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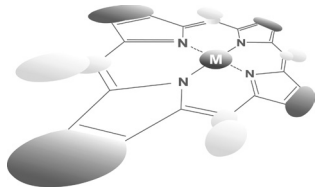

Ni(II)porphyrins as pH dependent light-driven coordination-induced spin-state switches (LD-CISSS) in aqueous solution

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Dedicated to Professor Atsuhiro Osuka on the occasion of his 65th birthday.

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ABSTRACT: A water-soluble Ni(II)-porphyrin substituted with a covalently attached azopyridine ligand was synthesized. Upon irradiation with violet and green light, the azo unit performs a reversible *cis–trans* isomerization. This geometry change triggers a coordination/de-coordination of the pyridine nitrogen at the central nickel(II) ion. The concomitant change in coordination number at the Ni ion in turn switches the spin state between high and low spin, a process we coined a "light-driven coordination-induced spin state switch (LD-CISSS). To increase the coordination power of the pyridine, particularly in aqueous environments, we introduced an electron donating OH group in 4-position. With increasing pH, the hydroxyl group is deprotonated, further enforcing coordination. We report on the properties of this pH-dependent spin switch, particularly the magnetic properties.

KEYWORDS: Ni(II)porphyrins, LD-CISSS, record player molecules, molecular spin switching, magnetic resonance imaging, water-soluble porphyrin, pH dependent contrast agent, longitudinal relaxivity.

INTRODUCTION

The light-driven spin switching of Ni-porphyrins in solution has been well-investigated and described in a number of publications [1–9]. Ni(II)-porphyrins are particularly suitable as molecular spin switches because they are always in the paramagnetic high-spin state ($S = 1$) in square pyramidal (one axial ligand) and square bipyramidal complexes (two axial ligands). The Ni^{2+} is always diamagnetic, low-spin ($S = 0$) in square planar complexes (no axial ligand) [10–14]. Changing between spin states by addition/removal of axial ligands was coined coordination-induced spin state switching (CISSS). If the ligands (de-) coordinate upon irradiation with light, the process is called light-driven coordination-induced spin-state switching (LD-CISSS) [3]. A promising application for these light-controlled spin switches are smart contrast agents (CA) for magnetic resonance imaging (MRI) [2, 7]. Paramagnetic salts or complexes (*e.g.* Gd^{3+} complexes, such as Gadobutrol®) decrease the water proton relaxation time, increase the MRI signal and enhance anatomical contrast. Consequently, a metal complex whose paramagnetism can be switched on and off with light could potentially be used as a switchable or responsive contrast agent.

Towards this end, the system has to meet some preconditions: The complex has to be soluble in water (blood), aggregation has to be prevented, and efficient spin switching in aqueous solution has to be achieved, leading to a shortened T_1 relaxation time of the water protons induced by the paramagnetic state of the complex.

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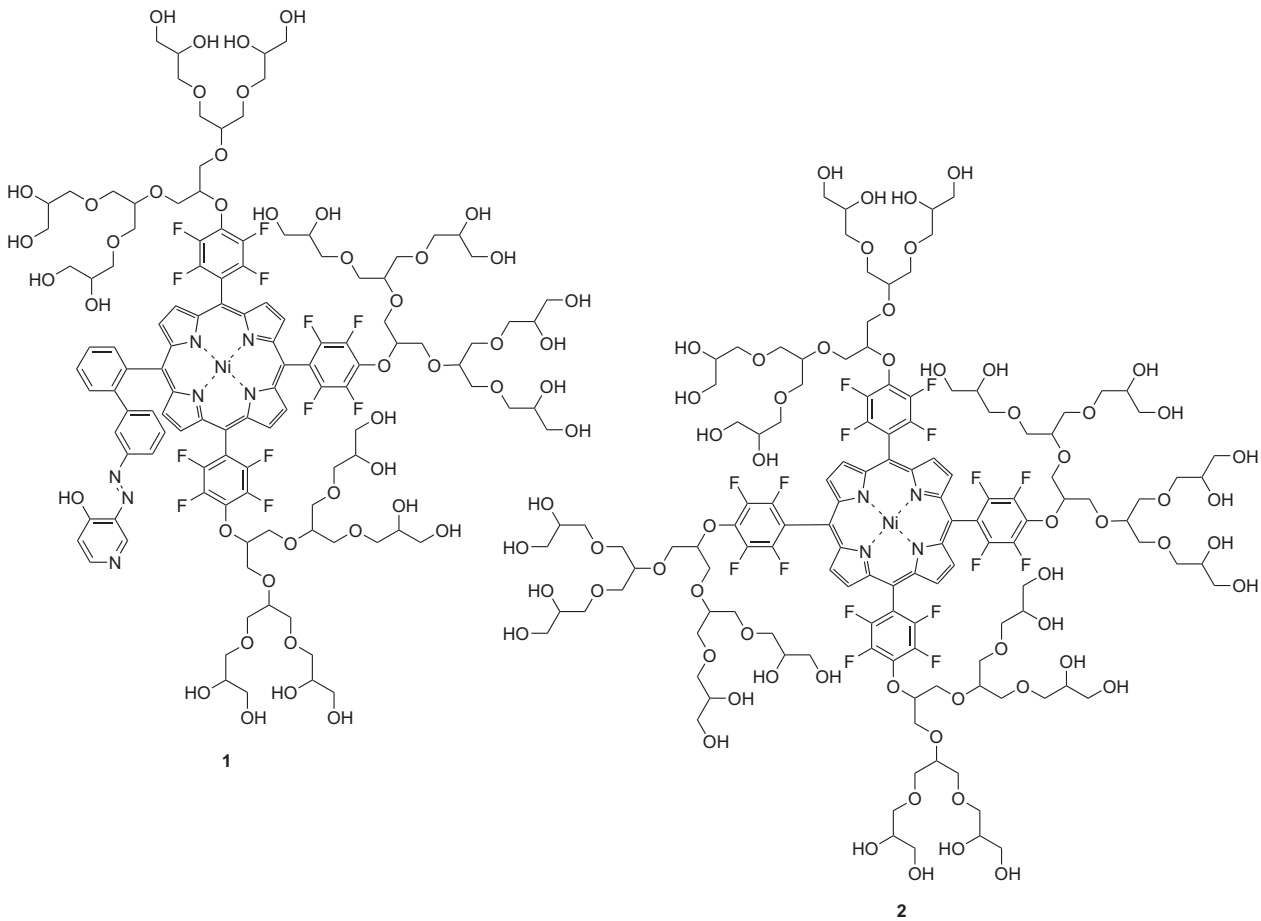
Very high spin-switching efficiencies (up to >98% conversion in both directions with 500 and 435 nm light) were achieved with the so-called record player (RP) design in organic solvents [9]. RP molecules consist of a Ni-porphyrin as a square planar base complex and a covalently attached azo heterocycle such as azopyridine [7, 8] or azoimidazole [15]. The latter act both as photoswitchable units and as (detachable) axial ligands. However, switching in water turned out to be a particularly persistent problem. Generally, solubility of porphyrins in water can be achieved with ionic substituents in *meso* position [16]. However, in our hands the frequently used phenylsulfonato or benzoato substituents, beyond providing hydrophilicity, are increasing the electron density of the Ni-porphyrin to such an extent that pyridine does not coordinate to the metal ion. Hence, the nickel ion always remains low-spin. On the other hand, alkylpyridinium or trialkyl anilinium substituents reduce the electron density, thereby increasing the coordination power of Ni^{2+}. Now even weak ligands, such as water coordinate permanently to the electron poor Ni-porphyrins, leading to a paramagnetic state and preventing a spin change to low-spin. Uncharged 2,3,5,6-tetrafluoro-phenyl substituents bearing glycerol dendrons in 4-position of the phenyl substituents turned out to exhibit just the balanced electronic nature to allow coordination of pyridines while avoiding coordination of water. However, after the pyridine coordinates as an axial ligand, the second axial coordination site is activated and a fast water exchange leads to an increased proton relaxation of the bulk water. The first CISSS in water was reported by Dommaschk *et al.* using a Ni-porphyrin with four dendritic glycerol substituents [17, 18]. Upon addition of an excess of piperidine, two molecules are bound as axial ligands, the coordination number changes from 4 to 6, and the spin switches from low- to high-spin (CISSS). Besides providing water solubility, the bulky dendron substituents completely prevent aggregation, even at high concentrations [18]. This approach was subsequently transferred to record player (RP) molecules [19]. As expected, the dendron substitution provides water solubility and prevents aggregation. However, switching to the high-spin state was completely inhibited. Obviously, in aqueous environment and in the presence of the dendrons, pyridine does not coordinate to the Ni^{2+} ion. Substitution of the pyridine with an electron donating methoxy group in 4 position (Hammett substituent constant of OMe: σ = -0.27) restores the switching capability; however the switching efficiency from low- to high-spin still remains quite low with 20%



