JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
pubs.acs.org/JACS

Photoswitchable Magnetic Resonance Imaging Contrast by Improved Light-Driven Coordination-Induced Spin State Switch

Marcel Dommaschk,[†] Morten Peters,[†] Florian Gutzeit,[†] Christian Schütt,[†] Christian Näther,[‡] Frank D. Sönnichsen,[†] Sanjay Tiwari,[§] Christian Riedel,[§] Susann Boretius,[§] and Rainer Herges*[,†]

[†]Otto-Diels-Institut für Organische Chemie, Christian-Albrechts-Universität, Otto-Hahn-Platz 4, 24098 Kiel, Germany
[‡]Institut für Anorganische Chemie, Christian-Albrechts-Universität, Otto-Hahn-Platz 6/7, 24098 Kiel, Germany
[§]Clinic for Radiology and Neuroradiology, Arnold Heller Straße 3, 24105 Kiel, Germany

W *Web-Enhanced Feature* *S* *Supporting Information*

ABSTRACT: We present a fully reversible and highly efficient on−off photoswitching of magnetic resonance imaging (MRI) contrast with green (500 nm) and violet-blue (435 nm) light. The contrast change is based on intramolecular light-driven coordination-induced spin state switch (LD-CISSS), performed with azopyridine-substituted Ni-porphyrins. The 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 >100 000 switching cycles in air at room temperature. Electron-donating substituents at the pyridine improve the LD-CISSS in two ways: better photostationary states are achieved, and intramolecular binding is enhanced.

Magnetic resonance imaging (MRI) is one of the most important noninvasive 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, >200 million doses of MRI contrast agents (CAs) have been administered to patients worldwide.[1] Commercially available CAs are mainly gadolinium(III) chelate complexes.[2] With a spin of $S = {}^{7}/_{2}$, 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; therefore, after intravenous injection, the complexes stay mainly in the blood circuit, leading to 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 using responsive or "smart" CAs whose relaxivity (capability of reducing the relaxation time of surrounding nuclei) is controlled by metabolic parameters. The design of responsive CAs reporting on parameters such as temperature, pH, or biochemical markers is a subject of intensive research because they are potentially capable of visualizing the site of a disease in a magnetic resonance image. Research in this field started in the mid-1990s. Most of the approaches since then have been based on Gd(III) complexes whose relaxivity is controlled by controlling water coordination to the Gd^{3+} ion, which is the most efficient relaxation mechanism. A number of CAs were developed that respond to proteins and enzymes,[3] carbohydrates,[4] pH values,[5] and ions like Ca^{2+},[6] Zn^{2+},[7] $Cu^{+/2+}$,[8] and K^{+}.[9] A less intensively investigated stimulus is light. Functionalization of Gd(III) chelates with photochromic spiropyrans gave rise to relaxivity changes of ∼20%.[10] 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 blocking water access, still exhibits a residual relaxivity by outer-sphere relaxation (through-space magnetic dipole interaction), a diamagnetic transition metal complex with $S = 0$ is completely MRI silent. Thus, spin state switching 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).[11] The change in contrast so far is obtained by administering additional CAs each time this is required. After multiple injections, the CAs accumulate in the bloodstream to a level where they are harmful, and the contrast change is gradually lost. Light-sensitive CAs have the advantages that they need 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.[12] We now present a systematic improvement of the effect and demonstrate that it can be used to switch MRI contrast on and off.

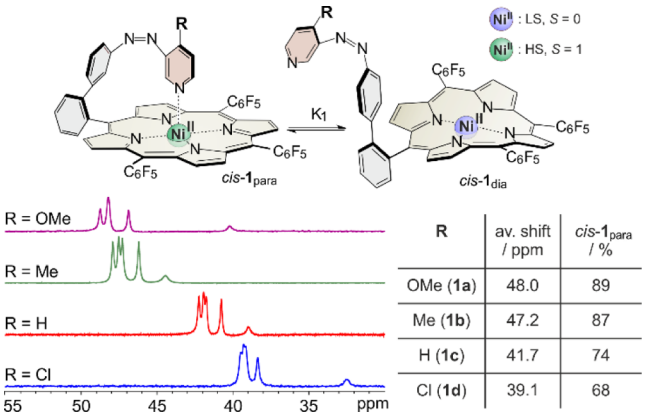
Addition of axial ligands to a solution of Ni-porphyrins results in a coordination-induced spin state switch (CISSS).[13] Upon increasing the coordination number (CN) from CN = 4 (no axial ligand, square planar, $S = 0$) to CN = 5 (one axial ligand, square pyramidal, $S = 1$) or CN = 6 (two axial ligands, square bipyramidal, $S = 1$), the Ni^{2+} ion is switched from diamagnetic (contrast off) to paramagnetic (contrast on). To achieve light-controlled addition and removal of axial ligands, we use a

