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Articles

Mechanistic Studies on the Nucleophilic Reaction of Porphyrins with Organolithium Reagents

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Porphyrins react readily with organolithium reagents under substitution of free meso positions. As this method has proven to be very versatile for the preparation of a wide range of meso substituted porphyrins, a mechanistic study of the reaction was undertaken using 5,15-diaryl- and dialkyl substituted porphyrins, 2,3,7,8,12,13,17,18-octaethylporphyrin, and the respective nickel(II) complexes. A combination of deuteration experiments, electronic absorption spectroscopy of the reactive intermediates, trapping of intermediates with organic electrophiles, and reaction at different pH values showed significant differences in the reaction pathways of free base porphyrins and metalloporphyrins. In both cases the reaction proceeds initially under formation of phlorin like intermediates which are stable in water. For the Ni(II)phlorins a mesomeric carbanionic form with a highly distorted structure exists that can react as a nucleophile with electrophiles such as RI, H^+, or D^+. In the latter case a protonation-deprotonation equilibrium involving porphodimethen intermediates has to be assumed. Free base phlorins do not react as nucleophiles but can undergo H/D exchange reactions in strongly acidic media.

Introduction

Porphyrins react readily with nucleophiles such as Grignard and organolithium reagents at the meso or β position.[1] Nevertheless, most examples required prior activation of the porphyrin, via macrocycle distortion, with electron withdrawing groups or by metalation with high valent metal ions severely limiting the application of such methods for porphyrin C−C bond formation. Only few examples have been given for S_N reactions with porphyrins without prior activation or for the use of reactive porphyrin intermediates obtained from such reactions.[1b,1d,2] Notable studies include Buchler's reductive alkylation,[3] systematic investigations of reduced porphyrin systems such as anion radicals, or mono- and dianions prepared by chemical or electrochemical methods,[4,5] and studies on the isomerization of reduced porphyrin derivatives (phlorins, porphodimethenes, chlorines).[6] None of these studies resulted in the development of general synthetic strategies amenable to overcome the limitations in the current methods for the preparation of asymmetrically meso substituted porphyrins.

In recent years we have developed such a method based on the reaction of unactivated porphyrins with organolithium reagents.[7−10] The reaction sequence involved addition of LiR, hydrolysis with water, and subsequent oxidation with DDQ. Initially, we proposed an addition-oxidation mechanism for the reaction of LiR with (2,3,7,8,-12,13,17,18-octaethylporphyrinato)nickel(II) **1** and postulated a Meisenheimer-type[11] structure **2** for the

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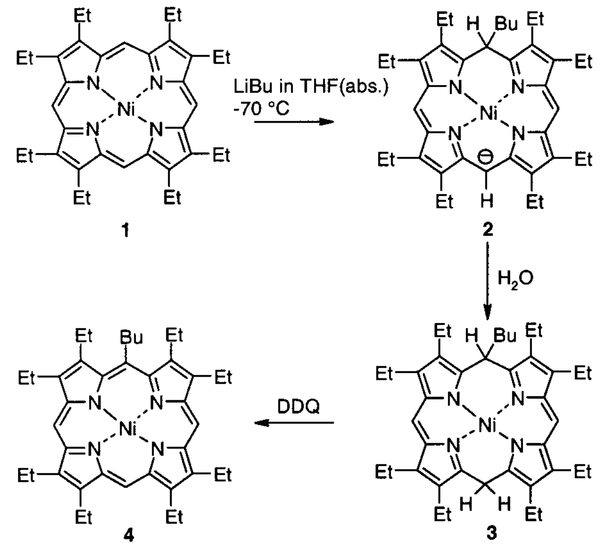
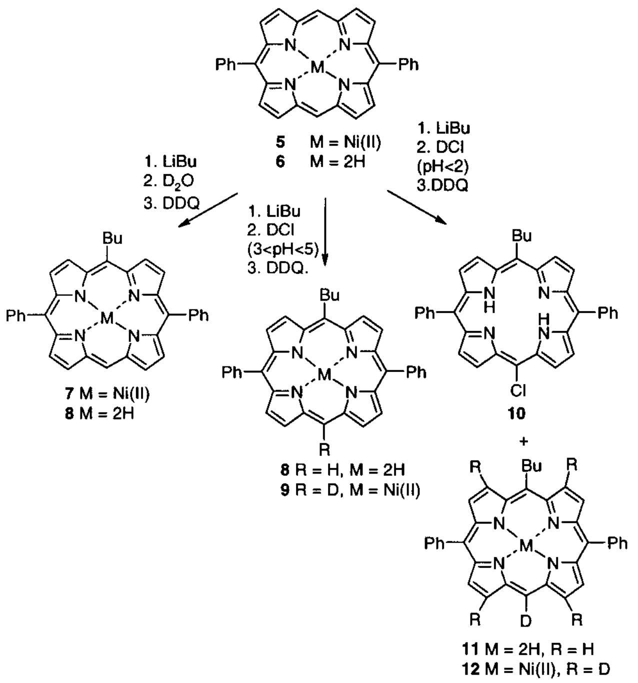
Scheme 1