Scheme 1. Structure of the title compound OH-G[2.0]-RP **1** and the reference structure $NiTPPF_{16}$-G[2.0] **2**

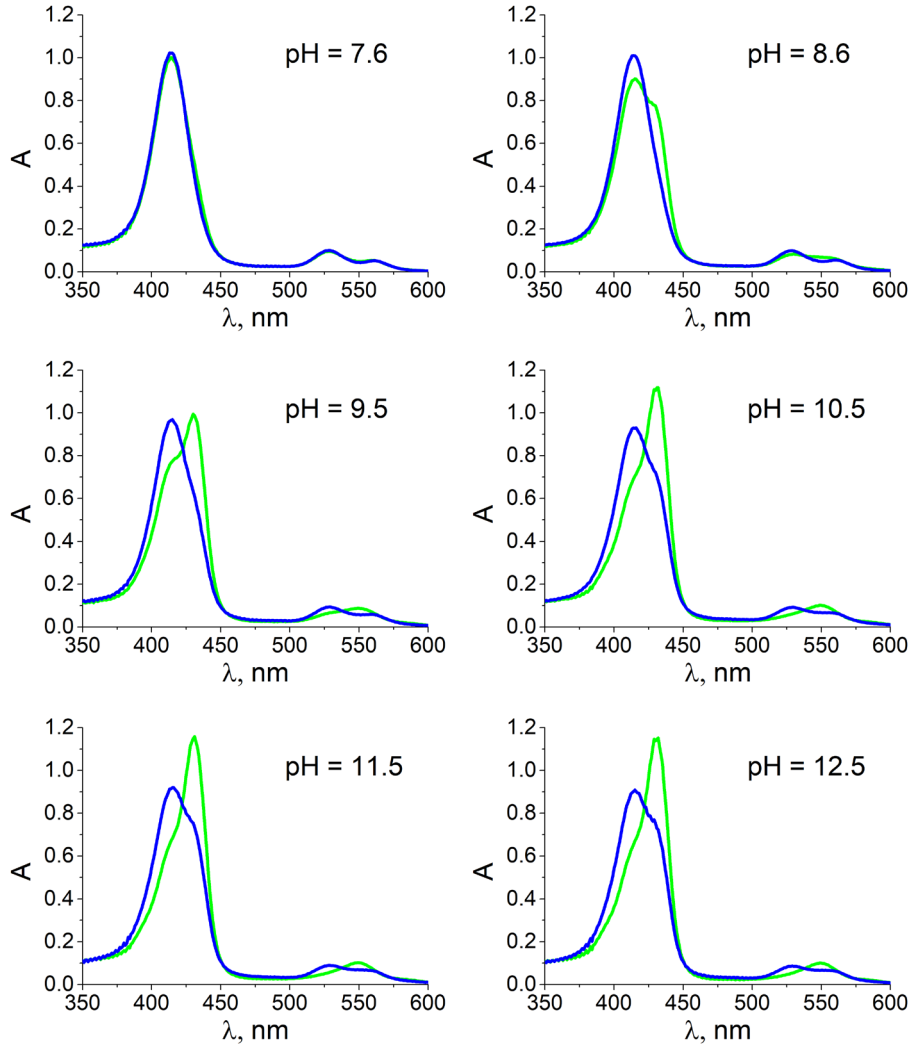


Fig. 1. UV-vis spectra of **1** in the PSS at 435 nm (blue) and 505 nm (green) at different pH values. The paramagnetic amount (green) increases for both PSS's upon increasing the pH of the solution

[19]. Following our observation that the coordination power (Lewis basicity) of 4-substituted pyridines to Ni-porphyrins strictly correlates with the Hammett parameter of the substituent [20], we now introduced an OH group (σ = -0.37) which after deprotonation (pK_a of 4-hydroxypyridine: 11.1 [21]) turns into an O^- group with a Hammett substituent constant of σ = -0.81. Hence, upon increasing pH the switching efficiency should increase substantially. We determined the switching efficiency as a function of pH and the T_1 relaxivity (r_1) of the complex in both switching states in NMR-experiments and in MRI-measurements.

