Communication

Photoswitchable MRI contrast by improved LD-CISSS

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Photoswitchable MRI contrast by improved LD-CISSS.

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Supporting Information Placeholder

ABSTRACT: We present a fully reversible and highly efficient on-off photo switching of magnetic resonance imaging (MRI) contrast with green (500 nm) and violet-blue (435 nm) light. The contrast change is based on the intramolecular Light-Driven Coordination-Induced Spin State Switch (LD-CISSS) which was performed with azopyridine substituted Ni-porphyrins. The T_1 relaxation time of the solvent protons in 3 mM solutions of the azoporphyrins in DMSO was switched between 3.5 and 1.7 s. The relaxivity of the contrast agent changes by a factor of 6.7. No fatigue or side reaction was observed even after more than 96000 switching cycles under air at room temperature. Electron donating substituents at the pyridine improve the LD-CISSS in two ways: Better photo stationary states are achieved and the intramolecular binding is enhanced.

Magnetic resonance imaging (MRI) is one of the most important, non-invasive tools in diagnostic medicine. As opposed to other deep tissue imaging modalities such as computer tomography (CT) or positron emission spectroscopy (PET) no ionizing radiation is used in MRI examinations and no radiation damage is induced. To date, more than 200 million doses of MRI contrast agents (CAs) have been administered to patients worldwide.[1,2] . Commercially available CAs are mainly gadolinium(III) chelate complexes.[3,4] With a spin of 7/2 these molecules are highly paramagnetic and decrease the NMR relaxation time of surrounding water protons (or other NMR active nuclei) which in turn leads to signal enhancement in MRI. The majority of clinically used Gd(III) chelates are strongly hydrophilic and therefore, after intravenous injection, the complexes stay mainly in the blood circuit leading high contrast of blood vessels. Since the MRI signal enhancement correlates with the concentration of CAs they primarily increase anatomical contrast. Further physiological information could be obtained by responsive or "smart" CAs whose relaxivity (capability of reducing the relaxation time of surrounding nuclei) is controlled by metabolic parameters. The design of responsive contrast agents reporting on parameters such as temperature, *p*H or biochemical markers is subject to intensive research because they are potentially capable to visualize the site of a disease in an MR image. Research in this field started in the mid-nineties. Most of the approaches since then are based on Gd(III) complexes whose relaxivity is controlled by controlling the water coordination to the Gd^{3+} ion which is the most efficient relaxation mechanism. A number of CAs were developed with response to proteins and enzyms,[5-11] carbohydrates,[12,13] *p*H value,[14-20] and ions like Ca^{2+},[21-26] Zn^{2+},[27-29] $Cu^{+/2+}$,[30] and K^{+}.[31] A less intensively investigated stimulus is light. Functionalization of Gd(III) chelates with photochromic spiropyrans gave rise to contrast changes of about 20%.[32,33] Our approach to the design of responsive and particularly light-controlled CAs is different from the above methods. We are not controlling the access of the solvent molecules to the paramagnetic ion, but we are switching the spin state of transition metal ions between paramagnetic and diamagnetic. Whereas a Gd complex in the "off-state" with a completely filled coordination sphere, which blocks water access, still exhibits a residual relaxivity by outer sphere relaxation (through space magnetic dipol interaction), a diamagnetic transition metal complex with S = 0 is completely MRI silent. Spin state switching, therefore, offers the potential to achieve a higher efficiency in relaxivity control. Contrast switching is very important in interventional radiology (catheter based surgery under imaging control).[34,35] The change in contrast so far is obtained by administration of additional CAs each time when this is required. After multiple injections the CAs accumulate in the blood circuit to a level where they are harmful and the contrast change is gradually lost. Light-sensitive CAs have the advantage that they have to be administered only once and the contrast can be switched rapidly via an optical fiber