Received: January 29, 2015
Published: April 27, 2015

DOI: 10.1021/jacs.5b00929
J. Am. Chem. Soc. 2015, 137, 7552−7555

photochromic azopyridine 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 the *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 named this approach the "record player" design, and the process is called light-driven, coordination-induced spin state switch (LD-CISSS). To achieve maximum efficiency in MRI contrast switching, every step in the cascade of events must be optimized: photoisomerization → coordination change → spin switch → MRI contrast change.

Even a perfect photoconversion between *trans* and *cis* isomers does not imply a complete change in CN. Incomplete intramolecular binding in the *cis* form, and intermolecular coordination of the *trans* isomer, particularly at higher concentrations, limit the efficiency. Previous work on our prototype system showed that the intramolecular coordination of the *cis* configuration is not complete.[11a] Obviously, there is a nonbinding conformation of the *cis* isomer with the azopyridine unit pointing away from the porphyrin ring that is in fast equilibrium (on the NMR time scale) with the binding conformation (Figure 1).[11b,12] It is known that the association



R	av. shift / ppm	*cis*-$\mathbf{1}_{para}$ / %
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*-$\mathbf{1}_{para}$ and the non-coordinated form *cis*-$\mathbf{1}_{dia}$ (top). From the chemical shifts of the pyrrole protons (average shift) in acetone-d_6 (bottom left), the percentage of paramagnetic Ni^{2+} (*cis*-$\mathbf{1}_{para}$) was calculated (bottom right).

constant of 4-substituted pyridines follows a Hammett relationship.[13c] To improve the intramolecular coordination, we therefore introduced electron-donating groups (Me and OMe) at the 4-position of the pyridine unit (for syntheses, see the Supporting Information (SI)).

To quantify intramolecular binding, the chemical shifts of pyrrole protons in the ^{1}H NMR spectra of **1a–d** were compared. We previously showed 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 and 53 ppm in pure pyridine-d_5 (complete axial coordination). Thus, the average chemical shift 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).

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

Obviously the pyridine substituent affects the axial binding to the Ni-porphyrin, but we were surprised to observe an improved photochemical *trans*/*cis* conversion as well. Irradiation of the *trans* isomers with 500 nm light (Q-bands of *trans* azoporphyrin **1a–d**: 523 and 557 nm) is most efficient to convert the *trans* to the *cis* isomer. This is surprising because the $\pi-\pi^*$ excitation that induces *trans*/*cis* isomerization in azobenzenes and azopyridines has a much shorter wavelength (~320 nm). The isomerization mechanism in our azoporphyrins 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.[14] To determine the *trans*/*cis* conversion rate, we used ^{1}H NMR spectroscopy. The protons on the phenyl ring in a position *meta* 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 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 of the amount of isomers, as 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*

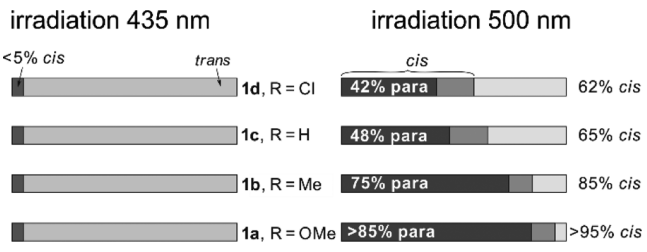


Figure 2. Photostationary states (% *cis* isomer) and percentage of paramagnetic Ni ions upon irradiation of solutions of **1a–d** in acetone-d_6 at 20 °C with 435 and 500 nm light. The *cis*/*trans* ratio and the percentage of paramagnetic Ni ions were determined by NMR spectroscopy (for details see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

isomer (Figure 1). Upon irradiation with 500 nm light, 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 light is quantitative within the detection limit of NMR (<5% remaining *cis*). Thus, overall conversion from the diamagnetic to the paramagnetic state improved considerably upon introduction of the methoxy substituent (**1a**, 85%) compared to the parent system (**1c**, 48%).