RESULTS AND DISCUSSION

Prior to the examination of the pH dependent switching behavior of compound OH-G[2.0]-RP **1** we had to ensure that the used carbonate-bicarbonate buffer solutions and the hydroxyl ions would not influence the spin state of our Ni-porphyrin by coordination. Towards this end, we used the similarly structured water-soluble $NiTPPF_{16}$-G[2.0] **2** (Scheme 1) [8] dissolved in aqueous buffer or sodium hydroxide solutions and performed UV-vis and NMR measurements (Supporting information I). Compound **2** is a suitable model compound because it lacks an intramolecular ligand, which could coordinate to the Ni-porphyrin intra- or intermolecularly, so we only observe solvent effects. In UV-vis measurements, coordination would increase the absorbance for the paramagnetic porphyrin at 430 nm and 550 nm. In ^{1}H NMR experiments, the average shift of the pyrrole protons moves downfield with increasing percentage of the paramagnetic species [8]. As presented in Figs S1–S4, no effect was detected in the presence of hydroxide ions or in the carbonate-bicarbonate buffer. Obviously no coordination of water, hydroxide ions or buffer components occurs. Using ^{1}H NMR spectroscopy at a series of concentrations, we further proved that the water-soluble RP molecule **1** does not

undergo aggregation at higher concentrations and after deprotonation (Fig. S5 and Supporting information II).

***Switching of OH-G[2.0]-RP* 1**. The switching behavior of **1** was investigated by UV-vis spectroscopy (Supporting information III.) because the very large and broad ^{1}H NMR signal resulting from the stereogenic centers in the dendron substituents and the broadening of the signals due to paramagnetism rule out ^{1}H NMR spectroscopic analysis. Therefore, extinction coefficients of porphyrin **1** in the diamagnetic and paramagnetic spin state were recorded (Figs S6–S7). The ideal wavelengths for switching between the spin states with the highest photostationary states (PSS) were determined as 505 nm (to the paramagnetic state) and 435 nm (to the diamagnetic state), independent of the pH (Fig. S8). Molecule **1** is very robust and can be switched more than 700 times without significant loss of efficiency (Fig. S9). In aqueous solution, a strong pH dependence of the photostationary state (PSS) was observed. The amount of paramagnetic species after irradiation with 505 nm strongly increases by increasing the pH value but also the remaining amount of paramagnetic species after irradiation with 435 nm follows this tendency (Fig. 1). This was associated to the stronger coordination of the pyridine-O$^-$ compared to the pyridine-OH ligand in **1**. The amount of paramagnetic porphyrin was quantified from the UV-vis spectra by Equation S1 (Supporting information III) and plotted as a function of the pH of the solution (Fig. 2).

The optimal switching efficiency of about 40% between the PSS at 505 nm and the PSS at 435 nm was found above pH 10.5, which is close to the pK_a of 4-hydroxypyridine (11.1) [21]. At pH 11, irradiation with light of 505 nm (green) and 435 nm (violet-blue) switches between 69% and 26% paramagnetic nickel in solution.

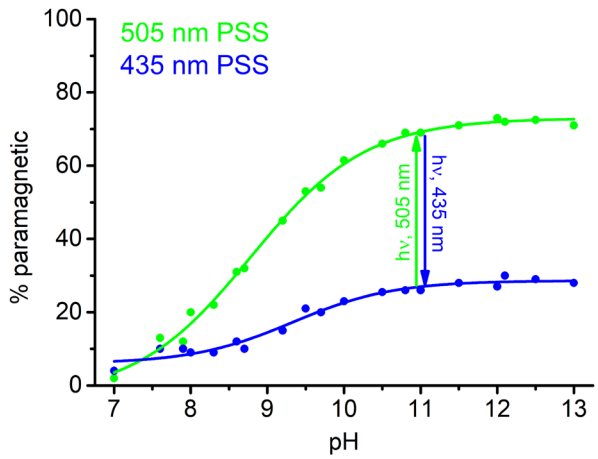


Fig. 2. Percentage of paramagnetic **1** in PSS at 435 nm (blue) and 505 nm (green) plotted as a function of the pH value in solution. The highest switching efficiency is about 40% (above pH 10.5). Note that there is always paramagnetic species remaining in solution after switching back to the diamagnetic state

T_1 relaxation. The longitudinal relaxivities (r_1) (T_1 proton relaxation times normalized to the concentration) [22] of OH-G[2.0]-RP **1** in both switching states were initially determined by ^{1}H NMR in D_2O (Fig. S10 and Supporting information IV), based on remaining traces of HDO and H_2O (note that these r_1 values cannot be directly compared to those measured in H_2O). A carbonate-bicarbonate buffer solution in D_2O (pH 11) was selected because the UV-vis experiments (Fig. 1) revealed a high switching efficiency at this pH. The relaxivity (r_1) of our complex **1** in D_2O buffer after irradiation with green light (505 nm) to the paramagnetic state is 0.026 $mm^{-1} \cdot s^{-1}$. After irradiation with blue light (435 nm) and switching to the diamagnetic state, a relaxivity (0.019 $mm^{-1} \cdot s^{-1}$) was detected (Fig. S11). The relaxivity of the frequently used clinical contrast agent gadobutrol (EuropePharmacopoeia (EP) Reference Standard) under the same conditions is 4.80 $mm^{-1} \cdot s^{-1}$ (Fig. S11). Hence, the relaxivity of **1** is quite small compared to the clinical contrast agent and the relaxivity switching is not efficient (factor 1.37).

