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Coordination-Induced Spin-State-Switch (CISSS) in water†

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We present a non-ionic water-soluble porphyrin that does not exhibit measurable aggregation even at high concentrations in water. The spin state of the corresponding nickel(II) complex changes from completely diamagnetic (low-spin) to paramagnetic (high-spin) upon addition of a strong axial ligand. This leads to a strongly reduced NMR relaxation time of the water protons even at low concentrations of the complex.

Ni-porphyrins are of strong interest for spin switching in solution.^{1–6} Square planar complexes are diamagnetic (low-spin, $S = 0$) while square pyramidal and square bipyramidal (distorted octahedral) complexes are paramagnetic (high-spin, $S = 1$). The transition between the two spin states was coined Coordination Induced Spin-State-Switch (CISSS). Until now this process was limited to organic solutions because porphyrins with the required electronic properties are not soluble in water. We present here the first dendronized porphyrin which undergoes a CISSS in water.

Most of the known water-soluble porphyrins bear solubilizing groups in the *meso* position. They are either anionic Ph-SO₃[−] (TPPS),^{7,8} Ph-COO[−] (TPPC),^{9–12} or cationic Ph-NMe₃⁺ (TAPP),^{13,14} Py-Me⁺ (*o*-, *m*-, *p*-TMPyP)^{8,15,16} or tetrafluoro-Ph-NMe₃⁺ (TAPPF₁₆)^{17,18} or they are equipped with neutral hydrophilic groups. None of the corresponding ionic Ni-porphyrins provides the required electronic environment for a CISSS (Fig. 1). Ni(II) complexes of TPPS, TPPC, and TAPP do not coordinate even strong axial ligands in water because they are too electron rich, whereas *o*-, *m*-, *p*-TMPyP and TAPPF₁₆ are so electron deficient that even water is coordinating.^{17–20} So far there is no known Ni-porphyrin that is completely diamagnetic in water (no coordination of water as the axial ligand) but which is still

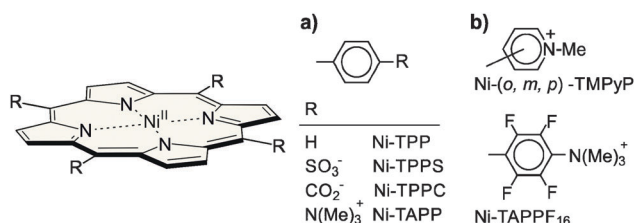


Fig. 1 Ni-tetraphenylporphyrin TPP and some water-soluble derivatives. (a) Electron rich porphyrins which do not bind axial ligands in water (diamagnetic). (b) Electron deficient porphyrins which bind water (partially paramagnetic in water).

sufficiently reactive for binding stronger ligands such as piperidine or 1-methylimidazole.

Non-ionic water-soluble porphyrins are gaining interest because they possess advantages in photooxygenation and photodynamic therapy (PDT).^{21,22} Water solubility was achieved by substitution with ethylene glycols,^{23,24} carbohydrates,^{25–28} and polyhydroxyamides.²⁹ Griesbeck *et al.* synthesized water-soluble TPP derivatives decorated with polyols.³⁰ Our approach is based on a different kind of polyols namely the dendritic glycerol. It has been shown that these groups are suitable for water solubilisation of organic compounds.^{31–33} In addition it has been demonstrated that oligoglycerol dendrons can provide sufficient shielding to prevent aggregation of planar perylene dye molecules and enhance their quantum yields to almost 100%.^{34,35}

We report here on the functionalisation of the established porphyrins TPPF₂₀ (1)³⁶ and Ni-TPPF₂₀ (2)⁵ with the second generation glycerol (G[2.0]-OH), and we present the properties of the corresponding water-soluble porphyrins. TPPF₂₀ (1) instead of TPP was chosen as the starting material because it is substantially more electron deficient, which is necessary to achieve axial coordination. Moreover, it is known that amines, alcoholates and thiolates can be introduced into the *para*-phenyl position by nucleophilic aromatic substitution which is a simple and efficient way of functionalisation.^{17,18,25,27,28} The second generation glycerol (G[2.0]-OH) was synthesised according to a procedure of Haag *et al.* as described previously.³² The reaction scheme of the functionalisation procedure

