

STRUCTURAL AND KINETIC DIFFERENCES AMONG AGENTS AND HOW THIS CAN AFFECT THEIR RELATIVE TOXICITY

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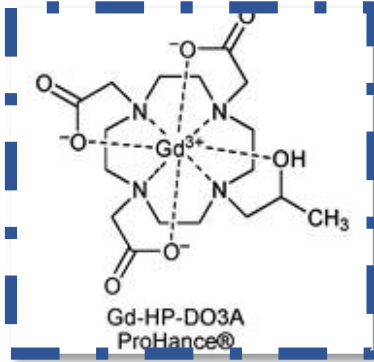
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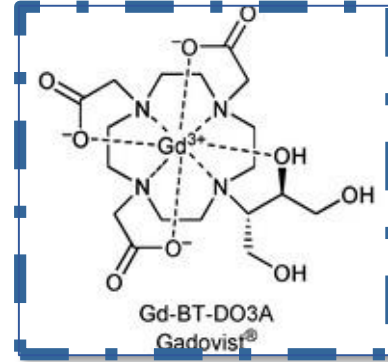
Conflicts of Interest

Research Agreement with Philips Healthcare; Scientific Advisor for Aspect Imaging; Participant in Two Panels for Bayer Healthcare in 2017; Participant in Two Key Opinion Leader Meetings for Guerbet LLC in 2017; Lecturer in CME program on Gadolinium Deposition for ICPME-5 Lectures, 1 Webinar in 2017.

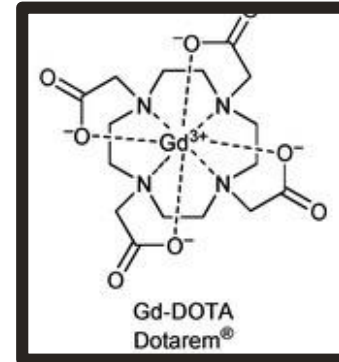
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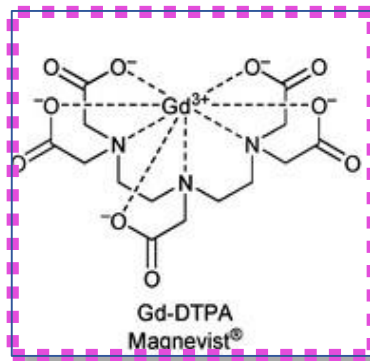
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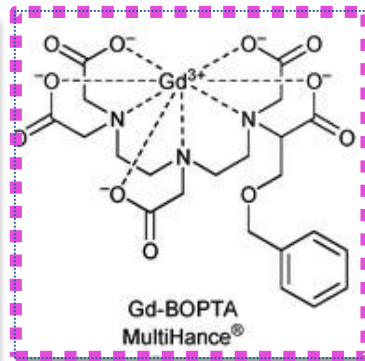
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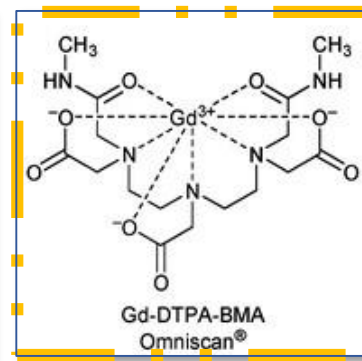
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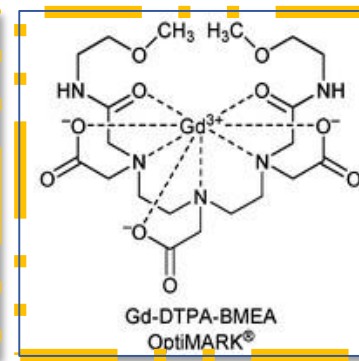
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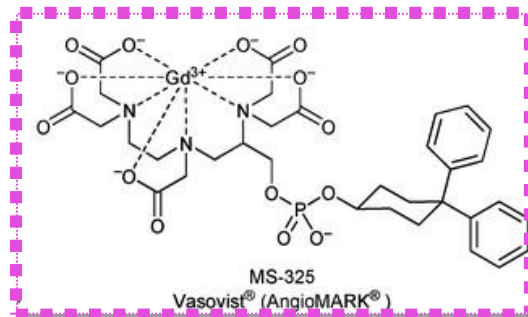
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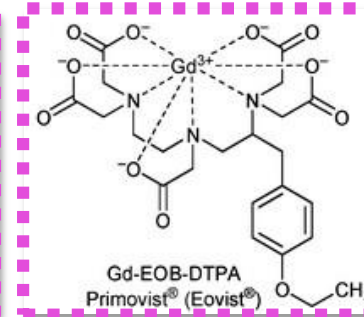
gadoversetamide