Since proton relaxation times are difficult to measure in pure H_2O by ^{1}H NMR, we performed MRI measurements to investigate the longitudinal relaxivity (r_1) of OH-G[2.0]-RP **1** in water. A carbonate-bicarbonate buffer solution in H_2O (pH 10.6) was used to keep the system at an optimal pH for switching. The T_1 relaxivity after irradiation with 505 nm is 0.044 $mm^{-1} \cdot s^{-1}$ and after irradiation with 435 nm it is 0.035 $mm^{-1} \cdot s^{-1}$ (Fig. S12). For gadobutrol we determined the T_1 relaxivity as 6.23 $mm^{-1} \cdot s^{-1}$ under the same conditions in MRI (Fig. S12 and Supporting information IV.).

Similar to the measurements in D_2O, the absolute relaxivities (r_1) in H_2O, as well as the relaxation switching efficiency again are very small.

This observation is surprising because the relaxivities r_1 of Ni^{2+} salts with 0.78 $mm^{-1} \cdot s^{-1}$ and most Ni^{2+} complexes, (*e.g.* the EDTA complex: 0.11 $mm^{-1} \cdot s^{-1}$) are much higher than r_1 of **1** in its paramagnetic state (0.044 $mm^{-1} \cdot s^{-1}$). We attribute the low relaxivity of **1** to a blocking of the water coordination/decoordination (inner sphere relaxation mechanism). A fast water exchange at the coordination site (paramagnetic metal ion) is important for a bulk magnetic relaxation of water. The three glycerol dendron substituents with 24 OH groups and 27 ether oxygen atoms, obviously form a hydrogen bond network of solvated water around the metal center that prevents water exchange and bulk relaxation.

EXPERIMENTAL

Equipment

Detailed information on spectrometers, analytical instruments, irradiation modules and other equipment

used in this work are reported in the Supporting information (V).

Measurements

Detailed information on performed measurements are provided in the Supporting information. Scheme S1 (supporting information VI) shows the atom numbering and denotation of groups for NMR spectroscopy. The figures of NMR and MS-spectra are given in section VII of the Supporting information (Figs S13–S26).

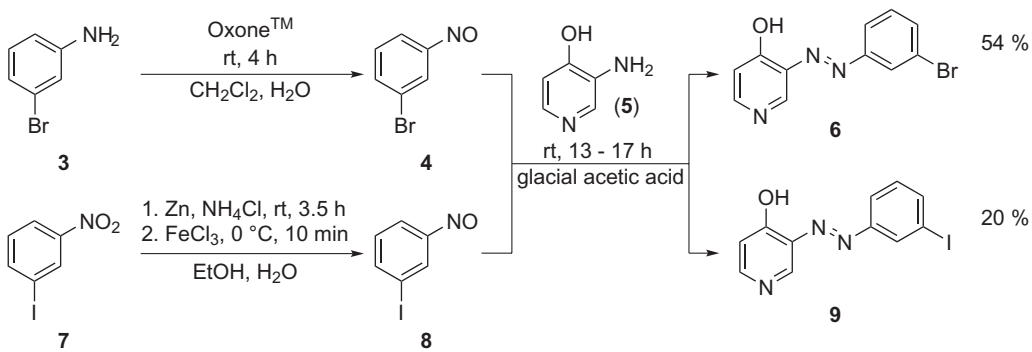
Synthesis

For the synthesis of Ni-porphyrin **15**, we performed a mixed-aldehyde approach described by Dommaschk *et al.* [7]. Azopyridines **6** and **9** were prepared in an acidic Baeyer–Mills reaction [23] (Scheme 2).

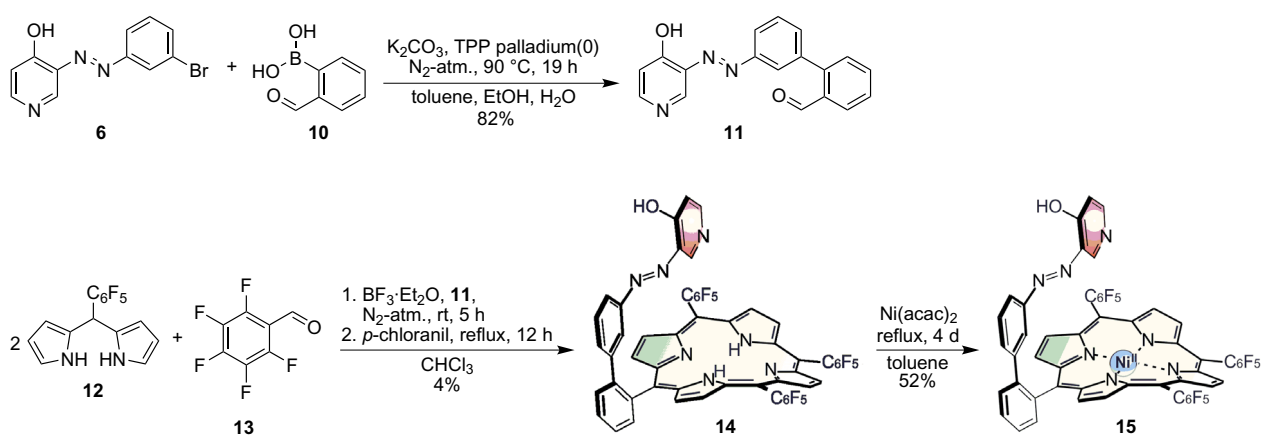
Azopyridine **6** was reacted in a Suzuki coupling reaction with 2-formylphenylboronic acid (**10**) to obtain aldehyde **11**, which was used to perform the mixed-aldehyde synthesis with *meso*-pentafluorophenyldipyrromethane (**12**) and pentafluorobenzaldehyde (**13**) to yield the metal-free porphyrin **14**. Ni(II) incorporation yielded Ni(II)-porphyrin **15** (Scheme 3).

To achieve water solubility of the Ni(II)-porphyrin **15** we used a method published by Dommaschk *et al.* [18] using dendrons synthesized as first described by Haag *et al.* [17]. Acidic cleavage of **16** gave the water-soluble porphyrin **1** (Scheme 4). As a reference for our measurements we also synthesized Ni(II)-$TPPF_{16}$-G[2.0] **2** as described by Dommaschk *et al.* [18].