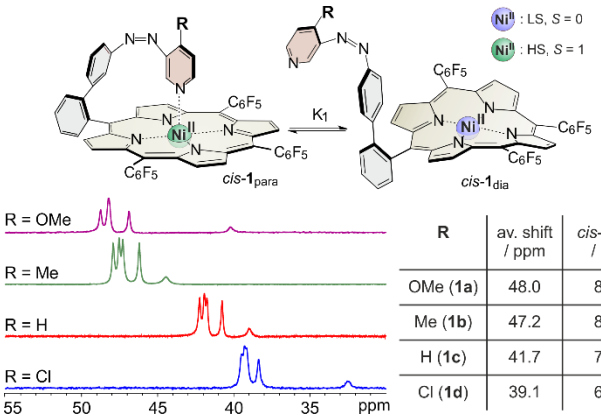
Recently, we developed a very efficient system for switching the spin state of Ni^{2+} complexes between diamagnetic (S=0) and paramagnetic (S=1) with light of two different wavelengths.[36,37] We now present a systematic improvement of the effect and demonstrate that it can be used to switch MRI contrast on and off.

Addition of axial ligands to a solution of Ni-porphyrins results in a coordination-induced spin-state switch (CISSS).[38-41] Upon increasing the coordination number (CN) from CN = 4 (no axial ligand, square planar, S = 0) to CN = 5 (one axial ligand, square pyramidal, S = 1) or CN = 6 (two axial ligands, square bipyramidal, S = 1) the Ni^{2+} ion switches from diamagnetic (contrast off) to paramagnetic (contrast on). To achieve light-controlled addition and removal of axial ligands we use a photochromic azopyridine which is covalently attached to a Ni-porphyrin. The geometry is designed in such a way that the pyridine unit coordinates to the Ni ion if the azo group is in *cis* configuration, however, intramolecular coordination is not possible in the *trans* form. Light of two different wavelengths is used to isomerize the azo group and to lift the pyridine ring up and down. For obvious reasons, we coined this approach the record player design and the process is called light-driven, coordination-induced spin state switch (LD-CISSS). To achieve a maximum efficiency in MRI contrast switching, every step in the cascade of events: photo-isomerization → coordination change → spin switch → MRI contrast change has to be optimized.

Even a perfect photo conversion between *trans* and *cis* isomers does not imply a complete change in coordination numbers. Incomplete intramolecular binding in the *cis* form, and

intermolecular coordination of the *trans* isomer, particularly at higher concentrations, are limiting the efficiency. Previous work on our prototype system has shown, that the intramolecular coordination of the *cis* configuration is not complete.[34] Obviously, there is a non-binding conformation of the *cis* isomer with the azopyridine unit pointing away from the porphyrin ring which is in fast equilibrium (on the NMR time scale) with the binding conformation (Figure 1).[35-37] It is known that the association constant of 4-substituted pyridines follows a Hammett relationship.[40] To improve the intramolecular coordination we therefore introduced electron donating groups (Me and OMe) at the 4-position of the pyridine unit (syntheses see SI).

To quantify intramolecular binding, the chemical shifts of pyrrole protons in ^{1}H NMR spectra of **1a-d** were compared. We have previously shown that coordination and de-coordination of axial ligands in Ni-porphyrins is fast on the NMR time scale. The chemical shift of the pyrrole protons of record player **1c** in non-coordinating solvents is 8.9 ppm and 53 ppm in pure pyridine-d5 (complete axial coordination). The average chemical shift therefore is an accurate measure of the ratio of diamagnetic and paramagnetic Ni-porphyrins in solution. Acetone-d_6 was chosen as the solvent for our experiments because of its low coordination power as an axial ligand and the high solubility of **1a-d** in acetone (Figure 1).



R	av. shift / ppm	*cis*-**1**$_{para}$ / %
OMe (**1a**)	48.0	89
Me (**1b**)	47.2	87
H (**1c**)	41.7	74
Cl (**1d**)	39.1	68

Figure 1. Equilibrium between the coordinated *cis*-**1**$_{para}$ and the non-coordinated form *cis*-**1**$_{dia}$ (top). From the chemical shifts of the pyrrole protons (av. shift) in acetone-d_6 (bottom left) the percentage of paramagnetic Ni^{2+} (*cis*-**1**$_{para}$) was calculated (bottom right).