gadofosveset



gadoxetate



— • — Macrocyclic nonionic

— Macrocyclic ionic

••••• Linear ionic

— ••• Linear nonionic

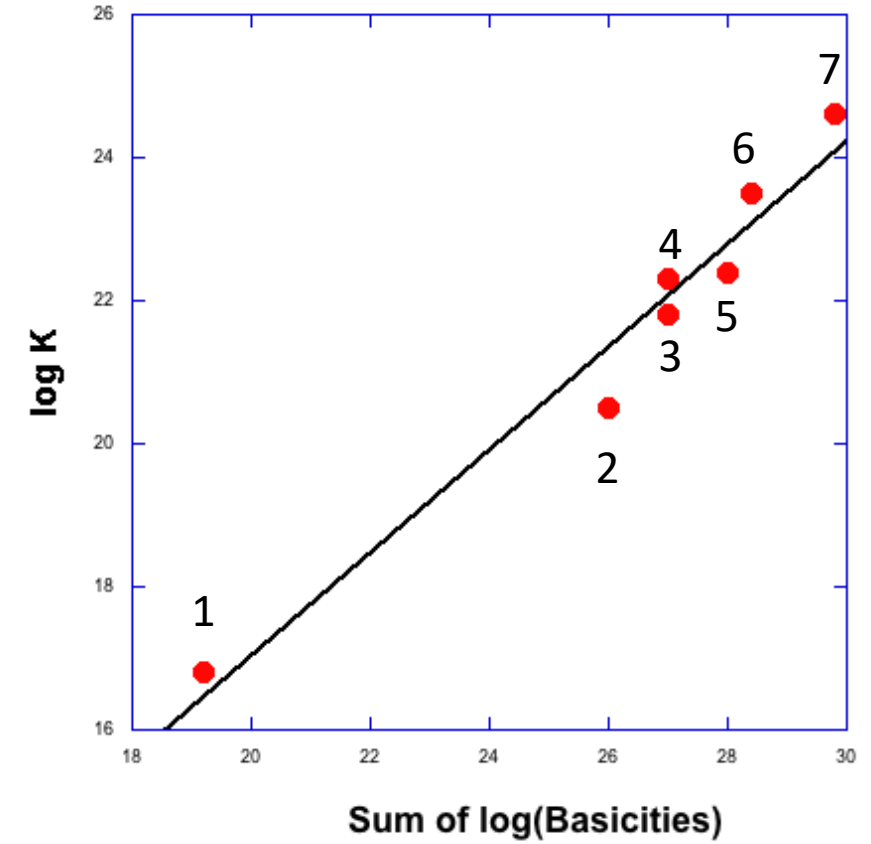
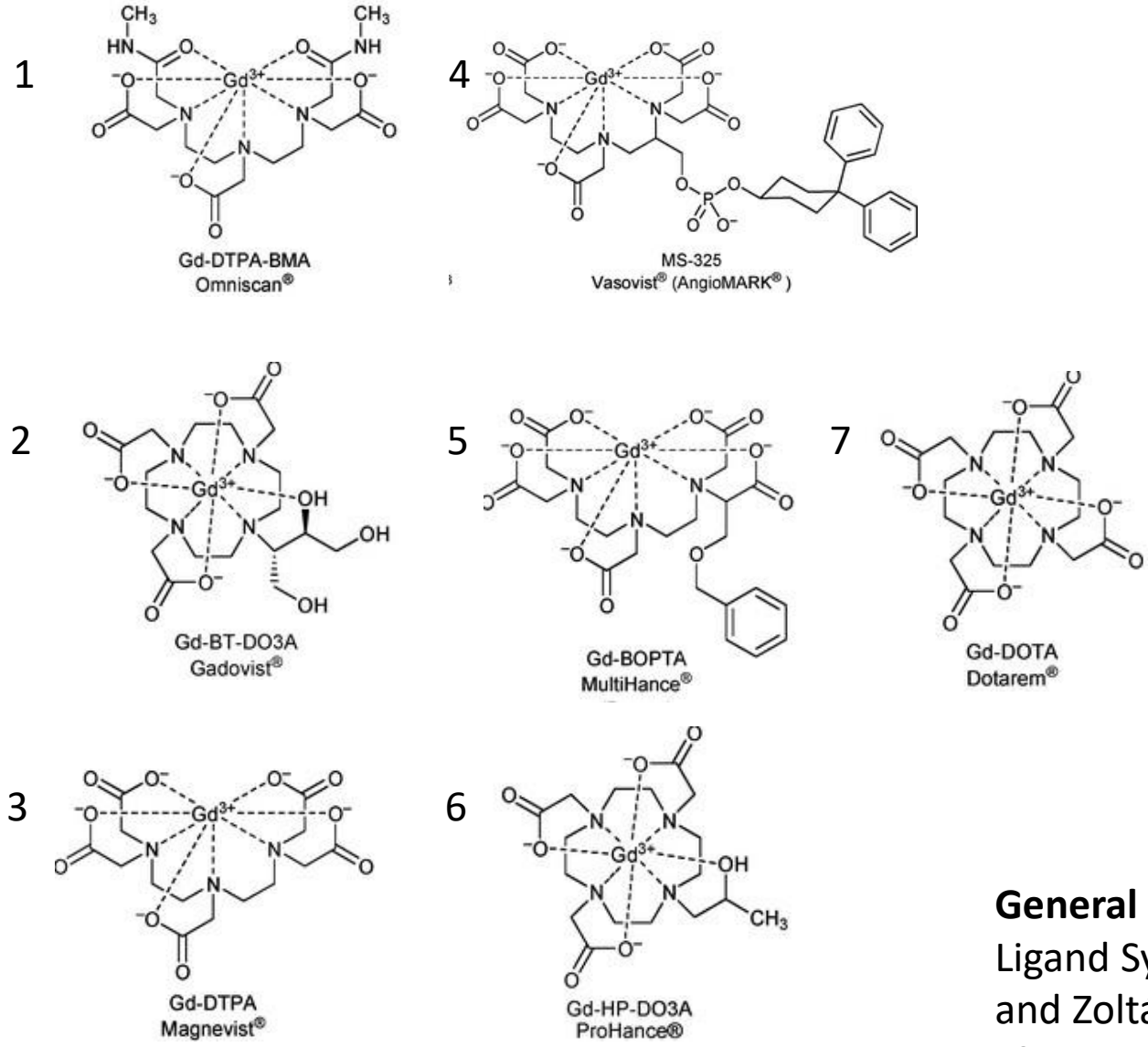