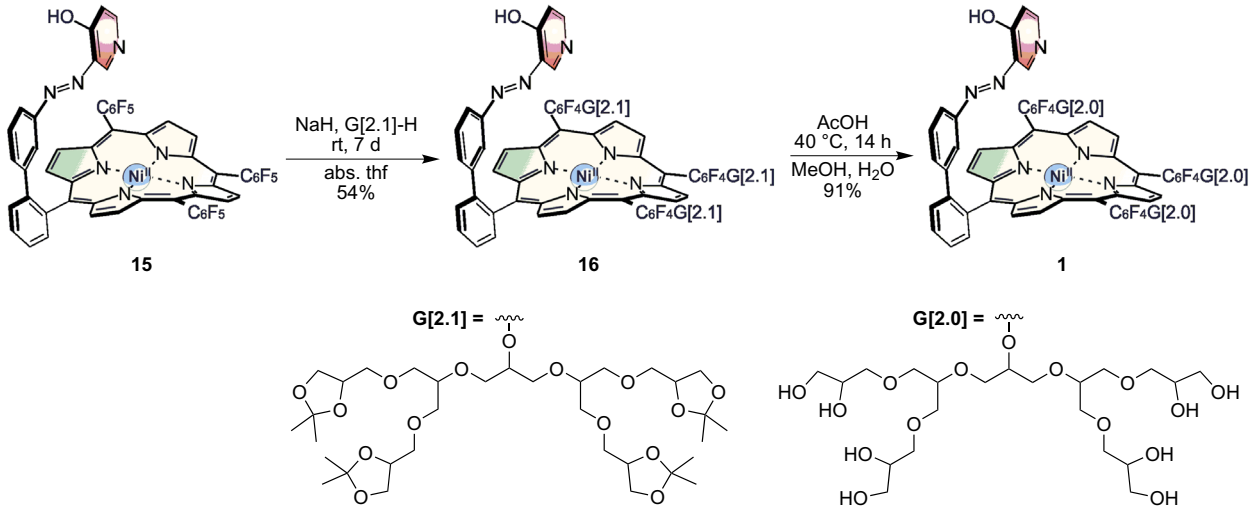
***Preparation of* 3-(3-*bromophenylazo*)-4-*hydroxypyridine* (6).** 3-Bromoaniline (7.90 g, 43.5 mmol, **3**) was dissolved in 150 mL of dichloromethane (DCM) and added to Oxone™ (66.3 g, 108 mmol) dissolved in 375 mL of deionized water. The two phases were vigorously stirred at ambient temperature for 4 h. The layers were separated and the aqueous layer was extracted twice with 50 mL of dichloromethane. The combined organic layer was dried over magnesium sulfate and the solvent was reduced *in vacuo* to about 10 mL which was filtered through a silica column with dichloromethane as eluent to remove unreacted starting material **3** (R_f (DCM) = 0.10). The solvent containing the green nitroso compound **4** (R_f (DCM) = 0.83) was reduced *in vacuo* to about 10 mL and added to 3-amino-4-hydroxypyridine (2.40 g, 21.3 mmol, **5**) dissolved in 400 mL of glacial acetic acid. The mixture was stirred for



Scheme 2. Synthesis of azopyridines **6** and **9** by conversion of nitroso compounds **4** and **8** with amine **5** in an acidic Mills reaction



Scheme 3. Synthesis of Ni(II)-porphyrin **15** performing a mixed-aldehyde approach described by Dommaschk *et al.* [7]



Scheme 4. Synthesis of the water-soluble Ni(II)-porphyrin **1**

17 h at ambient temperature. The solvent was removed under reduced pressure and the residue was co-distilled twice with 400 mL of toluene. The crude product was applied on silica and column chromatography on silica at biotage (SNAP Ultra 340 g, DCM/MeOH: 99:1 → 9:1, R_f (DCM/MeOH, 9:1) = 0.26) was performed. The product was obtained as an orange solid. Yield: 3.23 g (54%), mp 216 °C (decomposition). Anal. Calcd. for $C_{11}H_8BrN_3O$: C, 47.51; H, 2.90; N, 15.11%. Found: C, 47.59; H, 2.79; N, 15.08%. ^{1}H NMR (600 MHz; DMSO-d_6, TFA-d_1; 298 K; Me_4Si): δ_H, ppm 8.72 (1H, d, ^4J = 0.82 Hz, *H*-2), 8.48 (1H, dd, ^3J = 6.91 Hz, ^4J = 0.83 Hz, *H*-6), 8.12 (1H, t, ^4J = 1.85 Hz, *H*-8), 8.02 (1H, ddd, ^3J = 7.92 Hz, ^4J = 1.64 Hz, ^4J = 0.79 Hz, *H*-12), 7.84 (1H, ddd, ^3J = 7.92 Hz, ^4J = 1.73 Hz, ^4J = 0.79 Hz *H*-10), 7.63 (1H, t, ^3J = 7.92 Hz, *H*-11), 7.36 (1H, d, ^3J = 6.91 Hz, *H*-5). ^{13}C NMR (151 MHz, DMSO-d_6, TFA-d_1; 298 K, Me_4Si): δ_C, ppm 169.3 (1C, *C*-4), 153.0 (1C, *C*-7), 142.6 (1C, *C*-6), 138.2 (1C, *C*-3), 135.0 (1C, *C*-10), 132.1 (1C, *C*-2), 131.8 (1C, *C*-11), 124.2 (1C, *C*-12), 124.0 (1C, *C*-8), 122.8 (1 C, *C*-9), 117.2 (1C, *C*-5). FT-IR (ATR) ν, cm^{-1}: 3027, 2443, 2008, 1915, 1638, 1606, 1563, 1506, 1445, 1368, 1293, 1268, 1234, 1194, 1169, 1152, 1125, 1080, 1058, 1024, 993, 979, 937, 903, 887, 857, 815, 782, 758, 677, 645, 623, 598, 577, 566, 534, 510. UV-vis (Acetonitrile): λ_{max}, nm (log ε): 238 (3.87), 342 (3.78). HR-EI-MS (70 eV): *m/z* 276.98474 (calcd. for [M]$^+$ 276.98507).

