

Synthesis of μ₂-Oxo-Bridged Iron(III) Tetraphenylporphyrin– Spacer–Nitroxide Dimers and their Structural and Dynamics Characterization by using EPR and MD Simulations

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Abstract: Iron(III) porphyrins have the propensity to form μ_2 oxo-dimers, the structures of which resemble two wheels on an axle. Whereas their crystal structure is known, their solution structure and internal dynamics is not. In the present work, the structure and dynamics of such dimers were studied by means of electron paramagnetic resonance (EPR) spectroscopy and quantum chemistry based molecular dynamics (MD) simulations by using the semiempirical tightbinding method (GFN-xTB). To enable EPR investigation of the dimers, a nitroxide was attached to each of the tetraphenylporphyrin cores through a linear and a bent linker. The inter-nitroxide distance distributions within the dimers were determined by continuous-wave (cw)-EPR and pulsed electron–electron double resonance (PELDOR or DEER) experiments and, with the help of MD, interpreted in terms of the rotation of the porphyrin planes with respect to each other around the Fe–O–Fe axis. It was found that such rotation is restricted to the four registers defined by the phenyl substituents. Within the registers, the rotation angle swings between 30° and 60° in the proximal and between 125° and 145° in the distal register. With EPR, all four angles were found to be equally populated, whereas the 30° and 145° angles are strongly favored to the expense of the 60° and 125° angles in the MD simulation. In either case, the internal dynamics of these dimers thus resemble the motion of a step motor.

Introduction

Porphyrins are heterocyclic organic compounds that display a large variability of molecular structures and physicochemical properties.^[1,2] The variability of porphyrin structures is achieved in several different ways, for instance, by metalation of the macrocycle core, alteration of peripheral substituents, or linkage of multiple macrocycles together. This provides a large playground for designing new materials with desired properties and, hence, causes tremendous interest for porphyrins in different fields of natural sciences and chemical engineering.^[2] The most common porphyrins include tetraphenylporphyrin (TPP) and octaethylporphyrin (OEP). Both have a singlet ground spin state, but can be photoexcited to a paramagnetic

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triplet spin state.^[3] This allows such porphyrins to be studied by time-resolved electron paramagnetic resonance (EPR) techniques^[4] and even to be considered for the role of spin labels for biomolecules.^[5] Furthermore, the porphyrin core can also host a number of different metal ions, such as Mg²⁺, Zn²⁺, Cu²⁺, Mn²⁺/Mn³⁺, Fe²⁺/Fe³⁺, or Co²⁺/Co³⁺.^[2] As several of these ions are paramagnetic, the corresponding metalloporphyrins can be studied by EPR.^[6] For instance, the EPR studies on iron porphyrins and their biological counterparts, known as hemes, has helped a lot in understanding the biological processes taking place in hemoproteins.^[7] Because of the increasing importance of pulsed EPR techniques for distance measurements in structural biology,^[8] metalloporphyrins^[9-14] or other metal complexes^[15-18] are also used as model systems to test such distance measurements to metal centers.

Previous studies on iron porphyrins revealed their interesting tendency to form dimeric species, in which the iron ions in two TPP rings are connected with each other through an oxygen atom.^[14, 19–21] This phenomenon is usually called μ_2 -oxodimerization. Many previous publications have dealt with the identification and structural characterization of such μ_2 -oxobridged Fe³⁺ porphyrins owing to their interesting physicochemical properties, such as their catalytic activity in oxidizing alkanes.^[22, 23] In some cases, the dimerization process was found to be reversible: treating the monomeric porphyrins with an aqueous basic solution resulted in formation of μ_2 oxo-bridged dimers, whereas the analogous treatment of the



dimers with an aqueous acidic solution led to the breakup into monomeric species.^[14] The presence of μ_2 -oxo-bridged dimers in solution was proven by several methods, for example, electrospray ionization (ESI) mass spectrometry^[23-25] and ultraviolet-visible (UV/Vis) spectroscopy.^[26] The UV/Vis spectra of Fe³⁺ porphyrins contain a Soret band, which corresponds to electronic transitions within the porphyrin, as well as several Q bands, which originate from charge transfer between the porphyrin and the Fe³⁺ ion. Upon μ_2 -oxo dimerization, a characteristic shift of the Soret band towards lower wavelengths as well as significant changes within the Q bands occur. These changes cause the observable difference in the color of the monomeric (green) and dimeric (red) Fe³⁺ porphyrins dissolved in organic solvents. Crystallographic studies on μ_2 -oxobridged FeTPPs revealed that the two TPP cores are almost coplanar, that the dihedral angle between them is only 3.7°, and that they form a staggered configuration with a twist angle of 54.6°.^[27] The two Fe–O bonds are 1.763 Å long and form an almost linear bridge between the porphyrins with an Fe-O-Fe angle of 174°. Although this crystallographic data provides a clear picture of the static molecular structure of μ_2 -oxo-bridged FeTPPs, its structure and dynamics in solution is unclear.

In the present study, the synthesis of two differently bridged Fe^{III}TPP/nitroxide pairs **1**·Cl and **2**·Cl (Figure 1) is described and their μ_2 -oxo-dimerization is confirmed. Different molecular linkers were used for the two porphyrins with the aim of disentangling the effect of these linkers on the dynamics of the μ_2 -oxobridged TPP cores. The TPP rotamer dynamics within the dimers in solution is unraveled by using a combination of EPR spectroscopy and molecular dynamics (MD) simulations based



Figure 1. Synthesis of model compounds 1-Cl and 2-Cl. a) $Zn(OAc)_2$, $CH_2Cl_2/MeOH$ (1:1), r.t., 16 h, quant. b) 4-Hydroxy-4'-azidobiphenyl, $CuSO_4$, sodium ascorbate, DMSO/H₂O (10:1), 70 °C, 72 h, 95%. c) HCl, CH_2Cl_2 , r.t., 5 min, 93%. d) FeCl₂, THF, 80 °C, 2 h, 66%. e) 2,2,5,5-Tetramethyl-3-pyrrolin-1-oxyl-3-carboxylic acid, CMPI (2-chloro-1-methylpyridinium iodide), DMAP, Et₃N, CH_2Cl_2 , r.t., 18 h, 78%. f) [Pd(PPh₃)₄], Et₃N, 70 °C, 4 h, 59%. g) FeCl₂, THF, 70 °C, 2 h, 91%.

on the semiempirical tight-binding method GFN-xTB.^[28] These data show that such dimers maybe regarded as molecular step motors.

