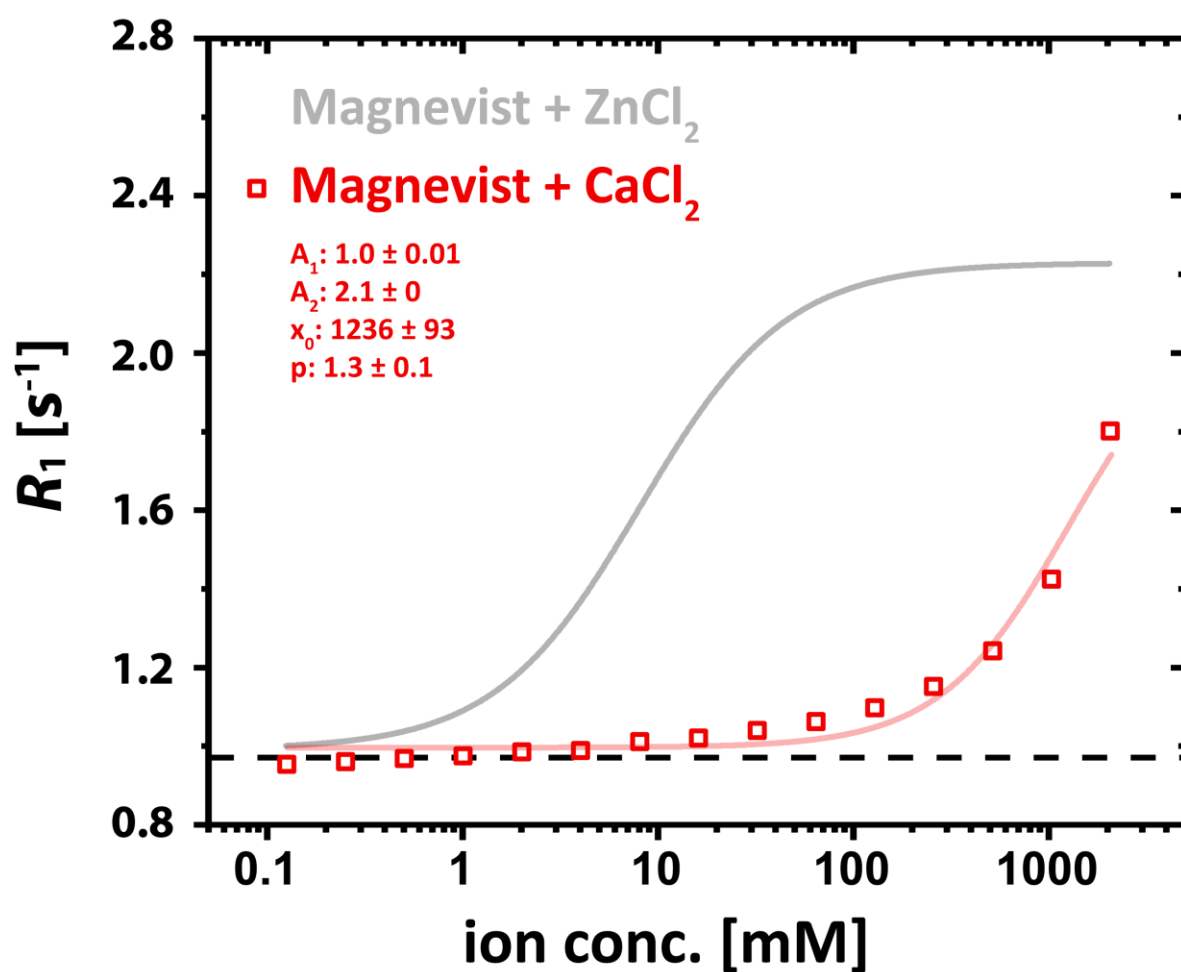


Figure S1: Quantification of the CaCl_2 -induced transmetallation of 150 μM Magnevist in nanopure water at 9.4 T and 25°C. The red solid line represents the fit using a logistic function (fit parameters are shown; A_2 was fixed to the theoretical value of 150 μM GdCl_3 in nanopure water). For comparison, the fitted curve of the ZnCl_2 -induced transmetallation (c.f. Fig. 3B) is shown as gray solid line.

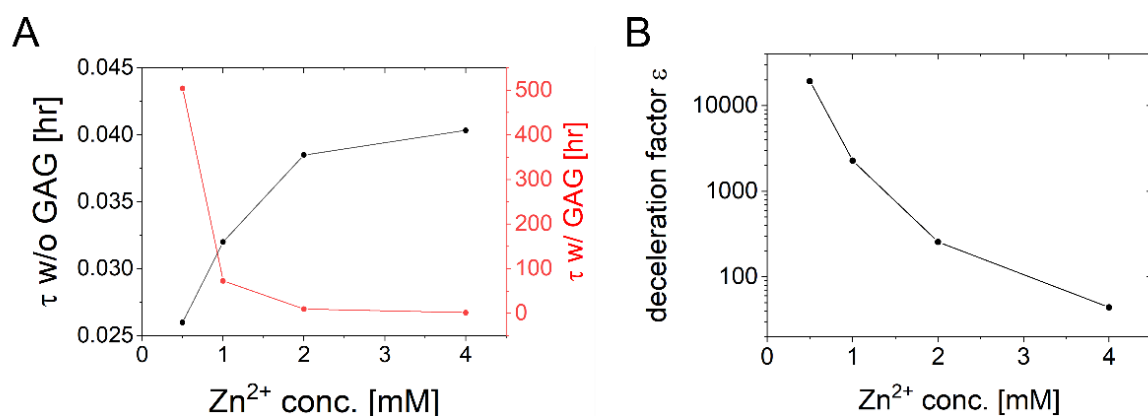


Figure S2: Kinetic stability aspects of transchelation vs. transmetallation at 9.4 T and 25°C. **(A)** Comparison of the time constants from Table 1 for the changes in r_1 relaxivity representing transmetallation (ZnCl_2 + Magnevist; black) or transchelation (ZnCl_2 + heparin + Magnevist; red). **(B)** The ratio ε of the time constants with and without heparin from (A) can be interpreted as a deceleration factor that represents the impact of heparin on withholding Zn^{2+} ions from the initial attack.