***Preparation of* 4-*hydroxy*-3-(3-*iodophenylazo*)*pyridine* (9).** 1-Iodo-3-nitrobenzene (6.00 g, 24.1 mmol, **7**) and ammonium chloride (1.93 g, 36.2 mmol) were dissolved in ethanol (300 mL) and deionized water (36 mL) and stirred at 50 °C until the dispersion became a clear solution. After cooling to ambient temperature, zinc dust (5.51 g, 84.3 mmol) was added and the mixture was stirred for 3.5 h. After filtration, the filtrate was poured into an aqueous ice-cooled solution of iron(III) chloride (anhydr. 5.88 g, 36.2 mmol in 222 mL deion. water) whereby a green solid **8** precipitated. After 10 min of stirring, the solid was filtered off and washed with cold deionized water before adding glacial acidic acid (80 mL) and 3-amino-4-hydroxypyridine (690 mg, 6.26 mmol, **5**) and stirring for 13 h at ambient temperature. The solvent was removed *in vacuo* and the residue was co-distilled with toluene (3 × 150 mL). The crude product was purified by column chromatography on silica (DCM/MeOH, 96:4, R_f = 0.25) to yield an orange solid. Yield: 410 mg (20%), mp 210 °C (decomposition). Anal. Calcd. for $C_{11}H_8IN_3O$: C, 40.64; H, 2.48; N, 12.93%. Found: C, 40.92; H, 2.47; N, 12.76%. ^{1}H NMR (500 MHz; DMSO-d_6, TFA-d_1; 298 K; Me_4Si): δ_H, ppm 8.77 (1H, d, ^4J = 1.15 Hz, *H*-2), 8.56 (1H, dd, ^3J = 6.87 Hz, ^4J = 1.19 Hz, *H*-6), 8.30 (1H, t, ^4J = 1.75 Hz, *H*-8), 8.05 (1H, ddd, ^3J = 7.95 Hz, 4J = 1.77 Hz, ^4J = 0.94 Hz, *H*-12), 8.00 (1H, ddd, ^3J = 7.86 Hz, ^4J = 1.60 Hz, ^4J = 1.00 Hz, *H*-10), 7.47 (1H, t, ^3J = 7.94 Hz, *H*-11), 7.47 (1H, d, ^3J = 6.87 Hz, *H*-5). ^{13}C NMR (125 MHz, DMSO-d_6, TFA-d_1; 298 K, Me_4Si): δ_C, ppm 169.1 (1C, *C*-4), 152.9 (1C, *C*-7), 143.0 (1C, *C*-6), 141.1 (1C, *C*-10), 138.1 (1C, *C*-3), 132.3 (1C, *C*-2), 131.9 (1C, *C*-11), 130.1 (1C, *C*-8), 124.8 (1C, *C*-12), 116.9 (1C, *C*-5), 95.7 (1C, *C*-9). FT-IR (ATR) ν, cm^{-1}: 3007, 2897, 2247, 1630, 1558, 1528, 1506, 1433, 1398, 1356, 1272, 1236, 1195, 1165, 1119, 1052, 1034, 993, 922, 907, 886, 838, 805, 782, 752, 683, 674, 642, 591, 564, 525, 504. HR-EI-MS (70 eV): *m/z* 324.97144 (calcd. for [M]$^+$ 324.97120).

***Preparation of* 3-(3-(2-*formylphenyl*)*phenylazo*)-4-*hydroxypyridine* (11).** Under an atmosphere of nitrogen, toluene (65.5 mL), ethanol (22.5 mL) and deionized water (400 µL) were flushed with nitrogen for 1 h. 3-(3-Bromophenyl)azo-4-hydroxypyridine (2.17 g, 7.80 mmol, **6**), 2-formylphenylboronic acid (1.29 g, 8.60 mmol, **10**), potassium carbonate (3.56 g, 25.8 mmol) and tetrakis(triphenylphosphine)palladium(0) (991 mg, 857 µmol) were added and stirred for 19 h at 90 °C. The

mixture was diluted with dichloromethane (150 mL) and deionized water (150 mL) and neutralized. The layers were separated and the aqueous layer was extracted with dichloromethane (3 × 100 mL). The combined organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo*. The crude product was absorbed on silica and column chromatography on silica (SNAP Ultra 340 g, DCM/MeOH: 99:1 → 9:1, R_f (DCM/MeOH, 85:15) = 0.56) was performed. The product was obtained as an orange solid. Yield: 1.93 g (82%), mp 211 °C (decomposition). Anal. Calcd. for $C_{18}H_{13}N_3O_2$: C, 71.28; H, 4.32; N, 13.85%. Found: C, 70.31; H, 4.37; N, 13.67%. ^{1}H NMR (500 MHz, DMSO-d_6, TFA-d_1; 298 K, Me_4Si): δ_H, ppm 9.98 (1H, s, CO*H*), 8.87 (1H, d, ^4J = 1.15 Hz, *H*-2), 8.63 (1H, dd, ^3J = 6.85 Hz, ^4J = 1.15 Hz, *H*-6), 8.12 (1H, dt, ^3J = 7.75 Hz, ^4J = 1.62 Hz, *H*-12), 8.07 (1H, t, ^4J = 1.57 Hz, *H*-8), 8.01 (1H, dd, ^3J = 7.66 Hz, ^4J = 1.14 Hz, *H*-15), 7.82 (1H, td, ^3J = 7.50 Hz, ^4J = 1.41 Hz, *H*-16), 7.79 (1H, t, ^3J = 7.62 Hz, *H*-11), 7.75 (1H, dt, ^3J = 7.55 Hz, ^4J = 1.37 Hz, *H*-10), 7.69–7.65 (1H, m, *H*-17), 7.62 (1H, dd, ^3J = 7.68 Hz, ^4J = 0.78 Hz, *H*-18), 7.51 (1H, d, ^3J = 6.85 Hz, *H*-5). ^{13}C NMR (125 MHz, DMSO-d_6, TFA-d_1; 298 K, Me_4Si): δ_C, ppm 191.4 (1C, *C*OH), 168.1 (1C, *C*-4), 151.5 (1C, *C*-7), 143.5 (1C, *C*-13), 142.7 (1C, *C*-6), 138.9 (1C, *C*-9), 137.5 (1C, *C*-3), 133.9 (1C, *C*-10), 133.9 (1C, *C*-16), 133.2 (1C, *C*-14), 132.1 (1C, *C*-2), 130.8 (1C, *C*-18), 129.6 (1C, *C*-11), 128.4 (1C, *C*-17), 127.9 (1C, *C*-15), 123.7 (1C, *C*-8), 123.4 (1C, C-12), 116.1 (1C, *C*-5). FT-IR (ATR) ν, cm^{-1}: 3027, 2597, 1993, 1685, 1633, 1598, 1558, 1520, 1505, 1455, 1411, 1372, 1291, 1274, 1244, 1199, 1184, 1174, 1154, 1102, 1031, 1000, 943, 900, 843, 815, 771, 743, 726, 663, 647, 619, 600, 572, 540, 506. UV-vis (acetonitrile): λ_{max}, nm (log ε): 232 (4.35), 342 (4.11). HR-EI-MS (70 eV): *m/z* 303.10050 (calcd. for $[M]^+$ 303.10078).