Basicity

Rigidity

Basicity of Chelate

Plot of thermodynamic stability of FDA-approved GBCAs versus basicity of the nitrogen atoms ($\Sigma \log K_i^H$) of the ligands



General Synthetic and Physical Methods

Ligand Synthesis and Characterization, Quyen N. Do, James S. Ratnakar, and Zoltán Kovács **In Contrast Agents for MRI: Experimental Methods, Chapter 1, 2018**

Rigidity of Chelate

Rate Constants Characterizing the Acid-catalyzed Dissociation of FDA Approved GBCA's

GBCA	Trade Name	Description	k_1 ($M^{-1} s^{-1}$)	Relative Rigidity Within Each Group
[Gd(DTPA)] ²⁻	Magnevist	Linear, ionic	0.58	
[Gd(BOPTA)] ²⁻	MultiHance	Linear, ionic	0.41	
[Gd(EOB-DTPA)] ²⁻	Eovist	Linear, ionic	0.16	
[Gd(MS-325)] ³⁻	Ablavar	Linear, ionic	2.9×10^{-2}	
[Gd(DTPA-BMA)]	Omniscan	Linear, non-ionic	12.7	
[Gd(DTPA-BMEA)]	Optimark	Linear, non-ionic	8.6	
[Gd(HP-DO3A)]	ProHance	Macrocyclic, non-ionic	6.4×10^{-4} , 2.6×10^{-4}	
[Gd(BT-DO3A)]	Gadovist	Macrocyclic, non-ionic	2.8×10^{-5}	
[Gd(DOTA)] ⁻	Dotarem	Macrocyclic, ionic	8.4×10^{-6} , 1.8×10^{-6}	