Results and Discussion

Synthesis

The linkage of the FeTPPCI to a nitroxide through a connecting bridge was achieved by two alternative synthetic routes depicted in Figure 1. The concept of click chemistry^[29] was used to synthesize compound 1-Cl, whereas Sonogashira-Hagihara coupling^[9] was adopted to obtain compound 2. Cl. Both syntheses make use of porphyrin 3 as a precursor, which was obtained in accordance with previous publications.^[30-33] For compound 1.Cl, zinc porphyrin 4 was generated by treating porphyrin 3 with zinc acetate. This step allows the incorporation of Cu²⁺ into the porphyrin core to be avoided during the click reaction performed later on. Next, the copper(I)-catalyzed azide alkyne cycloaddition (CuAAC)^[34] reaction of **4** with 4azido-4'-hydroxybiphenyl, obtained from 4-iodo-4'-hydroxy-biphenyl by an Ullmann-type reaction, [35] was carried out to yield porphyrin 5. Note that it was also possible to perform these two subsequent reactions in one pot starting from 4-iodo-4'hydroxybiphenyl and generating the azide in situ by using Cul in DMSO as the copper(I) source for the Ullmann step. Subsequently, the zinc ion of 5 was removed by hydrochloric acid, which resulted in porphyrin **6**. The Fe^{3+} -chlorido center was incorporated into **6** by reaction with Fe²⁺-chloride. This reaction was carried out in THF in the presence of oxygen. Note that these conditions are much milder than the ones proposed by Adler et al.,^[36] who used DMF at 150 °C as a solvent. The obtained iron porphyrin 7 was then used for Mukaiyama esterification^[37] with 2,2,5,5-tetramethyl-3-pyrrolin-oxyl-3-carboxylic acid, which provided the final compound 1.Cl. An overall yield of 9% was achieved for 1.Cl starting from 3. For compound 2-Cl, a more divergent approach was realized. First, Sonogashira-Hagihara coupling of 3 with the nitroxide-labeled biphenyl 8^[9,10] was carried out to provide porphyrin 9. Finally, the Fe^{3+} ion was introduced into **9** by the same procedure as described above for compound 7. This gave an overall yield of 6% for porphyrin 2.Cl. The μ_2 -oxo-bridged dimers 1_2 .O and $\mathbf{2}_2$ ·O were obtained upon treatment with aqueous sodium hydroxide (see Experimental Section for details). The reversibility of the dimerization process was tested by treatment of these dimers with aqueous hydrochloric acid, which yielded the monomeric porphyrins 1-Cl and 2-Cl again. Both monomers **1**·Cl and **2**·Cl as well as dimers 1_2 ·O and 2_2 ·O were analyzed by mass spectrometry, UV/Vis, and EPR spectroscopy.

Mass spectrometry

2

The MALDI mass spectra of compounds 1-Cl and 2-Cl revealed that they undergo partial dimerization during or after the synthesis, probably upon exposure to air moisture. However, significant dimerization of 1-Cl and 2-Cl could be detected only after base treatment. The MALDI mass spectra of the base-

Chem. Eur. J. **2019**, 25, 1–12

www.chemeurj.org



treated porphyrins are depicted in Figure 2. These spectra display intense peaks at m/z = 2154.6 for $1_2 \cdot O$ and m/z = 2068.6for 2_2 ·O, respectively. The peaks correspond to the dimers of 1.Cl and 2.Cl in which the Fe³⁺ ions lost their chloride ligands and are bridged to each other through an oxygen atom. In addition, both spectra contain two minor peaks, which appear at m/z = 1069.3 and 1104.3 in the case of the sample derived from 1·Cl and at m/z = 1026.3 and 1061.3 in that derived from 2. Cl. These peaks are assigned to the monomeric porphyrins with and without the chloride atom occurring as $[M^*]^+$ and $[M-CI]^+$ respectively. Each of the MALDI mass spectra of the acid-treated samples of the dimeric porphyrins shows only the two peaks of the corresponding monomeric porphyrins listed above but no peaks of the μ_2 -oxo-bridged dimers. Although MALDI mass spectra do not provide a quantitative estimate for the relative amount of detected species, it seems that the acid treatment leads to quantitative conversion into monomers, whereas the base treatment forms dimers but monomers can still be detected. An additional peak at m/z = 2133.7 for $2_2 \cdot O$ can be assigned to a reduced adduct with H₂O and Na⁺, which has the composition $[(2-CI)_2 \cdot O + 4H_2O + Na]^+$.



Figure 2. MALDI mass spectra of a) μ_2 -oxo-bridged dimer 1_2 ·O (black) and monomer 1·Cl (red) and b) μ_2 -oxo-bridged dimer 2_2 ·O (black) and monomer 2·Cl (red). For the sake of comparison, the spectra of 1·Cl and 2·Cl are plotted inverted.

Chem. Eur. J. **2019**, 25, 1–12

www.chemeurj.org

3

UV/Vis spectroscopy

As a means of reference, UV/Vis spectra of the monomers 1.Cl and 2.Cl were measured first (Figure 3). Both spectra display a Soret band at 422 nm and Q-bands at 372, 508, 573, and 689 nm. These values are in agreement with those found earlier for the Fe(TPP)Cl complex dissolved in toluene.[38] The UV/Vis spectra of the dimers 1_2 ·O and 2_2 ·O show the expected shift of the Soret band to shorter wavelengths, 415 nm for 1_2 ·O and 413 nm for 2_2 ·O, and the expected change in the Qbands, showing now only two bands at 571 and 612 nm in the 1_2 ·O sample and at 573 and 613 nm in the 2_2 ·O sample. Such differences were previously reported in the literature and were assigned to μ_2 -oxo-dimerization of Fe³⁺ porphyrins.^[26,39] Note that these changes in the Q-bands lead to the noticeable difference of the color of their solutions. The toluene solutions of dimeric porphyrins 1_2 ·O and 2_2 ·O feature a greenish color, whereas their monomeric counterparts have a reddish color.