The systems were tested regarding their long-term switching stability. The methoxy-substituted derivative **1a** does not exhibit any fatigue after >100 000 switching cycles at room temperature under air (Figure 3). To test the stability of compounds **1a–c** in a biologically relevant environment, we treated them with a 10 mM solution of glutathione in acetonitrile/PBS buffer (1:1). We observed no reduction of the azo function and no degradation of the switching efficiency, which are requirements for in vivo applications.[15]

Crystals of the *cis* isomer of **1b** (R = Me) suitable for X-ray structure determination were obtained (Figure 4, left). The Ni center is complexed in a distorted octahedral coordination

DOI: 10.1021/jacs.5b00929
J. Am. Chem. Soc. 2015, 137, 7552–7555

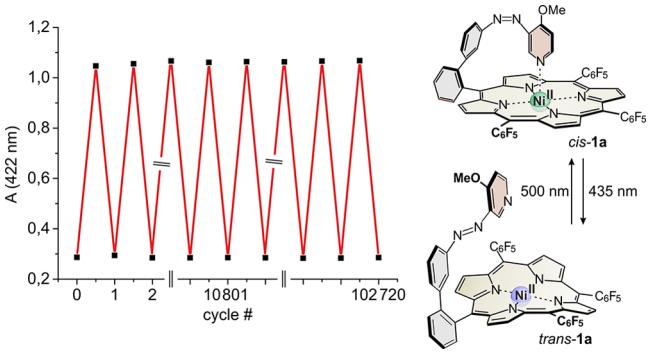


Figure 3. Long-term switching stability of **1a** (5.0 μM, MeCN, 20 °C) during alternating irradiation with 500 and 435 nm light. The UV–vis absorption at 422 nm is plotted as a function of the number of switching cycles.

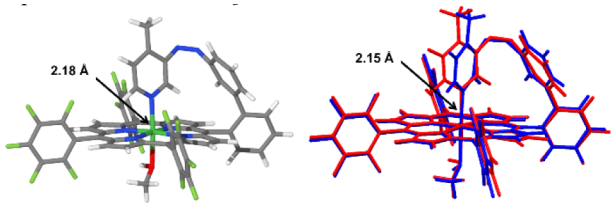


Figure 4. Crystal structure of *cis*-**1b** (left) and overlay of the crystal structure (red) and calculated structure (blue, PBE/SVP) (right).

geometry. The equatorial plane is formed by the porphyrin N-atoms with bond lengths ranging from 2.03 to 2.05 Å. The axial positions are occupied by the pyridine N-atom of the azopyridine and the O-atom of a methanol molecule, with longer distances of Ni–N = 2.18 Å and Ni–O = 2.27 Å. The Ni 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 root-mean-square deviation is 0.31 Å (for details see SI).

The application of the record player molecules **1a–c** as light-switchable CAs was investigated by MRI (3 and 7 T) and independently by NMR relaxation time measurements (200 MHz NMR). Switching between the diamagnetic and paramagnetic states in a homogeneous solution of **1a–d** allows us 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 435 and 500 nm light. As expected, the increased rate of conversion 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.

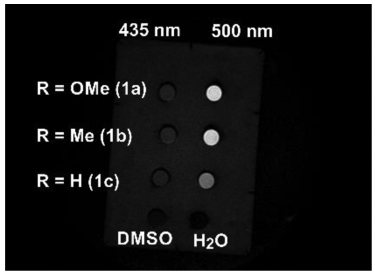


Figure 5. 3 T magnetic resonance image of 3 mM solutions of **1a–c** irradiated with 435 and 500 nm light. For details, see the SI.