Lability of Metal Complexes

GYULA TIRCSO,* ZSOLT BARANYAI, FERENC KRISZTIAN KALMAN, ZOLTÁN KOVACS, ERNOBRUCHER AND IMRE TOLTH

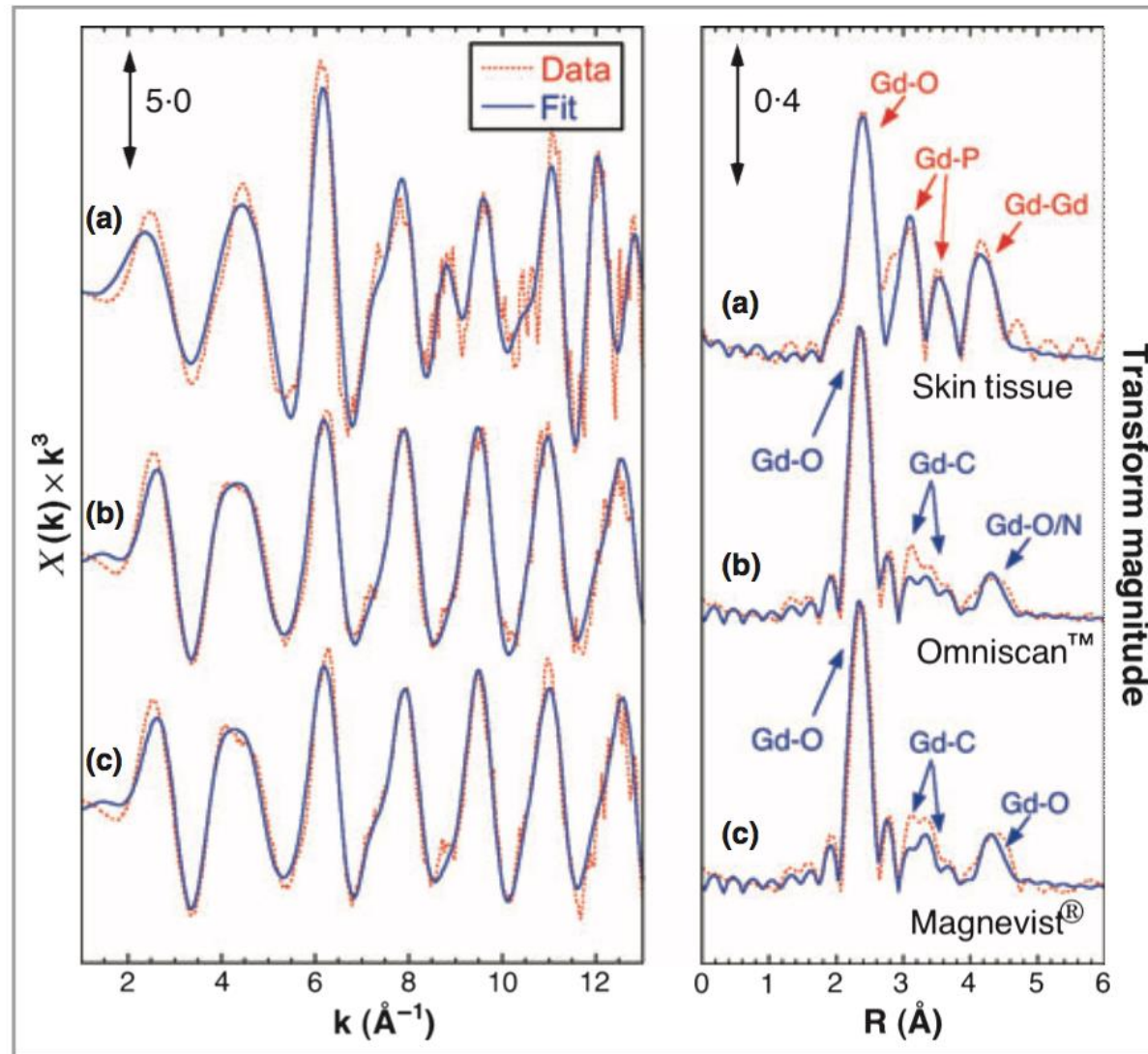
In Contrast Agents for MRI: Experimental Methods, Chapter 1, pg 92, 2018

We Are Not at Equilibrium After GBCA is Injected

The system will try to re-establish equilibrium (Le Chatelier's Principle).