Figure 3. UV/Vis spectra of a) 1_2 -O (black) and 1-Cl (red) and b) 2_2 -O (black) and 2-Cl (red). The insets show the magnified region of the Q-bands.

Continuous-wave (cw)-EPR spectroscopy

Both porphyrins 1-Cl and 2-Cl contain paramagnetic centers, the nitroxide and the Fe³⁺ center, and thus can be investigated by means of continuous-wave EPR (cw-EPR) spectroscopy.



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As the relaxation rates of both spin centers differ, the cw-EPR experiments on the porphyrin samples were performed at two different temperatures, at 10 K for the Fe^{3+} center (Figure 4) and at 100 K for the nitroxide (Figure 5).



Figure 4. X-band cw-EPR spectra of a) 1_2 ·O (black) and 1·Cl (red) and b) 2_2 ·O (black) and 2·Cl (red). All spectra were recorded at 10 K.

Figure 4 depicts the cw-EPR spectra of the monomeric (1.Cl and 2·Cl) and dimeric $(1_2 \cdot O \text{ and } 2_2 \cdot O)$ porphyrins recorded at 10 K. Both monomers, 1.Cl and 2.Cl display an intense peak at g = 5.92, which proves that the Fe³⁺ ions are in the high-spin state.^[40,41] The other component of the axial spectrum of highspin Fe³⁺ ions usually appears at $q \approx 2$, but is overplayed by the more intense nitroxide spectrum. In the dimer samples 1_2 ·O and 2_2 ·O, the line at g = 5.92 almost disappears, whereas the nitroxide spectrum preserves the intensity observed in the acid-treated samples. The disappearance of the high-spin Fe³⁺ signal in 1_2 ·O and 2_2 ·O can be attributed to the strong antiferromagnetic exchange interaction between two μ_2 -oxo-bridged Fe^{3+} ions, which results in a total spin of S = 0.^[21] By comparing the integral intensities of the high-spin Fe³⁺ signal in 1.Cl and 1_2 ·O, as well as in 2·Cl and 2_2 ·O, the amount of the monomeric porphyrins in the samples of 1_2 ·O and 2_2 ·O was estimated to be 6% in the case of 1_2 . O and 3% in the case of 2_2 . These values reveal that the base treatment led to efficient formation



Figure 5. X-band cw-EPR spectra of the nitroxide at 100 K. a) The reference spectrum of nitroxide **8** is overlaid with the spectra of **1**-Cl and **2**-Cl. b) The spectrum of **1**₂-O is overlaid with the spectrum of **1**-Cl. The inset shows the magnified part of the spectra, in which the strong dipolar couplings of the nitroxides in **1**₂-O manifest themselves (marked by asterisk). The simulation of the **1**₂-O spectrum is depicted by a blue dashed line. c) The spectrum of **2**₂-O is overlaid with the strong dipolar couplings of the nitroxides in **2**₂-O manifest themselves (marked by asterisk). The simulation of the spectra, in which the strong dipolar couplings of the nitroxides in **2**₂-O manifest themselves (marked by asterisk). The simulation of the **2**₂-O spectrum is depicted by a blue dashed line.

of the μ_2 -oxo-bridged porphyrins independently of the type of the molecular bridge between the porphyrin core and the nitroxide group.

Chem. Eur. J. 2019, 25, 1–12 www

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4



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The 100 K nitroxide spectra of all four porphyrins samples as well as the spectrum of nitroxide 8 are depicted in Figure 5. The nitroxide spectra of the monomeric porphyrins 1.Cl and 2.Cl have, at the same concentration and within the same solvent, very similar shapes and linewidths as the spectrum of the uncoupled nitroxide 8 (Figure 5a). This reveals that the highspin Fe³⁺ in 1·Cl and 2·Cl, which is roughly 25 Å apart from the nitroxide center (see computational results below), has a negligible effect on the nitroxide spectrum at the given temperature. The nitroxide spectra of 1_2 ·O and 2_2 ·O are similar to 1-Cl and 2-Cl in shape and linewidth, but they have additional broad signals on both sides of the nitroxide spectrum (asterisk in the insets in Figures 5 b,c). These signals result from the pairs of nitroxides, which experience a strong dipolar coupling between each other owing to their proximity in the structure of some of the μ_2 -oxo-bridged dimers (see below). The strong dipolar coupling between the pairs of nitroxide centers leads to an additional splitting of the corresponding EPR lines. The value of this splitting is determined by the inter-spin distance r in two ways.^[42] First, the dipolar splitting is proportional to r^{-3} . Second, the dipolar splitting is 3/2 times larger for the strong coupling regime, which is realized for r < 7 Å, than for the weak coupling regime, which corresponds to r > 15 Å. The distances in the range 7 Å < r < 15 Å result in an intermediate dipolar coupling, which is not adequately described neither by the weak coupling nor by the strong coupling model. In the weak coupling regime, the dipolar splitting cannot be resolved in the cw-EPR spectrum but contributes to the EPR linewidth.

To estimate the corresponding inter-nitroxide distance distributions and the percentage of the dimers with such short distances, the spectra of 1_2 ·O and 2_2 ·O were simulated. In the

simulations, both spectra were considered as a superposition of unbroadened and dipolar broadened nitroxide spectra. The spectra of 1.Cl and 2.Cl were used for the unbroadened part. The dipolar broadened spectrum was calculated by convolution of the unbroadened spectra with a dipolar spectrum corresponding to a normal distribution of the inter-nitroxide distances (see Experimental Section for details).^[42,43] A good fit to the nitroxide spectrum of 1_2 ·O was obtained with 25% μ_2 -oxobridged dimers having a mean inter-nitroxide distance of 6.3 Å with a standard deviation of 0.4 Å (dashed lines in Figure 5 b). The other 75% of μ_2 -oxo-bridged dimers in $\mathbf{1}_2$ ·O should then have inter-nitroxide distances above 15-20 Å, yielding the almost unbroadened nitroxide spectrum owing to the absence of a strong dipolar coupling between the two nitroxides. In the case of 2_2 ·O, good agreement with the experimental spectrum was obtained with 15% μ_2 -oxo-bridged dimers having a mean inter-nitroxide distance of 7 Å with a standard deviation of 2 Å (dashed lines in Figure 5 c).