The amount of paramagnetic *cis* isomer (*cis*-**1**$_{para}$) depends strongly on the 4-pyridine substituent (R). Electron donating groups increase the amount of *cis*-**1**$_{para}$ drastically (from 74% for R=H to 89% for R=OMe). Electron withdrawing groups (R=Cl) have a contrary effect (Figure 1). Thus, the switching efficiency to the paramagnetic state has been strongly improved by introduction of the OMe group at the 4-position of the pyridine.

While it is obvious that the pyridine substituent affects the axial binding to the Ni-porphyrin we surprisingly observed an improved photochemical *trans-cis* conversion as well. Irradiation of the *trans* isomers with light of 500 nm (Q-bands of *trans* azo-porphyrin **1a-d**: 523 and 557 nm) is most efficient to convert the *trans* to the *cis* isomer. This is surprising because the π-π* excitation which induces *trans-cis* isomerization in azobenzenes and azopyridines has a much shorter wavelength (~320 nm). The isomerization mechanism in our azo-porphyrins obviously is completely different from the usual azobenzene isomerization pathway. Recently, a theoretical investigation suggested an excitation of the porphyrin and a subsequent thermal isomerization of the azopyridine unit.[42] To determine the *trans-cis* conversion rate we used ^{1}H NMR spectroscopy. The protons at the phenyl ring in *meta* position to the azo group resonate between 6.5 and 6.8 ppm for all four derivatives. Signals for *cis* and *trans* isomer are well separated so that the *trans*/*cis* ratio could be determined by integration of the corresponding signals (see SI). Although the *cis* isomer has decreased ^{1}H relaxation times due to its paramagnetism, the integral is still representative for the amount of the isomers which was demonstrated by comparison with external signals (see SI). Photochemical conversion of the *trans* to the *cis* isomer (Figure 2) follows the same trend as the coordination of the *cis* isomer (Figure 1). Upon irradiation with light of 500 nm the photostationary state increases from 62% (R=Cl) to >95% (R=OMe) conversion to the *cis* form. Back-reaction to the *trans* form upon irradiation with 435 nm is quantitative within the detection limit of NMR (<5% remaining cis). Thus, overall conversion from the diamagnetic to the paramagnetic state improved considerably by introduction of the methoxy substituent (**1a**: 85%) compared to the parent system (**1c**: 48%).

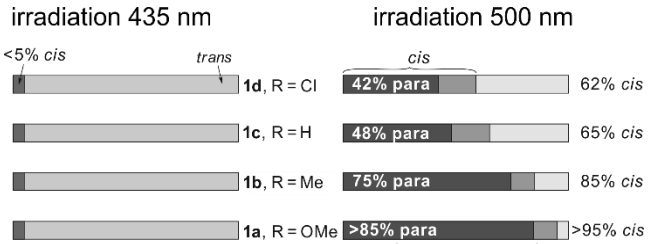


Figure 2. Photo stationary states (% *cis* isomer) and percentage of paramagnetic Ni ions upon irradiation of solutions of **1a-d** in acetrone-d_6 at 20° C with light of 435 and 500 nm. The *cis-trans*-ratio and the percentage of paramagnetic Ni ions were determined by NMR spectroscopy (for details see text).

The systems were tested regarding their long term switching stability. The methoxy substituted derivative **1a** does not exhibit any fatigue after more than 96000 switching cycles at room temperature under air (Figure 3). To test the stability of compounds 1a-1c in a biological relevant environment we treated them with a 10 mM solution of glutathione in acetonitrile/PBS buffer (1:1). No reduction of the azo function and no degradation of the switching efficiency was observed which are requirements for in vivo applications.[43-46]