Phosphate ions are present in the blood-
GdPhosphate is highly insoluble.

Fig 2. Extended X-ray absorption fine structure (EXAFS) spectra at the Gd L₃-edge and analysis of the tissue sample compared with that from selected gadolinium-based contrast agents. (Left) EXAFS spectra and (right) Fourier transforms (FTs) with simulated fits of (a) skin tissue, (b) Omniscan™, (c) Magnevist®. The Fourier transforms are phase corrected assuming Gd–O interactions. Indicated are the atomic origins of the observed peaks.



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BJD © 2010 British Association of Dermatologists 2010 163, pp1077–1081

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Full Paper

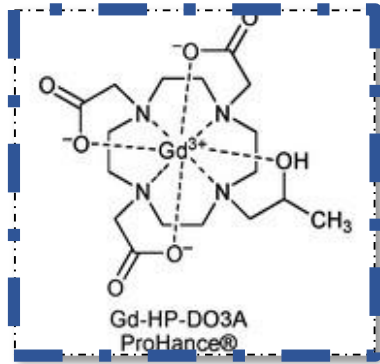
Comparative study of the physicochemical properties of six clinical low molecular weight gadolinium contrast agents[†]

*Sophie Laurent, Luce Vander Elst and Robert N. Muller**

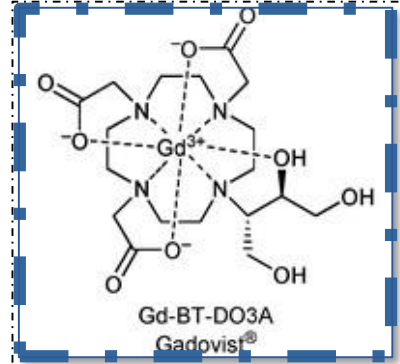
Department of General, Organic and Biomedical Chemistry, NMR and Molecular Imaging Laboratory, University of Mons-Hainaut, 24 Avenue du Champ de Mars, B-7000 Mons Belgium