PELDOR spectroscopy

To test whether longer nitroxide–nitroxide distances are also present in the dimers, pulsed electron–electron double resonance (PELDOR or DEER)^[44,45] measurements were performed. The results of these measurements are summarized in Figure 6 (see Experimental Section for details). The PELDOR time traces of 1·Cl and 2·Cl display only a monotonous decay, which is due to the inter-molecular dipolar interactions, but no dipolar modulation (Figure 6a, dotted curves). This indicates that the acid-treated samples contain only the monomeric porphyrins, as also found by MALDI, and that the used PELDOR settings



Figure 6. PELDOR measurements of the acid-treated and base-treated samples of 1-Cl and 2-Cl. a) Original PELDOR time traces. The background fits for the time traces of 1_2 -O and 2_2 -O are shown as red dashed lines. b) Background-corrected PELDOR time traces of 1_2 -O and 2_2 -O and their fits obtained by Tikhonov regularization. c) Inter-nitroxide distance distributions of 1_2 -O and 2_2 -O. The gray shades depict the estimated errors of the distance distributions, which were obtained by means of the validation toolbox of the DeerAnalysis program.

Chem. Eur. J. 2019, 25, 1-12

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exclude the measurement of Fe³⁺/nitroxide distances. In contrast, the PELDOR time traces of 1_2 ·O and 2_2 ·O show a prominent dipolar modulation with a modulation depth of 32% (Figure 6a, solid curves). The obtained value of modulation depth is in agreement with the expected value for the used pump pulse lengths of 14 ns (see Figure S1 in the Supporting Information), which provides further evidence for quantitative dimerization of the porphyrin molecules into $1_2 \cdot 0$ and $2_2 \cdot 0$. To obtain the inter-nitroxide distance distributions, the PELDOR time traces were analyzed by means of the program DeerAnalysis (see Experimental Section for details).^[46] The optimal fits to the PELDOR time traces and the corresponding inter-nitroxide distance distributions are shown in Figure 6. Interestingly, the inter-nitroxide distance distributions of both μ_2 -oxo-bridged dimers consist of two regions of non-zero probability with zero probability between them. The first region is between 15 and 35 Å, the second between 40 and 55 Å. The short distances around 6-7 Å seen in the cw-EPR experiments are not seen in the PELDOR experiment. This is related to the distance dependence of the modulation depth factor, leading to a lower distance limit for PELDOR of around 15 Å.^[42,46] In more detail, in the case of 1_2 ·O, the distance distribution displays an asymmetric peak with a maximum at 19.9 Å and a shoulder at about 27 Å, as well as a symmetric peak centered at 46.6 Å. The distance distribution of 2_2 ·O exhibits an asymmetric peak with a maximum at 27.7 Å and a bi-modal peak with maxima at 44.7 and 47.4 Å. The high signal-to-noise ratio, the length of the PELDOR time traces, and the clearly resolved oscillation periods render the mean values and the shape of the inter-nitroxide distance distributions as being reliable (see the validation results in Figure 6).

A possible explanation for the multiple peaks in the experimental inter-nitroxide distance distributions can be provided in terms of the relative orientation of two porphyrins in the μ_2 oxo-bridged dimers. If the two porphyrin ring planes could rotate freely around the Fe-O-Fe axis, which would lead to a uniform distribution of the dihedral angle ϕ (C₁-Fe₁-Fe₂-C₂ in Figure 7) between the two porphyrin planes, a smooth nitroxide-nitroxide distance distribution covering a large distance range would have to be expected. This is clearly not the case. In contrast, in a very simple geometric model, steric clashes between the orthogonal phenyl substituents are minimized if ϕ takes values around (45°+90° \cdot n), where n=0, 1, 2, 3. This defines four registers, of which two are symmetry related in the case of 1,0 and 2,0, leading to two principally different orientations. Interestingly, an available crystal structure^[27] of [Fe(TPP)]₂O reveals that the porphyrin planes do indeed adopt a staggered configuration but with a twist angle ϕ of 54.6° (Figure 7). The crystallographic value of ϕ deviates by 10° from 45°, which might be due to attractive interactions between the phenyl rings of two adjacent TPPs. Because of the symmetry within a register, an angle of 35.4° is equivalent to an angle of 54.6°. Thus, the twist angle ϕ can adopt eight possible values in 1₂·O and 2₂·O, \pm 35.4° and \pm 54.6° in the proximal register and $\pm 125.4^{\circ}$ and $\pm 144.6^{\circ}$ in the distal register (Figure 7). The proximal and distal register are defined by the two nitroxide arms being close to or far away from each other, respectively.



Figure 7. A schematic representation of the μ_2 -oxo-bridged porphyrin conformers. The coplanar mean porphyrin planes of the adjacent porphyrins are drawn as red and gray polygons. The dihedral angle between two porphyrins planes, C₁-Fe₁-C₂-Fe₂, is denoted as ϕ .

If these ϕ values would indeed be occupied, this would lead to a rough distance distribution with relatively short inter-nitroxide distances for the proximal register with $\phi=\pm 35.4^\circ$ and $\pm 54.6^\circ$ and significantly longer inter-nitroxide distances for the distal register with $\phi=\pm 125.4^\circ$ and $\pm 144.6^\circ$. To test this hypothesis and to correlate the predicted inter-nitroxide distances with the experimentally determined values, in silico structure simulations were performed for the μ_2 -oxo-bridged dimers $\mathbf{1}_2$ -O and $\mathbf{2}_2$ -O.