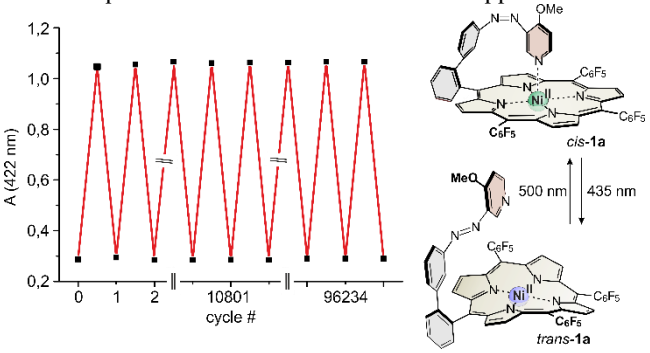


Figure 3. Long-term switching stability of **1a** (5.0 μM, MeCN, 20 °C) during alternating irradiation with 500 nm and

435 nm. The UV-vis absorption at 422 nm is plotted as a function of the number of switching cycles.

Crystals of the *cis* isomer of **1b** (R=Me) suitable for X-ray structure determination were obtained (Figure 4, left). The nickel center is complexed in a distorted octahedral coordination geometry. The equatorial plane is formed by the porphyrine nitrogen atoms with bond length ranging from 2.03 to 2.05 Å. The axial positions are occupied by the pyridine nitrogen atom of the azopyridine and the oxygen atom of a methanol molecule with longer distances of Ni-N = 2.18 Å and Ni-O = 2.27 Å. The nickel center is situated almost exactly in the porphyrin plane with a deviation of 0.08 Å. The X-ray structure is in good agreement with the DFT (PBE/SVP) optimized structure (Figure 4, right). The RMSD (route main square deviation) is 0.31 Å (for details see SI).

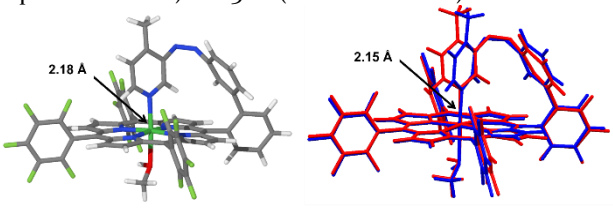


Figure 4. Crystal structure of *cis*-**1b** (left) and overlay of the crystal structure (red) and calculated structure (blue, PBE/SVP) (right).

The application of the record player molecules **1a-c** as light-switchable contrast agents was investigated by MRI (3 and 7 Tesla) and independently by NMR relaxation time measurements (200 MHz NMR). Switching between the diamagnetic and paramagnetic state in a homogenous solution of **1a-d** allows to switch the relaxation time of the solvent protons and thus to switch MRI contrast using violet-blue and green light. Figure 5 shows the MRI contrast of 3 mM solutions of **1a-d** in DMSO after irradiation with light of 435 and 500 nm. As expected, the increased conversion rate to the paramagnetic state (**1c** < **1b** < **1a**) also leads to an increase of the signal in the MRI images (Figure 5). The diamagnetic *trans* state is MRI silent in all cases.

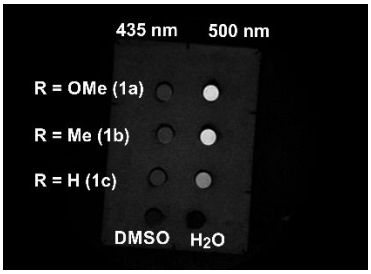


Figure 5. 3 T MR-image of 3 mM solutions of **1a-c** irradiated with 435 nm and 500 nm. For details see supporting information.

The efficiency of paramagnetic ions to shorten the relaxation time of solvent protons, normalized by their concentration, is called relaxivity (R in $mM^{-1}s^{-1}$). R_1 and R_2 are the relaxivities corresponding to the longitudinal (T_1) and transversal relaxation time (T_2). In the following we only present results for T_1 and R_1 because there are no significant differences to T_2 and R_2 in homogeneous solutions (see SI). The T_1 relaxivity was determined by relaxation time measurements at different contrast agent concentrations. The experiments were performed with **1a-c** in a mixture of 99% DMSO-d_6 and 1% DMSO in a 200 MHz (4.7 T) NMR-spectrometer (Table 1, SI).

Table 1. Relaxivities of **1a-c** in a mixture of 99% DMSO-d_6 and 1% DMSO measured in a 200 MHz NMR spectrometer.