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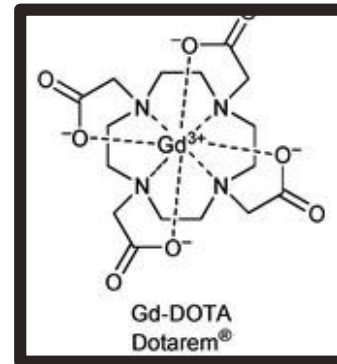
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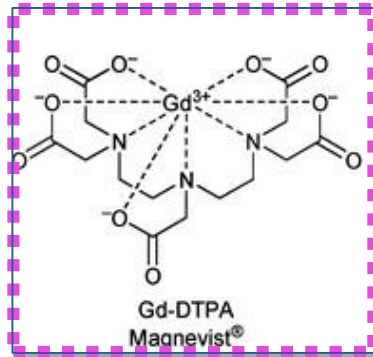
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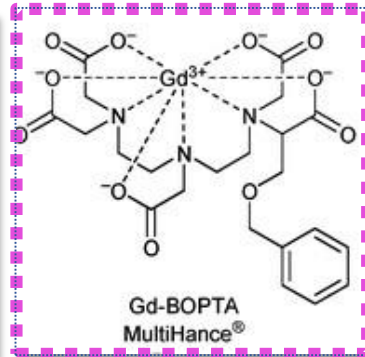
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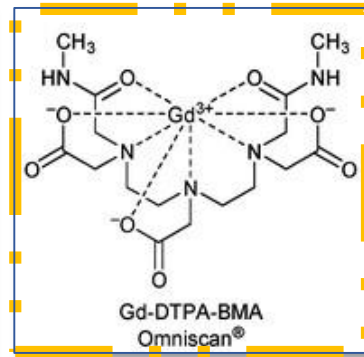
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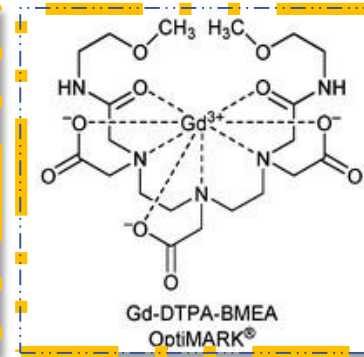
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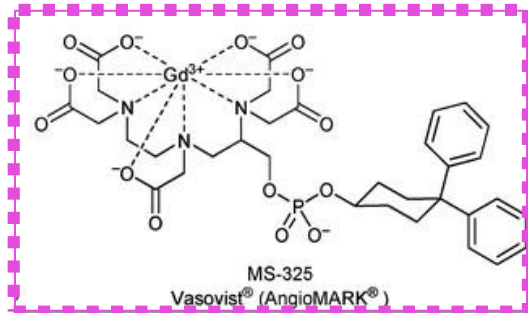
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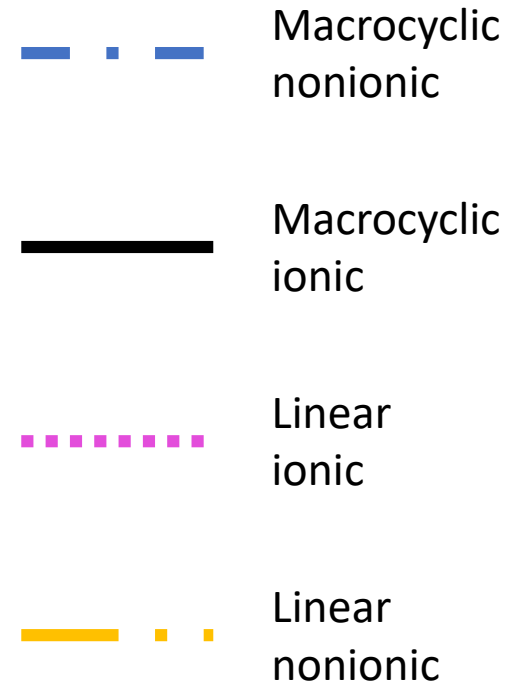
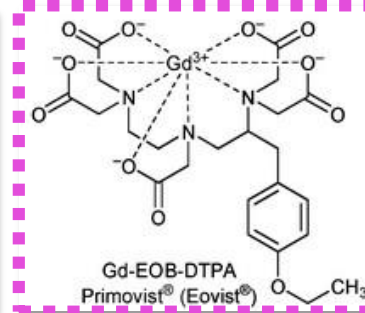
gadoversetamide



gadofosveset



gadoxetate



Full Paper

Comparative study of the physicochemical properties of six clinical low molecular weight gadolinium contrast agents[†]