Molecular modeling and dynamics simulations

The μ₂-oxo-bridged porphyrin systems are difficult to describe by ab initio electronic structure theory. The bi-radical ground state cannot be properly described in conventional density functional theory (DFT) owing to the partial multireference nature of such states. More importantly, the system's size of about 250 atoms introduces an impractical computational price at the DFT level of theory, as the desired simulation techniques are MD simulations and the calculation of energetic barriers. Owing to the non-trivial electronic structure and the molecular size of the investigated systems, the semiempirical GFN-xTB/GBSA^[47,48] method was applied and solvation effects were only treated implicitly.

First, two initial structures with a dihedral angle ϕ of 54.6° and 144.6°, corresponding to the conformers in the proximal

Chem. Eur. J. **2019**, 25, 1–12

www.chemeurj.org

6





and the distal registers were generated and optimized at the GFN-xTB/GBSA(toluene) level of theory. Second, a conformer/ rotamer ensemble (CRE) was generated for each initial structure by using the MF-MD-GC/GFN-xTB algorithm^[49] and the energetically lowest conformer was determined for each CRE. This procedure yielded two conformers for each of the dimers: $1_2 \cdot O_{\alpha}$ and $1_2 \cdot O_{\beta}$ for the dimer $1_2 \cdot O$, and $2_2 \cdot O_{\alpha}$ and $2_2 \cdot O_{\beta}$ for the dimer 2_2 ·O. GFN-xTB analysis of the rotation profile around the dihedral angle ϕ was carried out to obtain a qualitative energetic overview. Energies were computed at the GFN-xTB/ GBSA(toluene) level of theory as well as the thermostatistical contribution for Gibbs free energy within the rigid-rotor-harmonic-oscillator (RRHO) approximation. The rotation profile around ϕ as well as the calculated relative Gibbs free energies of the two conformers for dimers 1_2 . O and 2_2 . O are shown in the energy diagram in Figure 8. Our semiempirical model predicts the α -conformer to be more stable than the corresponding β -conformer by approximately 2 kcal mol⁻¹ for both dimers 1_2 ·O and 2_2 ·O. The difference in energy is due to attractive dispersion and $\pi - \pi$ interactions between the linker, which is only present in the α -conformer of each dimer. Optimization of the rotation path from the α - to β -conformer around the dihedral angle ϕ produced a low activation barrier profile passing through the transition states TS1 and TS2. The associated computed Gibbs barrier for rotation ΔG^+ at 298.15 K amounts to approximately +19 kcal mol⁻¹ relative to $\mathbf{1}_2 \cdot \mathbf{O}_{\alpha}$ and $\mathbf{2}_2 \cdot \mathbf{O}_{\alpha}$ and approximately +17 kcal mol⁻¹ relative to $\mathbf{1}_2 \cdot \mathbf{O}_{\beta}$ and $\mathbf{2}_2 \cdot \mathbf{O}_{\beta}$. To get deeper insight into the mechanism of rotation, the rotation path optimization and transition state search was repeated for an artificial porphyrin dimer system where the residues attached to the porphyrin core (see Figure 7) were replaced by methyl groups. GFN-xTB analysis of the rotation path leads to the same energetic barrier of approximately +17 kcal mol⁻¹ as for the untruncated system, revealing the steric hindrance of the phenyl substituents upon rotation as the cause for the high rotation barrier.

For the energetically lowest conformers, MD simulations were carried out for 1 ns at the GFN-xTB/GBSA(toluene) level of theory (see Experimental Section for details) and the internitroxide distances were calculated to determine the corresponding distance distributions. The obtained inter-nitroxide distance distributions are plotted together with the corresponding experimental distributions in Figure 9. Note that two distance distributions were calculated for each dimer, one with the starting structure $\mathbf{1}_2 \cdot \mathbf{O}_{\alpha}$ or $\mathbf{2}_2 \cdot \mathbf{O}_{\alpha}$ and the other with the



Figure 8. Energy diagram for the rotation along the angle ϕ and the corresponding structures of the μ_2 -oxo-bridged dimers $\mathbf{1}_2$ ·O and $\mathbf{2}_2$ ·O calculated at the GFN-xTB level of theory. The molecules are drawn as ball-and-stick models with carbon atoms colored gray, oxygen atoms colored red, nitrogen atoms colored blue, and iron atoms colored orange. The inter-nitroxide distances and the ϕ angles are listed below the names of the corresponding conformers.

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Figure 9. Comparison of the experimental and calculated inter-nitroxide distance distributions in the μ_2 -oxo-bridged dimers a) $\mathbf{1}_2$ -O and b) $\mathbf{2}_2$ -O.

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Chem. Eur. J. 2019, 25, 1-12



starting structure $1_2 \cdot O_\beta$ or $2_2 \cdot O_\beta.$ This was necessary, because the phenyl substituents pose high-energy barriers that the conformer dynamics cannot overcome. This in turn means that the conformers are confined to their registers at normal temperature. Accordingly, the two MD derived distributions do not overlap with each other: the distributions that correspond to the starting structures $1_2 \cdot O_a$ and $2_2 \cdot O_a$ display a non-zero probability for the distance in the range 0-30 Å, whereas the distributions that correspond to the starting structures $1_2 \cdot O_\beta$ or $\mathbf{2}_{2}$ ·O_{β} have a non-zero probability between 30 and 55 Å, showing that the MD simulations exclude the transition between the two starting structures of the dimers. It should be mentioned that the MD-derived distributions calculated with different starting structures are weighted equally in Figure 9, which is justified because the α - and β -conformers of each dimer are similar in energy (Figure 8).

Comparison of EPR and MD results

Comparison of the in silico derived distance distributions with the experimental ones reveals several similarities. First, the MD simulations reproduce the distance peak between 40 and 50 Å of the PELDOR-derived distributions for both dimers, although the shape of the distributions is different. Second, the distance peak below 10 Å, which was found from cw-EPR experiments for both dimers, is also confirmed by the MD simulations. Both methods, MD and EPR, also agree on the width of the short distance peak for 2_2 ·O, but in the case of 1_2 ·O the experimental distance peak is significantly narrower than the MD result. The most prominent discrepancy between the in silico and experimental distance distributions is observed in the range 15 to 35 Å. The PELDOR-derived distributions of 1_2 ·O and 2_2 ·O contain an intense distance peak in this range. In contrast, the MD-derived distributions predict almost zero probability for these distances.