The efficiency of paramagnetic ions for shortening 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 transverse (T_2) relaxation times. In the following we present results only for T_1 and R_1 because there are no significant differences to T_2 and R_2 in homogeneous solutions (see SI). The R_1 relaxivity was determined by relaxation time measurements at different CA 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 and 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_1/mM^{-1} s^{-1}	
R (compd)	at 500 nm	at 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 light increased by factors of 3.5, 5.3, and 6.7. Upon irradiation with 435 nm, the relaxivity drastically decreased again but was different from zero, probably due to some residual paramagnetism from intermolecular coordination. The absolute value of R_1 is lower by a factor of ~25 compared to that of standard Gd-CAs, 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}, good agreement with the literature (see SI).[16] To realize the switching in a physiological medium, we attach glycerol dendrimers to the *meso*-pentafluorophenyl substituents by nucleophilic aromatic substitution. It was already shown that this concept is applicable for symmetric porphyrins.[13d] 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 toward application of the switchable CAs, we performed the photoswitching 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 the accompanying video).

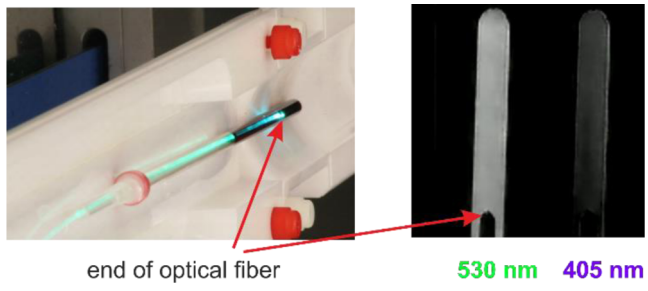


Figure 6. Experimental setup for the contrast switching in a 7 T MRI scanner (left). A 3 mM solution of **1c** was irradiated with 530 and 405 nm light, and MRI images were recorded after irradiation (right). A video that demonstrates MRI contrast switching is also available.

DOI: 10.1021/jacs.5b00929
J. Am. Chem. Soc. 2015, 137, 7552–7555

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 >2, and the relaxivity (R_1) of the contrast agent changes by a factor 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 that includes photoisomerization of an azopyridine ligand, coordination change at Ni^{2+}, spin switch, and 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 >100 000 switching cycles. The metastable *cis* form (contrast "on" state) has a half-life of >1 year at room temperature. Our light-driven coordination-induced spin state switch approach has the potential to provide the basis for the development of a number of interesting applications, including the design of temperature- or pH-responsive contrast agents for MRI. The latter would be useful to detect tumors because they exhibit a higher temperature and a lower pH than surrounding tissue.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectral data, details of computational studies, and crystallographic data. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b00929.

Ⓦ Web-Enhanced Feature

A video that demonstrates MRI contrast switching is available in the online version of this paper.

■ AUTHOR INFORMATION

Corresponding Author

*rherges@oc.uni-kiel.de

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors gratefully acknowledge funding from the collaborative research center SFB 677 Function by Switching. High field MRI measurements were performed at the Molecular Imaging North Competence Center, CAU, Kiel.

■ REFERENCES

(1) (a) Kulaksiz, S.; Bau, M. *Appl. Geochem.* **2011**, *26*, 1877. (b) Hao, D.; Ai, T.; Goerner, F.; Hu, X.; Runge, V. M.; Tweedle, M. *J. Magn. Reson. Imaging* **2012**, *36*, 1060.

(2) (a) Aime, S.; Botta, M.; Fasano, M.; Terreno, E. *Acc. Chem. Res.* **1999**, *32*, 941. (b) Caravan, P.; Ellison, J. J.; McMurry, T. J.; Lauffer, R. B. *Chem. Rev.* **1999**, *99*, 2293.