Sophie Laurent, Luce Vander Elst and Robert N. Muller*

Department of General, Organic and Biomedical Chemistry, NMR and Molecular Imaging Laboratory, University of Mons-Hainaut, 24 Avenue du
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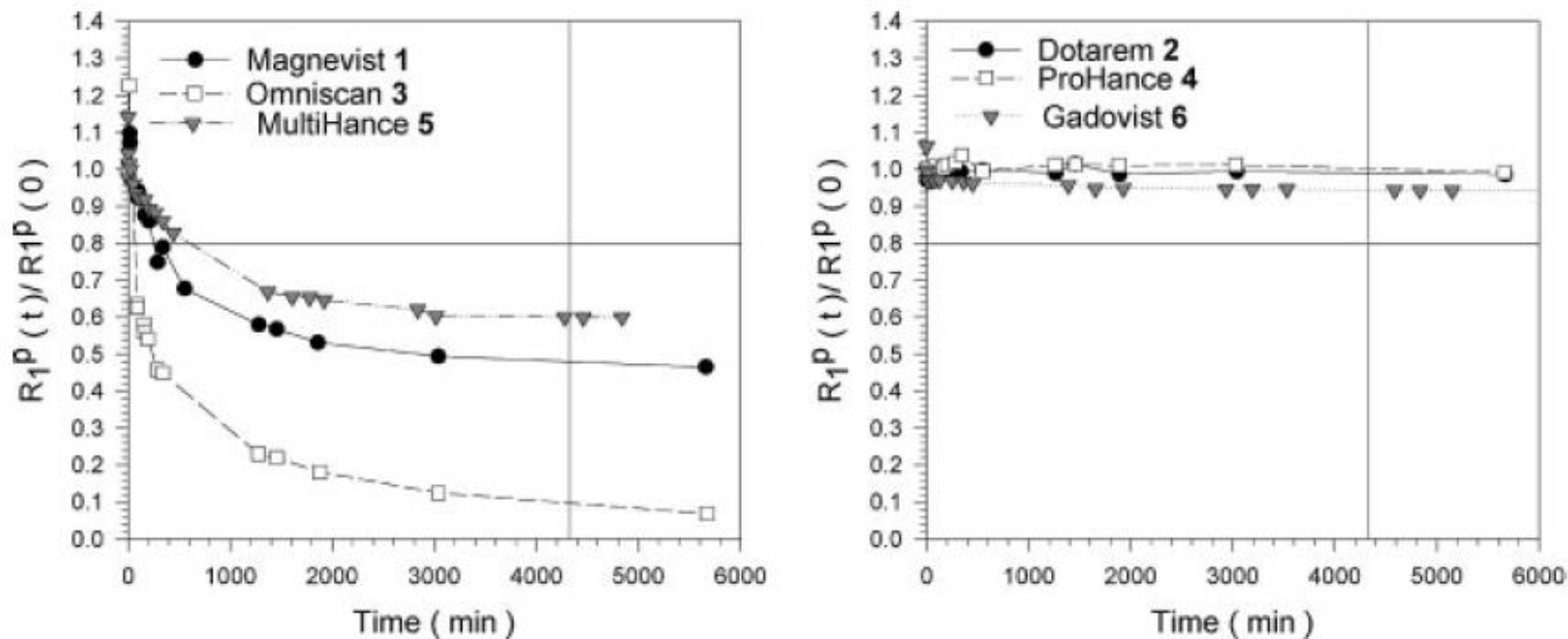
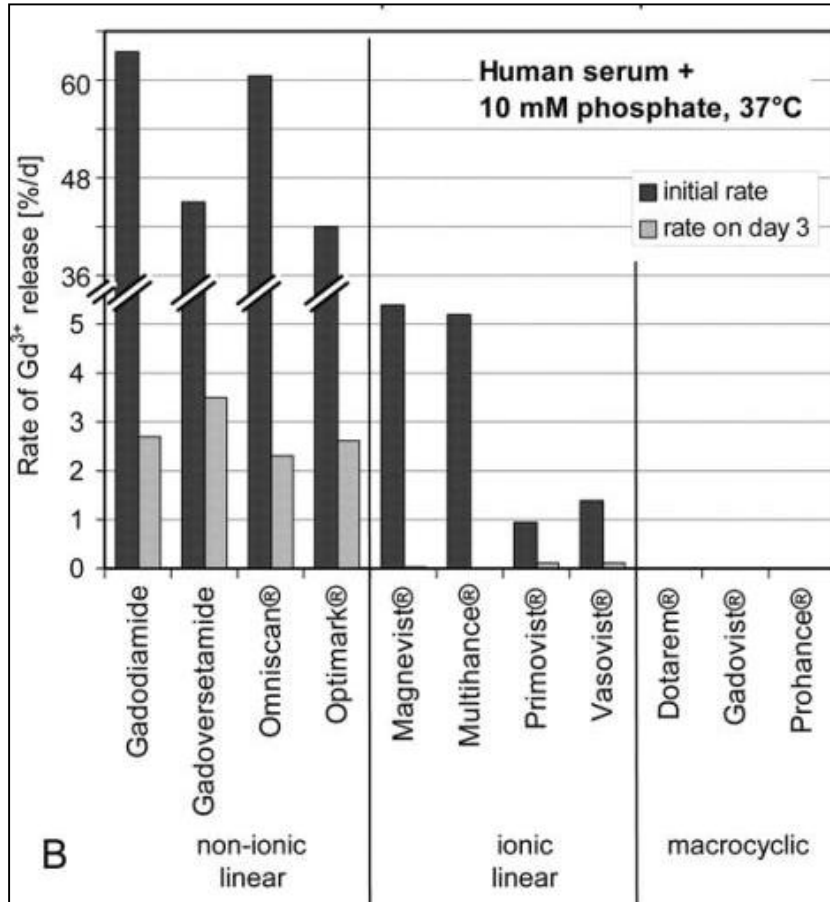