To interpret the outlined similarities and differences between the MD- and EPR-derived distance distributions, the correlation between the inter-nitroxide distance and the twist angle ϕ was investigated by using the MD data (Figure 10). Remarkably, only few distinct correlation peaks were obtained for both dimers. The MD simulations on the α -conformers of both dimers (proximal register) yielded an intense correlation peak around $\phi \!=\! 30^\circ$ and only a very weak correlation peak around $\phi = 60^{\circ}$, which is almost absent for 1_2 . The MD simulations on the β -conformers led to an intense correlation peak around $\phi = 145^{\circ}$ and again a weaker correlation peak around $\phi = 125^{\circ}$. All four values of the ϕ angle are in good agreement with the ϕ angles determined from the crystal structure of [Fe(TPP)]₂O (see above). The correlation peaks at $\phi \approx 125^{\circ}$ and 145° (distal register) correspond in the MD simulation to inter-nitroxide distances of 47.7 and 49.5 Å for 1₂·O, and 42.3 and 49.5 Å for 2_2 ·O. These distances are very close to the distance observed by PELDOR (46.6 Å for 12.0, 44.7 and 47.4 Å for 22.0). Moreover, the larger distance difference for the two conformers in the distal register for 2_2 ·O (7.2 Å) compared with 1_2 ·O (1.8 Å) mirrors itself in the bi- (resolved distances) versus uni-modality (unresolved distances) of the long-distance peak in the experi-



Figure 10. Correlation between the inter-nitroxide distances and the twist angle ϕ as determined from MD simulations on the μ_2 -oxo-bridged dimers a) $\mathbf{1}_2$ -O and b) $\mathbf{2}_2$ -O. The arrows denote the correspondence of the correlation peaks to the starting structures used for the MD simulations.

mental PELDOR data (Figure 9). The similar intensity of the two long-distance maxima in the PELDOR-derived distance distribution of $\mathbf{2}_2$ -O reveals that the two conformers with $\phi \approx 125^\circ$ and 145° are equally abundant. In contrast, the conformer with $\phi \approx 145^\circ$ is favored against the conformer with $\phi \approx 125^\circ$ by the MD simulation. This discrepancy causes the difference in the shape of the PELDOR- and MD-derived inter-nitroxide distance distributions in the range 40–50 Å (Figure 9).

Another pair of correlation peaks, around $\phi = 30^{\circ}$ and 60° , is associated with inter-nitroxide distances in the range 5 to 35 Å. The correlation peak at $\phi \approx 30^{\circ}$ corresponds to an internitroxide distance of 8.5 Å for both dimers. This prediction is close to the distances determined by cw-EPR (6.3 Å for 1_2 ·O, 7 Å for 2_2 ·O). The correlation peak around $\phi = 60^{\circ}$, corresponding to the distance range of 15 to 30 Å, is almost absent in the MD of 1_2 ·O (Figure 10a) and very weak and smeared for 2_2 ·O (Figure 10b). In contrast to the MD simulations, the PELDORderived distance distributions contain a clear peak in this distance region for both 1_2 ·O and 2_2 ·O. Thus, it seems that although both methods, EPR and MD, show that both registers are populated, the weight of the conformers within each register differs. This might be attributed to the simulation of the dynamics of 12.0 and 22.0 having been performed in liquid solution, whereas the corresponding EPR results were obtained on glassy frozen solutions. Usage of an implicit solvation model may also introduce a deviation between theory and experiment, as steric effects are not taken into account.

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8



In addition, MD predicts a non-zero probability for the ϕ angles between 125° and 145°, as well as between 30° and 60° (can be seen only for 2_2 ·O). This shows that the two porphyrin planes can rotate relative to each other within each of the registers in a "scissors-like" motion. For the 2,0 molecule, in which the linker is linear and fairly rigid, such a "scissorslike" motion should result in two bimodal inter-nitroxide distance peaks, corresponding to proximal and distal registers. Indeed, the bimodal peaks between 0 and 35 Å as well as between 40 and 50 Å can be seen in the EPR-derived distance distributions of 2_2 ·O (Figure 9b). In the case of 1_2 ·O, the kinked linker makes it difficult to resolve the bimodality of the peaks. Nevertheless, for both dimers, EPR and MD show clearly a zero probability for angles/distances between registers. As shown by GFN-xTB analysis, the conformations with $\phi = 90^{\circ} \cdot n$, where n = 0, 1, 2, 3, have high energetic barriers posed by steric clashes of the phenyl rings, which prevents an exchange between registers. This also means that different registers can only be occupied during dimer assembly. By using the distance distributions of the EPR data, one can estimate the relative occupation of the proximal versus distal register. For 12.0, this yields 59% and 41% for the proximal and the distal register, respectively, and for 22.0, 44% and 56% for the proximal and distal register, respectively. Thus, both registers are, within experimental error, equally populated.