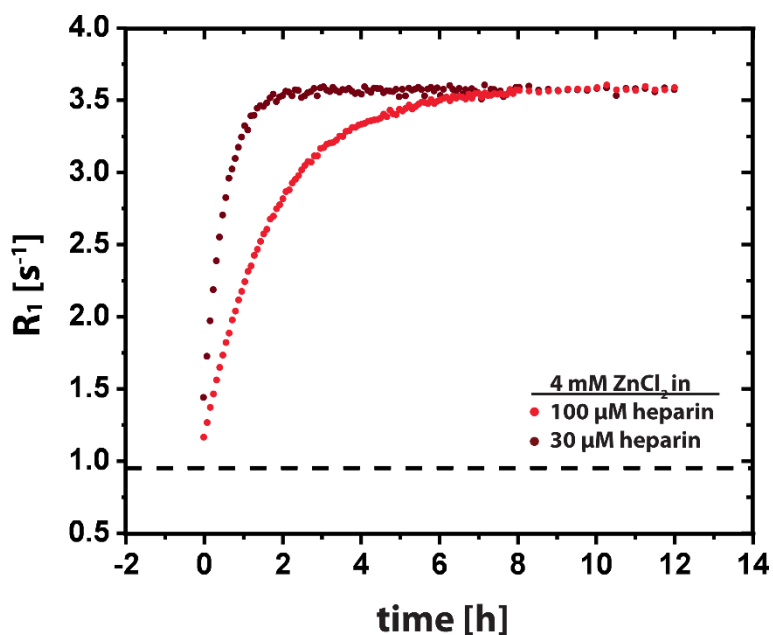


Figure S3: Comparison of transchelation kinetics of 150 μM Magnevist and 4 mM ZnCl_2 in 30 μM (dark red) and 100 μM (light red) aqueous heparin solution at 9.4 T and 25°C. The black dashed line represents the theoretical value of 150 μM Magnevist in water. The R_1 values of both experiments increase after the addition of ZnCl_2 at time point 0 and reach the same new plateau value of $R_1 \approx 3.55 \text{ s}^{-1}$. The time constant for the observed transchelation processes decrease from 1.78 h to less than 35 min when decreasing the heparin concentration from 100 μM to 30 μM .

Table S1: Determined relaxivities (mean $\pm$ sd) at 9.4 T of all compounds used in the manuscript. The exact concentrations used for the relaxivity quantifications are listed in supplemental table S2. The relaxivity of ZnCl_2 was determined to be smaller than 10^{-4} and thus neglected in all calculations.

	r_1 in H_2O $[\text{mM}^{-1} \text{s}^{-1}]$		r_1 in heparin $[\text{mM}^{-1} \text{s}^{-1}]$	
	25 °C	37 °C	25 °C	37 °C
Magnevist	4.08 ± 0.03	3.33 ± 0.03	4.04 ± 0.02	3.33 ± 0.01
Dotarem	3.72 ± 0.13	3.04 ± 0.10	3.72 ± 0.01	3.06 ± 0.01
GdCl_3	11.82 ± 0.13	9.16 ± 0.12	26.31 ± 0.23	25.57 ± 0.27
ZnCl_2	$< 10^{-4}$	$< 10^{-4}$	$< 10^{-4}$	$< 10^{-4}$
heparin	0.013 ± 0.001	0.009 ± 0.001	-	-

Table S2: Concentrations used for the determination of the relaxivities (r_1) of all compounds used in the manuscript.

sample #	1	2	3	4	5	6
Magnevist [μM]	50	100	150	200	300	450
Dotarem [μM]	50	100	150	200	300	450
GdCl₃ [μM]	10	20	40	60	80	100
ZnCl₂ [mM]	64	128	256	512	1024	2048
heparin [mM]	0.5	1	2	3	4	5

Table S3: Concentrations used for the two sets of sample solutions for the titration experiments. Both sets consist of 16 samples, each. One set was prepared with, the other set without the addition of 833 μM ZnCl_2 .

sample #	[heparin]/ [GdCl ₃]	GdCl ₃ [μM]	ZnCl ₂ [μM]	heparin [μM]
1	0.0001	25	(833)	0.00250
2	0.0003	25	(833)	0.00790
3	0.0010	25	(833)	0.02500
4	0.0018	25	(833)	0.04450
5	0.0032	25	(833)	0.07900
6	0.0056	25	(833)	0.14050
7	0.0100	25	(833)	0.25000
8	0.0147	25	(833)	0.36750
9	0.0215	25	(833)	0.53750
10	0.0316	25	(833)	0.79000
11	0.0464	25	(833)	1.16000
12	0.0681	25	(833)	1.70250
13	0.1000	25	(833)	2.50000
14	0.3160	25	(833)	7.90000
15	1.0000	25	(833)	25.0000
16	10.000	25	(833)	250.000

Table S4: Concentrations used for the transmetallation experiments.

sample #	ZnCl ₂ [μ M]	GBCA [μ M]
1	0	150
2	0.125	150
3	0.25	150
4	0.5	150
5	1	150
6	2	150
7	4	150
8	8	150
9	16	150
10	32	150
11	64	150
12	128	150
13	256	150