intermediary porphyrin carbanion formed by addition of LiR, where the negative charge is located at the meso position opposite to the one attacked by the nucleophile.[7] This carbanion can then be protonated with water to yield a 5,15-dihydroporphyrin (a porphodimethene or calixphyrin) **3**, which subsequently is oxidized to the meso substituted porphyrin **4** (Scheme 1). During studies aimed at expanding the synthetic applications we noted a distinct difference in the reactive behavior of metalloporphyrins and free base porphyrins. Thus, a more detailed mechanistic investigation is necessary and we report here on comparative deuteration experiments and spectroscopic investigations using free base porphyrins and metal complexes of an octa-β-substituted porphyrin (**1**, **16**) and a β-unsubstituted porphyrin possessing two meso substituents (**5**, **6**).

Scheme 2



Results and Discussion

When porphyrins were treated with organolithium reagents the deep red porphyrin solution turned brown immediately after addition of LiR. Upon hydrolysis with water the color remained unchanged in experiments with nickel(II) complexes while for free base porphyrins an additional color change from brown to blue-green occurred. This could indicate the existence of different intermediates during S_NAr reactions of free base versus metalloporphyrins. Using our postulated mechanism for orientation, we first attempted deuteration experiments by replacing H_2O with D_2O in the hydrolysis step. We expected a >50% incorporation of the deuterium label at the meso position opposite to that of the carbanion attack after oxidation with DDQ. Nevertheless, performing such experiments for the four compounds **1**, **5**, **6**, and **16** under the standard conditions described in our synthetic communications (using LiBu, D_2O, and DDQ), resulted in the formation of the respective mono-butylated porphyrins (**4**, **7**, **8**, and **17**, respectively). Based on ^1H NMR and mass spectrometry data, no evidence for a deuterium incorporation was found (Scheme 2).

Before performing further labeling experiments we decided to obtain more information on the structure of the intermediates via electronic absorption spectroscopy. As reactions of both **5** and **6** with butyllithium proceed quantitatively to the mono-butylated products **7** and **8**, respectively,[10] we expected pure UV−vis spectra of the intermediates without any interference from starting materials or byproducts. The relevant spectra for the reaction of the nickel(II) complex **5** with LiBu are shown in Figure 1. Upon addition of LiBu an intermediate with a strong absorption band at 450 nm and a broad band around 770 nm was observed. Similar spectra of reduced metalloporphyrins were described by Closs when the dianionic porphyrin intermediate derived from the two-electron reduction of (5,10,15,20-tetraphenylporphyrinato)zinc(II) with sodium anthracenide was protonated in methanol.[4b] Spectra of this type were assigned to met-

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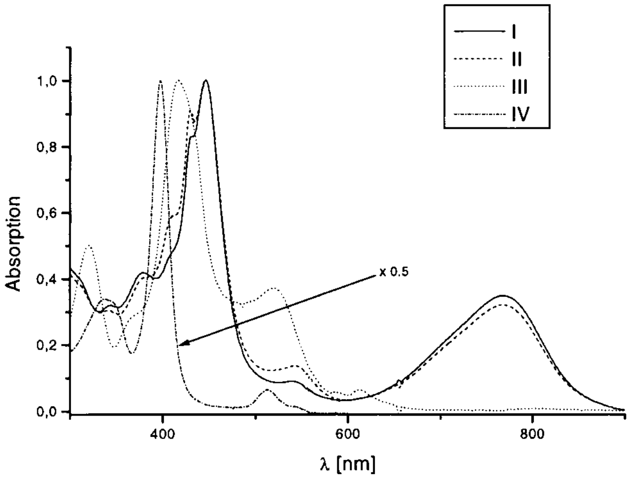

Figure 1. Electronic absorption spectra of the intermediates in the reaction of the nickel(II) complex **5** with butyllithium after addition of various reactants. (I) LiBu, (II) H_2O, (III) HCl (dilute), (IV) DDQ.