(3) (a) Touti, F.; Maurin, P.; Hasserodt, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 4654. (b) Louie, A. Y.; Huber, M. M.; Ahrens, E. T.; Rothbacher, U.; Moats, R.; Jacobs, R. E.; Fraser, S. E.; Meade, T. J. *Nat. Biotechnol.* **2000**, *18*, 321. (c) Duimstra, J. A.; Femia, F. J.; Meade, T. J. *J. Am. Chem. Soc.* **2005**, *127*, 12847. (d) Querol, M.; Chen, J. W.; Weissleder, R.; Bogdanov, A. *Org. Lett.* **2005**, *7*, 1719. (e) Giardiello, M.; Lowe, M. P.; Botta, M. *Chem. Commun.* **2007**, 4044. (f) Hanaoka, K.; Kikuchi, K.; Terai, T.; Komatsu, T.; Nagano, T. *Chem.—Eur. J.* **2008**, *14*, 987. (g) Mizukami, S.; Takikawa, R.; Sugihara, F.; Hori, Y.; Tochio, H.; Wälchli, M.; Shirakawa, M.; Kikuchi, K. *J. Am. Chem. Soc.* **2008**, *130*, 794.

(4) (a) Trokowski, R.; Zhang, S.; Sherry, A. D. *Bioconjugate Chem.* **2004**, *15*, 1431. (b) Aime, S.; Delli Castelli, D.; Fedeli, F.; Terreno, E. *J. Am. Chem. Soc.* **2002**, *124*, 9364.

(5) (a) Hall, J.; Häner, R.; Aime, S.; Botta, M.; Faulkner, S.; Parker, D.; de Sousa, A. S. *New J. Chem.* **1998**, *22*, 627. (b) Aime, S.; Crich, S. G.; Botta, M.; Giovenzana, G.; Palmisano, G.; Sisti, M. *Chem. Commun.* **1999**, 1577. (c) Zhang, S.; Wu, K.; Sherry, A. D. *Angew. Chem.* **1999**, *111*, 3382. (d) Lowe, M. P.; Parker, D.; Reany, O.; Aime, S.; Botta, M.; Castellano, G.; Gianolio, E.; Pagliarin, R. *J. Am. Chem. Soc.* **2001**, *123*, 7601. (e) Woods, M.; Kiefer, G. E.; Bott, S.; Castillo-Muzquiz, A.; Eshelbrenner, C.; Michaudet, L.; McMillan, K.; Mudigunda, S. D. K.; Ogrin, D.; Tircsó, G.; Zhang, S.; Zhao, P.; Sherry, A. D. *J. Am. Chem. Soc.* **2004**, *126*, 9248. (f) Tóth, E.; Bolskar, R. D.; Borel, A.; González, G.; Helm, L.; Merbach, A. E.; Sitharaman, B.; Wilson, L. J. *J. Am. Chem. Soc.* **2005**, *127*, 799. (g) De Leon-Rodriguez, L. M.; Lubag, A. J. M.; Malloy, C. R.; Martinez, G. V.; Gillies, R. J.; Sherry, A. D. *Acc. Chem. Res.* **2009**, *42*, 948.

(6) (a) Li, W.-h.; Fraser, S. E.; Meade, T. J. *J. Am. Chem. Soc.* **1999**, *121*, 1413. (b) Li, W.-h.; Parigi, G.; Fragai, M.; Luchinat, C.; Meade, T. J. *Inorg. Chem.* **2002**, *41*, 4018. (c) Dhingra, K.; Fousková, P.; Angelovski, G.; Maier, M. E.; Logothetis, N. K.; Tóth, E. *J. Biol. Inorg. Chem.* **2007**, *13*, 35. (d) Angelovski, G.; Fouskova, P.; Mamedov, I.; Canals, S.; Toth, E.; Logothetis, N. K. *ChemBioChem* **2008**, *9*, 1729. (e) Dhingra, K.; Maier, M. E.; Beyerlein, M.; Angelovski, G.; Logothetis, N. K. *Chem. Commun.* **2008**, 3444. (f) Mishra, A.; Fousková, P.; Angelovski, G.; Balogh, E.; Mishra, A. K.; Logothetis, N. K.; Tóth, E. *Inorg. Chem.* **2008**, *47*, 1370.