Figure 5. Evolution of $R_1^P(t)/R_1^P(0)$ versus time for Magnevist (**1**), Omniscan (**3**) and MultiHance (**5**) (left-hand graph) and Dotarem (**2**), ProHance (**3**) and Gadovist (**6**) (right-hand graph). Initial concentrations of Gd complexes and $ZnCl_2$ are 2.5 mM in phosphate buffer (pH 7), $T = 310$ K, $B = 0.47$ T. The vertical line corresponds to time = 4320 min, the horizontal line corresponds to an $R_1^P(t)/R_1^P(0)$ value of 0.8.

GBCA	Ratio Index (min)	k_1 ($M^{-1} s^{-1}$)
[Gd(DTPA-BMA)]	70	12.7
[Gd(DTPA)] ²⁻	250	0.58
[Gd(BOPTA)] ²⁻	600	0.41
[Gd(HP-DO3A)]	>5000	6.4×10^{-4} , 2.6×10^{-4}
[Gd(BT-DO3A)]	>5000	2.8×10^{-5}
[Gd(DOTA)] ⁻	>5000	8.4×10^{-6} , 1.8×10^{-6}



Stability of Gadolinium-Based Magnetic Resonance Imaging Contrast Agents in Human Serum at 37[degrees]C.

Frenzel, Thomas; Lengsfeld, Philipp; Schirmer, Heiko; Hutter, Joachim; Weinmann, Hanns-Joachim

Investigative Radiology. 43(12):817-828, December 2008.

FIGURE 6B. Comparison of the rates of Gd³⁺ release for 1 mmol/L solutions of all GBCAs in native human serum from healthy volunteers at 37[degrees]C with 10 mmol/L phosphate added (B). The initial rates (dark bars) of Gd³⁺ release and the release rates on day 3 (gray bars) are shown.

Preclinical Mechanistic Studies of Gd Deposition in the Brain

OPEN

Quantification and Assessment of the Chemical Form of Residual
Gadolinium in the Brain After Repeated Administration
of Gadolinium-Based Contrast Agents
Comparative Study in Rats

Thomas Frenzel, PhD, Chirag Apte, BSc,† Gregor Jost, PhD,* Laura Schöckel, PhD,*
Jessica Lohrke, PhD,* and Hubertus Pietsch, PhD**

Investigative Radiology, 52(7), 396-404, 2017

Estimates of the relative amounts of Total Gd, intact GBCA, insoluble fraction and fraction of macromolecular complex in the cerebellum of rats 24 days post injections

	GBCA	Total Gd*	Insoluble Gd*	Macromolecular Complex*	k_1 ($M^{-1} s^{-1}$)
Macrocyclic	[Gd(HP-DO3A)]	1.4	0.2	0.008	2.8×10^{-5}
	Gd-(DOTA)] ⁻	1.1	0.3	0.014	8.4×10^{-6} , 1.8×10^{-6}
Linear	[Gd(DTPA-BMA)]	5.5	3.8	0.70	12.7
	[Gd(DTPA)] ²⁻	3.8	2.2	0.58	0.58
	[Gd(BOPTA)] ²⁻	2.8	1.8	0.44	0.41

* nanomoles/gram of tissue

Summary of Animal Studies

GBCA's reach the CSF intact

The CSF can communicate with the interstitial spaces in the brain and thus the injected GBCA's indirectly cross the blood-brain barrier intact

The GBCA's are then cleared from the brain by diffusion and renal clearance

Within experimental error, the macrocyclic GBCA's remain largely intact over at least 24 days

The linear GBCA's can be found as intact GBCA's (ca 20%), macromolecular complexes and insoluble products over a 24 day period