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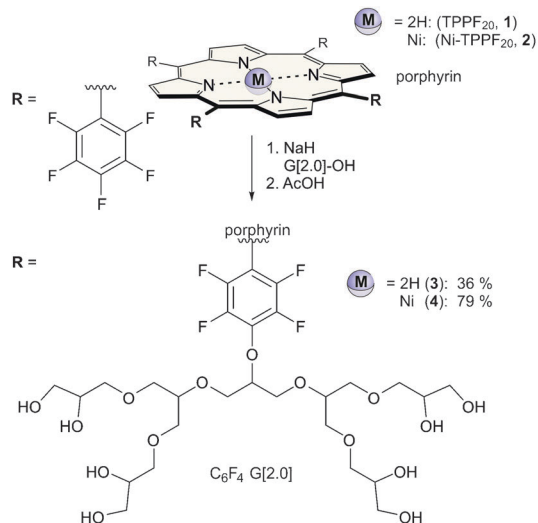


Fig. 2 Syntheses of the glycerol functionalised porphyrins **3** and **4**. Experimental details are given in the ESI†

is shown in Fig. 2. Deprotection of the 32 alcohol functions was achieved quantitatively with acetic acid (Fig. 2).

In contrast to many other water-soluble porphyrins^{8,14,28,37} the glycerol functionalised derivatives **3** and **4** do not exhibit aggregation or excimer formation which is probably due to the large steric hindrance of the polyols.^{34,35} Solutions of **3** and **4** perfectly follow the Lambert–Beer law up to a concentration of 50 μ M. NMR experiments do not show any changes in the line shape suggesting that there is no aggregation even at concentrations of 0.8 mM (see ESI†).

Compound **4** in water exhibits a Soret band at 409 nm, which is indicative of a diamagnetic low-spin state. Addition of piperidine gives rise to a new band at 428 nm due to axial coordination and the associated spin state switch to the high-spin triplet state (Fig. 3).

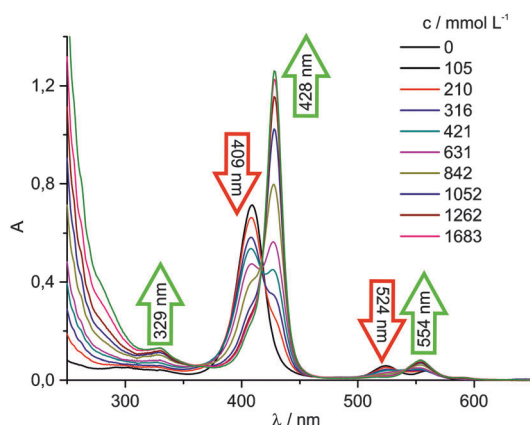


Fig. 3 UV-Vis spectra (top) of titration series of piperidine to Ni-porphyrin **4** (4.05 μ M, 20 °C) in water. Association constants for addition of one piperidine ligand ($K_1 = 0.48$ L mol⁻¹), and the association of a second piperidine ligand ($K_2 = 14.7$ L mol⁻¹) were determined from the UV-visible data (see ESI†). The green arrows correspond to increasing absorption upon increasing piperidine concentration.

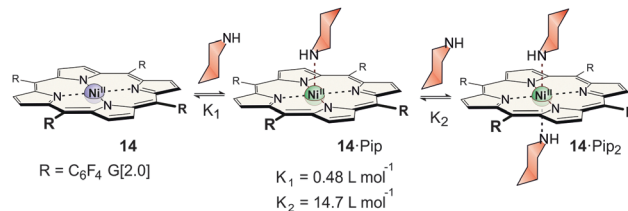


Fig. 4 Formation of the square pyramidal (**4-Pip**) and the square bipyramidal complexes (**4-Pip**₂).

The titration experiment reveals very low values for the association constants (K_1 , K_2) (Fig. 4, for details see the ESI†) compared to the values for Ni-TPPF₂₀ (**2**) obtained in organic solution by similar experiments.^{3–5} Water is an adverse solvent for axial coordination because it reduces the donor strength of ligands by hydrogen bonding. Nevertheless, the association constants obtained for piperidine are higher than those for many alkyl- and aryl-substituted Ni-porphyrins in organic solution.^{38–42} Except for very strong donor ligands, and very electron poor porphyrins, K_1 is known to be much smaller than K_2 .^{17,41,42} Spin change occurs upon binding of the first axial ligand which in turn activates the second axial binding site. Usually, the predominant species, therefore, is the 2:1, square bipyramidal complex. This is in agreement with our findings: K_2 is approximately 30 times larger than K_1 (see ESI†).