(7) (a) Hanaoka, K.; Kikuchi, K.; Urano, Y.; Nagano, T. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1840. (b) Major, J. L.; Parigi, G.; Luchinat, C.; Meade, T. J. *Proc. Natl. Acad. Sci. U.S.A.* **2007**, *104*, 13881. (c) Major, J. L.; Boiteau, R. M.; Meade, T. J. *Inorg. Chem.* **2008**, *47*, 10788.

(8) Que, E. L.; Gianolio, E.; Baker, S. L.; Wong, A. P.; Aime, S.; Chang, C. J. *J. Am. Chem. Soc.* **2009**, *131*, 8527.

(9) Hifumi, H.; Tanimoto, A.; Citterio, D.; Komatsu, H.; Suzuki, K. *Analyst* **2007**, *132*, 1153.

(10) (a) Tu, C.; Louie, A. Y. *Chem. Commun.* **2007**, 1331. (b) Tu, C.; Osborne, E. A.; Louie, A. Y. *Tetrahedron* **2009**, *65*, 1241.

(11) (a) Herges, R.; Jansen, O.; Tuczek, F.; Venkatamarani, S. Molecular Switch. Patent WO 2012022299 A1, Feb 23, 2012. (b) Herges, R.; Jansen, O.; Tuczek, F.; Venkatamarani, S. Photosensitive metal porphyrin complexes with pendant photoisomerizable chelate arm as photochromic molecular switches undergoing photoinduced spin transition. Patent DE 102010034 A1, Feb 16, 2012.

(12) (a) Venkataramani, S.; Jana, U.; Dommaschk, M.; Sönnichsen, F. D.; Tuczek, F.; Herges, R. *Science* **2011**, *331*, 445. (b) Dommaschk, M.; Schütt, C.; Venkataramani, S.; Jana, U.; Nather, C.; Sonnichsen, F. D.; Herges, R. *Dalton Trans.* **2014**, *43*, 17395.

(13) (a) Thies, S.; Sell, H.; Bornholdt, C.; Schütt, C.; Köhler, F.; Tuczek, F.; Herges, R. *Chem.—Eur. J.* **2012**, *18*, 16358. (b) Thies, S.; Sell, H.; Schütt, C.; Bornholdt, C.; Näther, C.; Tuczek, F.; Herges, R. *J. Am. Chem. Soc.* **2011**, *133*, 16243. (c) Thies, S.; Bornholdt, C.; Köhler, F.; Sönnichsen, F. D.; Näther, C.; Tuczek, F.; Herges, R. *Chem.—Eur. J.* **2010**, *16*, 10074. (d) Dommaschk, M.; Gutzeit, F.; Boretius, S.; Haag, R.; Herges, R. *Chem. Commun.* **2014**, *50*, 12476.

(14) Alcover-Fortuny, G.; de Graaf, C.; Caballol, R. *Phys. Chem. Chem. Phys.* **2015**, *17*, 217.

(15) (a) Samanta, S.; McCormick, T. M.; Schmidt, S. K.; Seferos, D. S.; Woolley, G. A. *Chem. Commun.* **2013**, *49*, 10314. (b) Yang, Y.; Hughes, R. P.; Aprahamian, I. *J. Am. Chem. Soc.* **2014**, *136*, 13190. (c) Samanta, S.; Beharry, A. A.; Sadovski, O.; McCormick, T. M.; Babalhavaeji, A.; Tropepe, V.; Woolley, G. A. *J. Am. Chem. Soc.* **2013**, *135*, 9777. (d) Kosower, E. M.; Kanety-Londner, H. *J. Am. Chem. Soc.* **1976**, *98*, 3001.

(16) (a) Vogler, H.; Platzek, J.; Schuhmann-Giampieri, G.; Frenzel, T.; Weinmann, H.-J.; Radbüchel, B.; Press, W.-R. *Eur. J. Radiol.* **1995**, *21*, 1. (b) Fenchel, M.; Franow, A.; Martirosian, P.; Engels, M.; Kramer, U.; Stauder, N. I.; Helber, U.; Vogler, H.; Claussen, C. D.; Miller, S. *Br. J. Radiol.* **2007**, *80*, 884.

DOI: 10.1021/jacs.5b00929
J. Am. Chem. Soc. 2015, 137, 7552−7555