R (#)	R_1 / $mM^{-1}s^{-}$	
	500 nm	435 nm
MeO (**1a**)	0.159	0.045
Me (**1b**)	0.155	0.029
H (**1c**)	0.121	0.0.18

The relaxivity of the *trans* isomers (**1a-c**) after irradiation with 500 nm increases by factor of 3.5, 5.3 and 6.7. Upon irradiation with 435 nm the relaxivity drastically decreases again but is different from zero which is probably due to some residual paramagnetism due to intermolecular coordination. The absolute values of the relaxivity R_1 is lower by a factor of about 25 compared to standard Gd-contrast agents which is mainly due to the lower magnetic moment (Ni(II): S = 1, Gd(III): S = 7/2). We determined relaxivity of gadobutrol in DMSO-d_6 to be 3.75 $mM^{-1}s^{-1}$ which in good agreement with the literature (see SI).[47,48] To realize the switching in a physiological medium we will attach glycerol dendrimers to the *meso*-pentafluorophenyl substituents by nucleophilic aromatic substitution. It was already shown that this concept is applicable for symmetric porphyrins.[41] We performed cell tests and proved that the dendronized water soluble Ni-porphyrin does not influence cell activity at physiologically relevant concentrations (see SI).

As a further step towards application of the switchable contrast agents we performed the photo switching in a MRI scanner to monitor the magnetic switching in situ. Light of 530 and 405 nm was applied by an optical fiber coupled to monochromatic LEDs (light intensity at the fiber outlet ~35 and 75 mW). A coaxial NMR tube with a 3 mM solution of record player **1c** in DMSO was irradiated. The on-off switching of the MRI constrast is shown in Figure 6 (right) (see also supporting video (web enhanced object)).

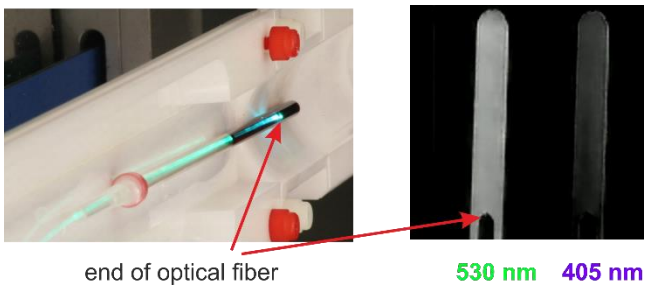


Figure 6. Experimental setup for the contrast switching in a 7 T MRI scanner (left). A 3 mM solution of **1c** was irradiated with 530 nm and 405 nm light, and MRI images were recorded after irradiation (right). A video which demonstrates contrast switching is available (web enhanced object).

In summary, we have developed a highly efficient, light-responsive molecular, magnetic switch. Green (500 nm) and violet-blue (435 nm) light was used to switch the relaxation time of solvent protons in a 3 mM solution by a factor of more than two, and the relaxivity (R_1) of the contrast agent changes by a factor of up to 6.7. The change in contrast is clearly visible in a clinical MRI scanner. Contrast control is based on a cascade of events which includes: photo-isomerization of an azopyridine ligand → coordination change at Ni^{2+} → spin switch → MRI contrast change. The system was optimized in

such a way that each step is close to quantitative. No side reaction or fatigue was detected after more than 96000 switching cycles. The metastable *cis* form (contrast-on state) has a half-life of more than 1 year at room temperature. Our Light-Driven Coordination-Induced-Spin-State-Switch (LD-CISSS) approach has the potential to provide the basis for the development of a number of interesting applications including the design of temperature or *p*H responsive contrast agents for MRI. The latter would be useful to detect tumors because they exhibit a higher temperature and a lower *p*H than surrounding tissue.

ASSOCIATED CONTENT

Supporting Information.

Experimental procedures and spectral data for all new compounds, details of computational studies, crystallographic data and a video (WEO) of MRI contrast switching. This material is available free of charge via the Internet at http://pubs.acs.org."

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Notes

The authors declare no competing financial interest.

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