Both magnetic species exhibit different ¹H NMR spectra, and their relative ratio can be quantified using ¹H NMR spectroscopy. Ligand exchange is fast on the NMR time scale, and an averaged shift of high-spin and low-spin species is observed at room temperature. Particularly, the chemical shift of the pyrrole protons is an excellent indicator of the ratio of high and low-spin Ni(II) in solution.^{2–5} In pure complex **4** these protons resonate at 9.1 ppm, which is typical for a completely diamagnetic Ni-porphyrin. Upon addition of piperidine (~1000 eq.), the corresponding peak is shifted downfield to 52.7 ppm which is the chemical shift of the pure triplet Ni-porphyrin. Hence, the molecule has almost completely switched to the high-spin state (Fig. 5).

Paramagnetic metal ions are known to decrease the proton relaxation time of the surrounding water molecules.⁴³ Gd³⁺ complexes (7 unpaired electrons), therefore, are widely used

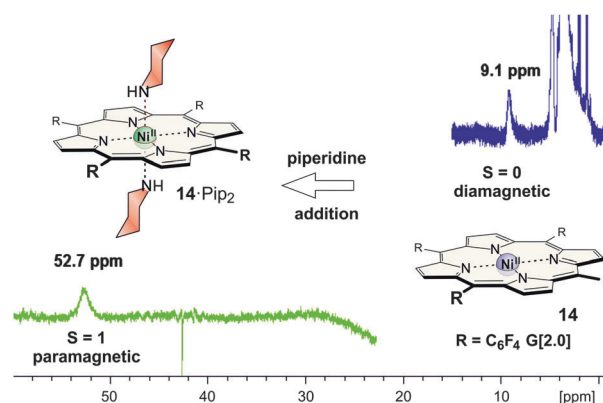


Fig. 5 NMR spectra (D₂O, 500 MHz, $T = 300$ K) of Ni-porphyrin **4** (0.8 mM) before (blue) and after (green) addition of piperidine.



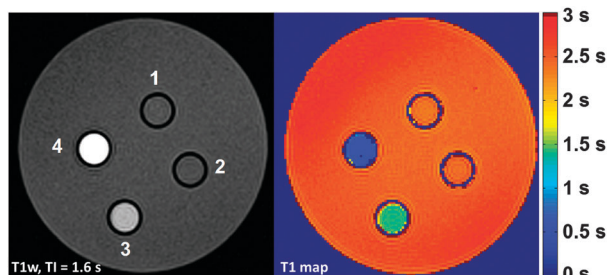


Fig. 6 MR images of 4 different solutions: 1. **4** (2 mM in water), 2. water, 3. water + 20% piperidine and 4. **4** (2 mM in water + 20% piperidine). For details see ESI.†

as contrast agents in magnetic resonance imaging (MRI).⁴⁴ Ni-porphyrin **4** in water is diamagnetic and inactive as a MRI contrast agent which is shown by 7 T MR images (note that nickel salts such as NiCl₂·6H₂O are paramagnetic). Upon addition of piperidine as a strong axial ligand the complex changes to the paramagnetic state ($S = 1$) and the contrast is turned on (Fig. 6). In a 2 mM solution in water the relaxation rate thereby rises from 0.71 s^{-1} (water + 20% piperidine) to 1.96 s^{-1} (factor ~ 2.8). The relaxivity (effectiveness in reducing the relaxation time of water protons, r_1) of the paramagnetic complex **4**-Pip₂ ($0.63 \text{ mM}^{-1} \text{ s}^{-1}$) is slightly lower than r_1 of Ni²⁺ salts (aquo complex: $0.78 \text{ mM}^{-1} \text{ s}^{-1}$) but is much higher than for other nickel complexes (e.g. EDTA complex: $0.11 \text{ mM}^{-1} \text{ s}^{-1}$). The MR images demonstrate that porphyrins such as **4** could be viewed as a first step towards the development of responsive contrast agents.^{45,46}

A neutral, water-soluble, oligoglycerol dendron substituted Ni-porphyrin was synthesised whose spin state was switched from completely diamagnetic (low-spin) to paramagnetic (high-spin) by addition of piperidine. Both, the Ni-porphyrin and the free base are easily accessible in a two-step procedure from commercially available starting materials. No aggregation or excimer formation was observed even at high concentrations in water. The hydrophilic Ni-porphyrin complex is an excellent candidate for spin switching in water. The longitudinal relaxivity r_1 of the paramagnetic state which is unusually high for an $S = 1$ complex ($0.63 \text{ mM}^{-1} \text{ s}^{-1}$) and the spin switching mechanism could provide a basis for responsive contrast agents for MRI. The metal-free porphyrin should be suitable for applications such as photooxidation or photodynamic therapy in physiological environments.

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