Conclusions

Two synthetic approaches, one based on click chemistry and the other on Sonogashira-Hagihara coupling, were successfully applied to synthesize two new Fe³⁺ porphyrins, 1·Cl and 2·Cl, each linked to a nitroxide group. Treating the monomeric samples with an aqueous basic solution, the monomers were converted almost quantitatively into μ_2 -oxo-bridged dimers $\mathbf{1}_2$ ·O and 2_{2} . The structure and dynamics of the μ_{2} -oxo dimers was then investigated by means of cw-EPR and PELDOR spectroscopy. The cw-EPR experiments were used to determine the short inter-nitroxide distances below 15 Å, whereas the PELDOR experiments allowed the determination of long internitroxide distances above 15 Å. Thus, both methods complement each other nicely. To interpret the obtained distance constraints in terms of structure and dynamics of the dimers, the combined cw-EPR/PELDOR derived inter-nitroxide distance distributions were compared with the results of the MD simulations. This comparison yielded several fruitful results. It was shown that the conformers of the μ_2 -oxo-bridged dimers occupy four registers that are defined by the phenyl substituents. The dimer rotamers cannot exchange their register by rotation owing to the high energetic barrier of $17-19 \text{ kcal mol}^{-1}$ posed by the phenyl substituents. Within each register, two favorable conformers were identified. They correspond to the twist angle between the two porphyrin cores of 30° and 60° in the case of the proximal register and 125° and 145° in the case of the distal registers. The population of these two conformers in each register was weighted differently by EPR and MD. Additionally, it was proposed based on MD simulations that μ_2 -oxo-bridged porphyrin planes can rotate relative to each other around the Fe-O-Fe axis within each of the registers. Such a "scissor-like" motion corresponds to an exchange of the favorable conformers within each register. Importantly, both synthesized porphyrin dimers display very similar dynamics of the central TPP core, which hints towards a minor effect of the linker on the intrinsic dynamics of the TPPs and, thus, allows us to extend the derived conclusions to other FeTPP-based μ_2 -oxo dimers. With respect to using such dimers within molecular machines, one might view them as molecular step motors. Furthermore, the present study provides a basis for using these compounds as models for testing pulsed EPR-based distance measurements to high-spin Fe³⁺ ions with large zero-field splitting constants.

Experimental Section

Synthesis

The details of the synthesis of 1.Cl and 2.Cl and their precursors, as well as the corresponding analytics (MS, NMR, elemental analysis, etc.), are given in the Supporting Information. The dimerization of 1·Cl and 2·Cl to the μ_2 -oxo-bridged dimers 1_2 ·O and 2_2 ·O, respectively, was achieved by treatment of the monomers with aqueous sodium hydroxide. In particular, a 200 µм solution of 1·Cl or 2·Cl in toluene was prepared and mixed with 0.05 M aqueous NaOH in a volume ratio of 1:1. The obtained solution was shaken for 2 min by means of a Vortex Genie 2 (Scientific Industries Inc.) and then incubated for 1 min to achieve separation of water and toluene layers. After this, the toluene layer was extracted and the entire procedure was repeated again to ensure efficient dimer formation. Subsequently, the toluene layer was transfused into a clean tube and the solvent was evaporated from the samples under high vacuum. The reversibility of the dimerization process was tested by treatment of the dimers with aqueous hydrochloric acid. This procedure was done in complete analogy to the treatment with NaOH except for the fact that 0.05 M aqueous HCl was used instead of 0.05 M aqueous NaOH. This procedure again gave rise to the monomers 1.Cl and 2.Cl.

Mass spectrometry

Matrix-assisted laser desorption/ionization (MALDI) mass spectra were measured by using an Autoflex II TOF/TOF (Bruker) spectrometer.

UV/Vis spectroscopy

UV/Vis spectra were recorded by using SPECORD 200 (Analytik Jena AG) and Cary 100 UV/Vis (Agilent Technologies) spectrometers. All spectra were taken in the range from 300 nm to 800 nm with a 1 nm step. All UV/Vis samples were prepared with the concentration of 10 μ m in deuterated toluene.

cw-EPR spectroscopy

cw-EPR experiments were carried out with an X-Band EPR spectrometer EMXmicro (Bruker) equipped with super-high-quality resonator (SHQ). cw-EPR spectra were collected at two different temperatures, 10 K and 100 K. To obtain 100 K, the variable-temperature accessory ER 4131VT (Bruker) was employed. For 10 K, the resonator was mounted inside a continuous-flow helium cryostat ER4112HE (Bruker), the temperature of which was controlled by

Chem. Eur. J. 2019, 25, 1–12 www.chemeurj.org These are not the final page numbers! 77



the Mercury iTC system (Oxford Instruments). The cw-EPR measurements at 100 K were performed with a microwave power of 0.1927 mW (30 dB), a modulation frequency of 100 kHz, a modulation amplitude of 0.2 mT, and a time constant of 10.24 ms. The 10 K cw-EPR spectra were acquired by using a microwave power of 17.22 mW (10 dB), a modulation frequency of 100 kHz, a modulation amplitude of 0.1 mT, and a time constant of 10.24 ms. All cw-EPR samples were prepared with a nitroxide spin concentration of 200 μ M in deuterated toluene. The sample volume was kept constant at 200 μ L. Moreover, the cw-EPR measurements at 10 K were performed with the same resonator Q factor (\approx 500) and the same receiver gain (40 dB) for all samples.

Determination of spin-spin distances from cw-EPR spectra

The nitroxide spectra of **2**-Cl and **2**₂-O were simulated by using the convolution method.^[42,43] Both spectra were considered as a superposition of unbroadened spectra $f_u(B)$ and dipolar broadened nitroxide spectra $f_h(B)$:

$$f(B) = w f_{\mathsf{b}}(B) + (1 - w) f_{\mathsf{u}}(B)$$

where *w* is the weight of the dipolar broadened part in the total spectra. The nitroxide spectra of 1·Cl and 2·Cl were used for the unbroadened part $f_u(B)$. The dipolar broadened spectrum was calculated by convolution of the unbroadened spectra with a dipolar spectrum $f_{dd}(B)$:

$$f_{\rm b}(B) = f_{\rm u}(B) \otimes f_{\rm dd}(B)$$

The dipolar spectrum was calculated in the strong coupling approximation for a normal distribution P(r) of the inter-nitroxide distances with a mean distance $\langle r \rangle$ and a standard deviation σ_r :

$$f_{dd}(B) = \int_{0}^{\infty} P(r) dr \int_{0}^{\pi/2} D(r,\theta) \sin\theta d\theta$$

in which:

$$D(r,\theta) = \frac{3}{4} \frac{\mu_0}{4\pi} \frac{g\beta}{r^3} (1 - 3\cos^2\theta)$$
$$P(r) = \frac{1}{\sqrt{2\pi\sigma_r}} \exp\left(-\frac{(r - \langle r \rangle)}{2\sigma_r^2}\right)$$

Here, μ_0 is the vacuum permeability, g is the g-factor of the nitroxide, β is the Bohr magneton, r is the inter-nitroxide distance, and θ is the angle between the distance vector and the direction of the external magnetic field. The integral of $f_{\rm dd}(B)$ was solved by means of Monte-Carlo method using 10⁶ samples.