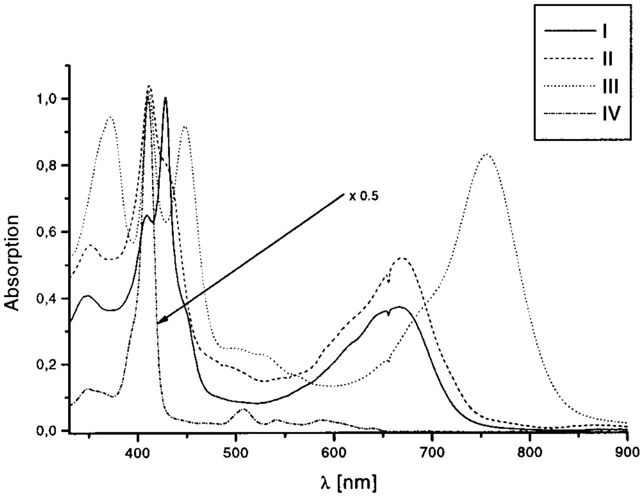

Figure 2. Electronic absorption spectra of the intermediates in the reaction of the free base porphyrin **6** with butyllithium after addition of various reactants. (I) LiBu, (II) H_2O, (III) HCl (dilute), (IV) DDQ.

allophlorin salts leading us to propose **28** as the structure for the intermediate. Upon addition of water the spectrum of the reaction mixture remained almost unchanged and gave no evidence for a porphodimethene type structure **29**. This indicates, that the intermediate **28** still exists in the presence of water and is not protonated under the basic reaction conditions (pH ~11) within 15 min at room temperature. Together with the observation, that Closs' zinc(II) phlorin salt is only slowly converted to a chlorin in the presence of excess methanol,[4b] this explains that no deuterium label was found in our initial labeling experiment (Scheme 3).

In the intermediate of the nickel(II) complex formulated as **28**, the negative charge is principally delocalized in the bilatriene unit while, due to its sterically relaxed conformation, a carbanionic nickel(II) complex of type **27** should be an energetically favorable mesomeric form. The stability of the intermediate in water indicates that only a small number of molecules will be protonated to the corresponding porphodimethene **29** under the basic conditions and can be deprotonated back to the monoanion **28** again. Thus, an equilibrium should exist in the "hydrolysis step". Indeed, addition of a strong base like DBU to a solution of the porphodimethene **29** formed in situ by addition of dilute acid resulted in a color change from deep red to brown[12] and gave a UV−vis spectrum identical to the one shown for the anion **27/28** in Figure 1. Similar protonation-deprotonation equilibria were studied by Mauzerall and Whitlock for uroporphomethen and chlorin.[13,6c]

In comparison, the intermediates of the reaction of the free base porphyrin **6** with butyllithium gave different spectra. The absorption spectrum of the putative lithium(I) complex **31**, obtained after addition of LiBu to **6**, exhibited a strong absorption band at 430 nm and a broad band at 660 nm (Figure 2). After addition of water some spectral changes occurred in the Soret band region and namely the Q-band became stronger and was shifted bathochromically to 670 nm. The latter is blue-shifted by more than 100 nm compared to the nickel(II) complex **28** (see Figure 1). Similar spectral differences between metallophlorins and free base phlorins were described by Fuhrhop[14] and the structure of the intermediate after hydrolysis has to be formulated as **32**. Thus, for both the free base and nickel(II) complex of 5,15-diphenylporphyrin a reaction mechanism involving phlorin-type intermediates appears likely (Scheme 4).

Results consistent with this proposal were obtained using 2,3,7,8,12,13,17,18-octaethylporphyrin **16** as starting material. This porphyrin gives the monobutylated compound **17** under standard conditions in 50% yield.[8b] When butyllithium was added to a red solution of **16** the color changed to brown and the UV−vis spectrum of the mixture showed the bands of the educt (Soret band: λ_{max} = 392 nm in THF) besides a strong band at 419 nm and a weak, but very broad band at 839 nm. Upon addition of water the solution turned green, but the UV−vis spectrum did not change significantly. The two bands at 419 and 839 nm were still present. Peycal-Heiling and Wilson have assigned such absorption bands to phlorin anions.[5b] Thus, the intermediate of the reaction of free base octaethylporphyrin with butyllithium also has a structure where the negative charge is located more at the nitrogen atoms than at the meso position. Similar experiments with the nickel(II) complex **1** were aided by the quantitative conversion to **4**. The UV−vis spectra of the reaction mixture at various stages indicate intermediates different from those of the reaction with the free base. Here, addition of butyllithium to a red solution of **1** resulted in a red-brown solution with five absorption bands at 289, 392, 448 (very strong), a broad one at 560, and a weak broad band at 873 nm (Figure 3). Under this reaction conditions educt (λ_{max} = 392 nm) was still present in the reaction mixture. The two bands at 447 and 878 nm are again indicative for a phlorin salt. The other two bands at 289 and 550 nm must belong to a different intermediate. A possible suggestion is a monoanionic porphodimethene where the negative charge is located predominantly at the meso position (akin to **2**).