***Preparation of metal-free porphyrin* 14.** 3-(3-(2-Formylphenyl)phenylazo)-4-hydroxypyridine (365 mg, 1.18 mmol, **11**), pentafluorobenzaldehyde (230 mg, 1.18 mmol, **13**) and boron trifluoride diethyl etherate (341 mg, 2.40 mmol) were dissolved under an atmosphere of nitrogen in chloroform (250 mL). *meso*-Pentafluorophenyldipyrromethane (733 mg, 2.35 mmol, **12**) was dissolved in chloroform (20 mL) and added over a period of 30 min. After 5 h of stirring at ambient temperature, *p*-chloranil (606 mg, 2.85 mmol) was added and refluxed for 12 h. The cold mixture was filtered through Celite®, the solvent was removed *in vacuo* and the crude product was purified by column chromatography on silica (cyclohexane/ethyl acetate, 6:1, R_f = 0.13). The product was obtained as a red solid. Yield: 51.7 mg (4%). ^{1}H NMR (500 MHz, acetone-d_6; 300 K, Me_4Si): δ_H, ppm 9.25 (4H, s, β-pyrrolic-*H*-3/4), 9.18 (2H, s, β-pyrrolic-*H*-2), 9.11 (2H, s, β-pyrrolic-*H*-1), 8.41 (1H, s, *H*-2), 8.36 (1H, d, ^3J = 7.67 Hz, *H*-15), 8.24 (1H, d, ^3J = 5.76 Hz, *H*-6), 8.07 (1H, t, ^3J = 7.70 Hz, *H*-17), 8.01 (1H, d, ^3J = 7.87 Hz, *H*-18), 7.92 (1H, t, ^3J = 7.49 Hz, *H*-16), 7.86 (1H, t, ^4J = 1.70 Hz, *H*-8), 7.21 (1H, d, ^3J = 7.88 Hz, *H*-10), 7.08 (1H, d, ^3J = 7.96 Hz, *H*-12), 6.76 (1H, d, ^3J = 5.76 Hz, *H*-5), 6.64 (1H, t, ^3J = 7.95 Hz, *H*-11). ^{19}F NMR (471 MHz, acetone-d_6; 300 K): δ_F, ppm -139.55– -140.16 (6F, *ortho-F*), -155.71– -155.75 (3F, *para*-F), -164.34– -164.88 (6F, *meta-F*). MALDI-TOF-MS (Cl-CCA): *m/z* 1082 (calcd. for $[M + H]^+$ 1082).

***Preparation of Ni-porphyrin* 15.** Metal-free porphyrin **14** (46.0 mg, 42.6 μmol) and nickel(II) acetylacetonate (87.5 mg, 699 μmol) were dissolved in toluene (40 mL) and refluxed for 4 d. The solvent was removed *in vacuo* and the crude product was purified by column chromatography on silica (chloroform, R_f = 0.15). The product was obtained as a red solid. Yield: 28.5 mg (52%), mp > 300 °C. ^{1}H NMR (500 MHz, acetone-d_6, TFA-d_1; 298 K, Me_4Si): δ_H, ppm 9.15 (4H, s, β-pyrrolic-*H*-3/4), 9.06 (2H, d, ^3J = 5.00 Hz, β-pyrrolic-*H*-2), 9.00 (2H, d, ^3J = 5.00 Hz, β-pyrrolic-*H*-1), 8.93 (1H, d, ^4J = 1.25 Hz, *H*-2), 8.81 (1H, dd, ^3J = 6.96 Hz, ^4J = 1.25 Hz, *H*-6), 8.38 (1H, dd, ^3J = 7.66 Hz, ^4J = 1.30 Hz, *H*-15), 8.03 (1H, td, ^3J = 7.71 Hz, ^4J = 1.32 Hz, *H*-17), 7.92 (1H, td, ^3J = 7.70 Hz, ^4J = 1.16 Hz, *H*-16), 7.90 (1H, dd, ^3J = 7.71 Hz, ^4J = 1.14 Hz, *H*-18), 7.77 (1H, t, ^4J = 1.75 Hz, *H*-8), 7.58 (1H, d, ^3J = 6.96 Hz, *H*-5), 7.21 (1H, ddd, ^3J = 7.98 Hz, ^4J = 1.75 Hz, ^4J = 1.02 Hz, *H*-10), 7.15 (1H, ddd, ^3J = 7.98 Hz, ^4J = 1.99 Hz, ^4J = 1.02 Hz, *H*-12), 6.74 (1H, t, ^3J = 7.98 Hz, *H*-11). ^{19}F NMR (471 MHz, acetone-d_6, TFA-d_1; 298 K): δ_F, ppm -138.67– -139.63 (6F, *ortho-F*), -154.42–-154.66 (3F, *para-F*), -163.14–-163.68 (6F, *meta-F*). FT-IR (ATR) ν, cm^{-1}: 2923, 2853, 2361, 1343, 1610, 1518, 1489, 1344, 1159, 1052, 987, 955, 937, 799, 726, 709, 695, 660,585. UV-vis (acetonitrile): λ_{max}, nm (log ε): 406 (5.20), 524 (4.08), 556 (3.92). MALDI-TOF-MS (Cl-CCA): *m/z* 1138 (calcd. for $[M + H]^+$ 1138). HR-ESI-MS: *m/z* 1136.07898 (calcd. for [M – H]- 1136.07705).