In the present analysis, the values of the mean distance $\langle r \rangle$, its standard deviation σ_n and the weight *w* were optimized manually until the convolution of the unbroadened cw-EPR spectra $f_u(B)$ with the dipolar spectrum provided the best fit to the cw-EPR spectra of 2·Cl and 2₂·O. The MATLAB-based source code of the optimization program is available at https://github.com/dinarabdul-lin/DipolarBroaderingFitting.

PELDOR spectroscopy

PELDOR experiments were performed on the same samples as the cw-EPR experiments. All samples had the nitroxide spin concentration of 200 μ M in deuterated toluene. The measurements were car-

ried out with an ELEXSYS E580 (Bruker) spectrometer using a Flex-Line probehead with a Q-band resonator ER5106QT-2 (Bruker). All microwave pulses were amplified by a 150 W TWT amplifier (model 187Ka). To achieve the working temperature of 50 K, a continuousflow helium cryostat CF935 (Oxford Instruments) and a temperature control system iTC 503S (Oxford Instruments) were employed. The PELDOR experiments were performed with the standard fourpulse sequence $\pi/2(\nu_{det}) - \tau_1 - \pi(\nu_{det}) - (\tau_1 + t) - \pi(\nu_{pump}) - (\tau_2 - t) - \pi(\nu_{det}) - \pi(\nu_{de$ τ_2 -echo. The frequency of the pump pulse and the magnetic field were adjusted to be in resonance with the maximum of the nitroxide spectrum, whereas the frequency of the detection pulse was set 100 MHz lower than the frequency of the pump pulse. All PELDOR measurements were performed with the lengths of detection $\pi/2$ - and π -pulses of 16 and 32 ns, respectively, and the pump pulse was 14 ns long. The π -pulse was phase-cycled to eliminate receiver offsets. The τ_1 interval was set to a starting value of 250 ns and was incremented during each experiment eight times with a step of 16 ns, to suppress the deuterium ESEEM (electron spin echo envelope modulation). The τ_2 interval was set to 10 μ s. The position of the pump pulse relative to the primary echo was incremented with a step of 8 ns. All PELDOR spectra were recorded at 50 K with a repetition time of 3 ms. The signal was averaged over 250 runs to achieve a good signal-to-noise ratio.

Determination of spin-spin distances from PELDOR data

The inter-nitroxide distance distributions were determined from the experimental PELDOR time traces by means of the program DeerAnalysis.^[46] First, the time traces were divided by an exponential decay to remove the background resulting from the inter-molecular interactions. Then, Tikhonov regularization was applied to the background-free time traces, yielding the desired distance distributions. The best regularization parameter was determined through the L-curve approach. The validation of the inter-nitroxide distance distributions was done by varying the background starting time from 2 μ s to 6 μ s with a step of 100 ns and the background dimension from 3.0 to 3.5 with a step 0.1.

Computational details

For all four initial structures, the generation of the conformer/rotamer ensemble (CRE) was performed by using the semiempirical tight-binding method GFN-xTB and the CRE search algorithm.^[49] The MF-MD-GC/GFN-xTB algorithm consists of three steps: normal mode following (MF), molecular dynamics (MD) simulations, and "pseudo-genetic" structure crossing (GC). In all steps, GFN-xTB is used as the underlying electronic structure method. The CRE generation was conducted in toluene as the solvent, simulated by the implicit GBSA solvation model.^[47,48] The energetically lowest conformer found for each initial structure was fully optimized at the GFN-xTB/GBSA(toluene) level of theory and molecular dynamics (MD) simulations were carried out with implicit solvent GBSA (toluene) on each structure at 298 K for 100 ps, 500 ps, and 1 ns with a time step of 4 fs and an equilibration phase of 10 ps. The SHAKE^[50] algorithm was used to constrain all bonds. For geometry optimization and MD simulation, the stand-alone program xtb^[51] was used. Evaluation of the trajectories was performed with the program TRAVIS.^[52]

The calculation of free energies was performed as follows. Singlepoint energies *E* were computed at the GFN-xTB level of theory. Harmonic vibrational frequencies were calculated at the same level to obtain the thermostatistical corrections G_{RRHO} . The solvation free energy ΔG_{solv} was calculated by GBSA at 298.15 K in the respective

Chem. Eur. J. 2019, 25, 1–12 www.chemeurj.org

10

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solvent (toluene). The free energy is then the sum of all contributions:

$$G = E + G_{\rm RRHO}^{\rm T} + \varDelta G_{\rm solv}^{\rm T}(X)$$

Reaction paths were calculated for all reactions to get a good guess of the transition state structure. To begin from reasonable geometries, the start and end structures were optimized with GFN-xTB/GBSA. The reaction path was then calculated with the growing string method GSM^[53] by using GFN-xTB/GBSA as the underlying electronic structure method. An additional frequency calculation was performed to check for a true transition state with only one imaginary mode.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: complex formation • DEER spectroscopy • metal centers • nitroxide • pulsed dipolar spectroscopy

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11

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FULL PAPER

Step Motors

D. Abdullin, N. Fleck, C. Klein, P. Brehm, S. Spicher, A. Lützen, S. Grimme, O. Schiemann*

 Synthesis of μ₂-Oxo-Bridged Iron(III) Tetraphenylporphyrin–Spacer– Nitroxide Dimers and their Structural and Dynamics Characterization by using EPR and MD Simulations



Like wheels on an axle: Two iron(III) tetraphenylporphyrin–spacer–nitroxide complexes were synthesized and their monomers and μ_2 -oxo-bridged dimers characterized. Continuous-wave and



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pulsed EPR spectroscopy in combination with molecular dynamics calculations show that the porphyrin moieties in the dimers rotate like a step motor around the Fe–O–Fe axis (see figure).

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