MODULATION OF MAGNETIC PROPERTIES IN MAGNETIC RESONANCE IMAGING CONTRAST AGENTS AND MOLECULAR MAGNETIC MATERIALS

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Abstract

This dissertation focuses on fundamental research in two areas of magnetism, the technologically advanced field of magnetic resonance imaging (MRI) and the nascent discipline of molecular magnetic materials. Contrast agents for MRI based on the gadolinium(III) ion were designed and studied to gain insight into the parameters that may be modulated to control contrast agent efficacy. Two parameters in particular, the inner-sphere coordination environment and the electronic relaxation of the gadolinium(III) ion, were examined. Investigations into the electronic relaxation of the gadolinium(III) ion led to insights that were applied to the synthesis and evaluation of a low dimensional magnetic material based on ruthenium(III) and nickel(II) ions.

Manipulation of the gadolinium(III) coordination sphere provided the basis for an MRI contrast agent designed to be sensitive to the oncologically relevant enzyme β-glucuronidase. This agent functions by restricting water access to the inner-sphere coordination sites of the gadolinium(III) ion. The design, synthesis, magnetic properties and biochemistry of the agent are described in detail. The agent displays good enzyme kinetics and complicated coordination equilibria with water and carbonate ion.

A second approach to modulating contrast agent efficacy consisted of varying the electronic relaxation time of the gadolinium(III) ion. Towards this goal, ligand frameworks were designed and synthesized to influence the relaxation time of the gadolinium(III) ion via remote redox activity. Structural characterization and in vitro assays of these ligand-metal constructs indicated more robust ligands were required for complex stability. Initial steps toward a ligand that fulfills these requirements proved successful.

The structural data from the electronic relaxation studies led to the synthesis of a one-dimensional coordination polymer comprised of chelated ruthenium(III) and nickel(II) ions bridged by cyanide ligands. The compound was studied by X-ray crystallography and its magnetic properties indicated that the ions were ferromagnetically coupled.

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Abbreviations

Abbreviation	Definition
units	
C	Celsius
cm^{-1}	wavenumber
cm	centimeter
h	hour
K	Kelvin
kOe	kilo Oersted
M	molar
MHz	megahertz
mM	millimolar
mmol	millimole
mol	mole
mV	millivolt
nm	nanometer
ns	nanosecond
Oe	Oersted
s	second
μm	micrometer
chemicals	
acac	acetylacetonoate
BSA	bovine serum albumin
CAM	cerium ammonium molybdate
CDI	carbonyl diimidazole
Cp*	pentamethyl cyclopentadienyl
cyclam	1,4,8,11-tetraazacyclotetradecane
cyclen	1,4,7,10-tetraazacyclododecane
DMAP	N,N-dimethylamino pyridine
DMF	N,N-dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DO3A	N,N',N''-tricarboxymethylene cyclen
DOTA	N,N',N'',N'''-tetracarboxymethylene cyclen
Et_2O	diethyl ether
EtOAc	ethyl acetate
EtOH	ethanol

Abbreviation	Definition
HSA	human serum albumin
IPA	isopropyl alcohol
Ln	lanthanide
MEK	methylethylketone
MeOH	methanol
MOPS	3-(N-morpholino)propanesulfonic acid
NBS	N-bromosuccinimide
ox	oxalato
Ph	phenyl
PNG	*p*-nitrophenyl-β-D-glucuronide
PPh_3	triphenylphosphine
PTFE	poly-tetrafluoroethylene
salen	ethylenebis(salicylimine)
TEA	triethylamine
TFA	trifluoroacetic acid
tmen	N,N, N',N'-tetramethylethylenediamine
TMS	tetramethylsilane

general

ac	alternating current
ADEPT	antibody directed enzyme-prodrug therapy
dc	direct current
EPR	electron paramagnetic resonance
fc	field cooled
FT	Fourier transform
FTIR	Fourier transform infrared
GDEPT	gene directed enzyme-prodrug therapy
HPLC	high performance liquid chromatography
ICP-MS	Ion coupled plasma mass spectroscopy
LC-MS	liquid chromatography-mass spectroscopy
MR	magnetic resonance
MRI	magnetic resonance imaging
NMR	nuclear magnetic resonance
ParaCEST	paramagnetic chemical exchange saturation transfer
PMT	prodrug monotherapy
RF	radio frequency
SCM	single chain magnet
SMM	single molecule magnet

Abbreviation	Definition
TIP	temperature independent paramagnetism
UV	ultraviolet
w/v	weight to volume
zfc	zero field cooled

symbols

br	broad
d	doublet
$E_{1/2}$	half reaction potential
H_o	applied magnetic field magnitude
$\boldsymbol{H_o}$	applied magnetic field vector
I	nuclear angular momentum quantum number
i_{pa}	peak anodic current
i_{pc}	peak cathodic current
$\mathcal{J}$	exchange coupling magnitude
J	NMR coupling constant
$J(\omega_H, \tau_c)$	spectral density function
k_B	Boltzmann constant
k_{cat}	catalysis rate
K_M	Michaelis constant
L	orbital angular momentum quantum number
M	magnetization magntitude
$\boldsymbol{M}$	magnetization vector
m	multiplet
m/z	mass to charge ratio
$\boldsymbol{M_o}$	equilibrated magnetization vector
M_s	saturation magnetization
P_m	mole fraction of contrast agent
q	number of coordinated water molecules
r_1	longitudinal relaxivity
R_f	retention factor
r_{strong}	relaxivity in the activated contrast agent
r_{weak}	relaxivity in the unactivated contrast agent
s	singlet
S	spin angular momentum quantum number
T	temperature

Abbreviation	Definition
t	triplet
T_1	longitudinal nuclear relaxation time
T_{1e}	longitudinal electronic relaxation time
T_2	transverse nuclear relaxation time
T_{2e}	transverse electronic relaxation time
T_c	critical temperature
T_e	electronic relaxation time
V_{max}	maximum velocity
γ_H	proton gyromagnetic ratio
ΔE_p	peak-to-peak potential difference
ε	molar absorptivity
λ_{em}	emission wavelength
λ_{ex}	excitation wavelength
$\boldsymbol{\mu}$	magnetic moment vector
μ_B	Bohr magneton
τ_c	total correlation time
τ_D	diffusional correlation time
τ_m	water residency lifetime
τ_R	rotational correlation time
χ	magnetic susceptibility
χ_m	molar magnetic susceptibility
ω_H	proton Larmor frequency