***Preparation of Ni-porphyrin-G*[2.1] 16.** In flame-dried glassware under nitrogen atmosphere, sodium hydride (42.2 mg, 1.05 mmol) and G[2.1]-H dendron (147 mg, 211 μmol) were suspended/dissolved in dry tetrahydrofuran (THF, 40 mL) and stirred for 30 min at ambient temperature. Ni-porphyrin **15** (40.0 mg, 35.1 μmol) was added and stirred for 7 d at ambient temperature. The mixture was diluted with deionized water, dichloromethane and a saturated solution of sodium chloride (each 50 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2 × 25 mL). The combined organic layer was dried over magnesium sulfate and the solvent was removed *in vacuo*. The crude product was purified by column chromatography on silica (toluene/diethyl ether/ethanol, 45:45:10, R_f = 0.24) to obtain a red oil. Yield: 65.0 mg (58%). ^{1}H NMR (500 MHz, acetone-d_6, TFA-d_1; 298 K, Me_4Si): δ_H, ppm 9.08–8.93 (8H, m, β-pyrrolic-*H*-1/2/3/4), 8.92 (1H, s, *H*-2) 8.78 (1H, d, ^3J = 6.11 Hz, *H*-6), 8.42–8.31 (1H, m, br, *H*-15), 7.99 (1H, t, ^3J = 7.81 Hz, *H*-17), 7.90 (1H, d, ^3J = 6.65 Hz, *H*-18), 7.97 (1H, t, ^3J = 6.40 Hz, *H*-16), 7.73 (1H, s,

br, *H*-8), 7.54 (1H, d, ^3J = 6.15 Hz, *H*-5), 7.22–7.09 (3H, m, *H*-10/11/12), 4.39–3.22 (105H, m, G[2.1]-C*H*/H_2), 1.38–1.25 (72H, m, G[2.1]-CH_3). ^{19}F NMR (471 MHz, acetone-d_6; 298 K): δ_F, ppm -139.90–-142.70 (6F, *ortho-F*), -155.71–-157.52 (6F, *meta-F*). MALDI-TOF-MS (IAA): *m/z* 3189 (calcd. for $[M + Na]^+$ 3189). HR-ESI-MS: *m/z* 3165.22998 (calcd. for $[M–H]^-$ 3165.23693).

***Preparation of Ni-porphyrin-G*[2.0] 1.** Ni-Porphyrin-G[2.1] **16** (61.7 mg, 19.5 μmol) was dissolved in a mixture of methanol (14.4 mL), glacial acetic acid (14.4 mL) and deionized water (7.2 mL) and stirred for 14 h at 40 °C. The solvent was removed *in vacuo* and the product was purified by washing with deionized water (4 × 200 mL) in Satorius Vivaspin 15R (2000 MWCO) centrifuge tubes in a Hettich Universal 320 centrifuge to obtain a red oil. Yield: 47.5 mg (91%). ^{1}H NMR (600 MHz, acetone-d_6, TFA-d_1; 298 K, Me_4Si): δ_H, ppm 9.12–8.86 (9H, m, β-pyrrolic-*H*-1/2/3/4, *H*-2), 8.79 (1H, s, *H*-6), 8.48–8.34 (1H, m, br, *H*-15), 8.01 (1H, t, ^3J = 7.40 Hz, *H*-17), 7.92 (1H, t, ^3J = 7.24 Hz, *H*-16), 7.88 (1H, d, ^3J = 7.20 Hz, *H*-18), 7.75 (1H, s, br, *H*-8), 7.60–7.51 (1H, m, br, *H*-5), 7.25–6.98 (H, m, br, *H*-10/12), 6.82–6.54 (1H, m, br, *H*-11), 4.99–3.45 (129H, m, G[2.0]-C*H*/H_2/O*H*). ^{19}F NMR (471 MHz, acetone-d_6, TFA-d_1; 298 K): δ_F, ppm -139.86–-142.52 (6F, *ortho-F*), -155.51–-157.66 (6F, *meta-F*). MALDI-TOF-MS (IAA): *m/z* 2687 (calcd. for $[M+H]^+$ 2687). HR-ESI-MS: *m/z* 1364.93567 (calcd. for $[M+COO]^{2-}$ 1364.93032).

CONCLUSION

A photoswitchable water-soluble Ni(II) porphyrin spin switch (**1**) was successfully synthesized and characterized. Water solubility was achieved by substitution with hydrophilic glycerol dendrons in the *meso* positions of the porphyrin. The pH dependence of the switching behavior was investigated and the relaxivity (r_1) was determined by ^{1}H NMR spectroscopy and MRI measurements. Switching of the central nickel ion between high-spin (S = 1) and low-spin (S = 0) in water was achieved by irradiation with green and blue light. The switching efficiency at pH 11 is 40% and thus higher than in previously published Ni-complexes. However, with r_1 = 0.044 $mm^{-1} \cdot s^{-1}$ the relaxivity of the title compound **1** in the paramagnetic state is considerably lower than r_1 in nickel salts or most other paramagnetic Ni complexes. We attribute the low relaxivity to blocking of the water exchange at the central nickel ion by the bulky glycerol dendron substituents. Obviously, the 24 OH groups and 27 ether oxygen atoms of the dendron substituents stabilize a quite rigid water solvation shell around the central nickel ion, preventing the inner shell relaxation mechanism. Further developments of transition metal porphyrins towards water soluble MRI contrast agents have to take this problem into account. Sulphated glycerol dendrons could provide a remedy to this problem [24].

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Supporting information

Coordination of solvents, experiments to determine aggregation of porphyrin, UV-vis experiments, relaxation time experiments, equipment, atom numbering and denotation of groups and NMR and MS spectra are given in the supplementary material. This material is available free of charge *via* the Internet at http://www.worldscinet.com/jpp/jpp.shtml.

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