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[12] One ml of DBU was added to the solution obtained by reaction of **5** with LiBu (synthesis of compound **12**) and the corresponding pH-value changed to >12.

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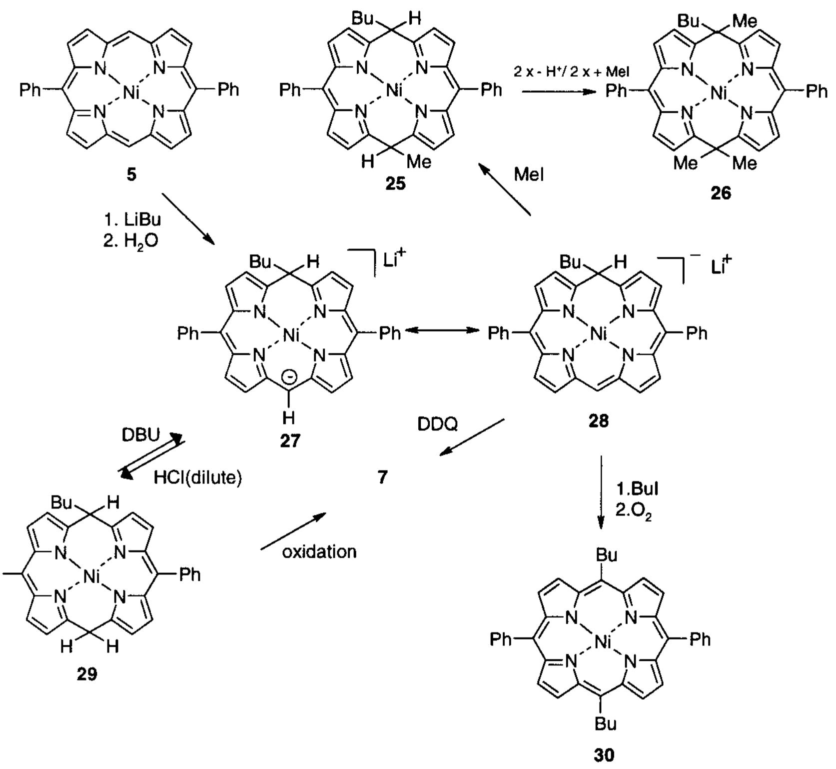
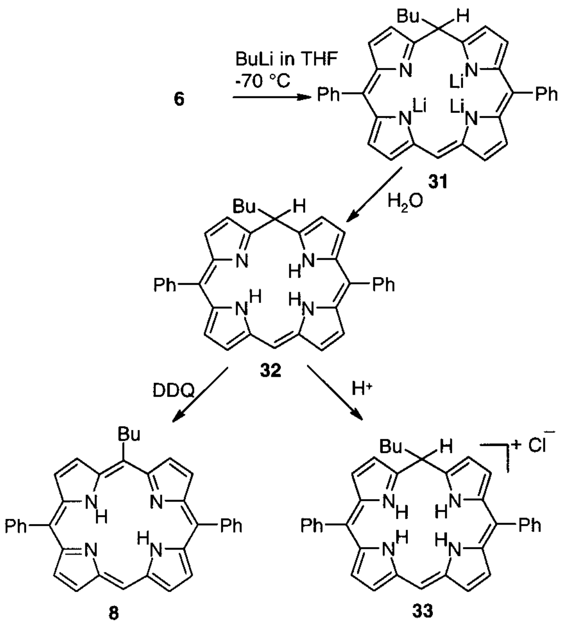
Scheme 3



Scheme 4



The higher degree of steric hindrance in substituted octaethylporphyrin derivatives might favor the formation of such intermediates. After addition of water the UV–vis spectral data remained almost unchanged pointing again to the stability of the intermediates against hydrolysis.

After the initial deuterium labeling experiments failed for the reasons shown above, we attempted to investigate the electron distribution and reactivity of the intermediates by utilizing the porphyrin carbanion as a nucleophile for trapping alkyl iodides. For 5,15-disubstituted porphyrins this method can be used effectively to introduce two additional meso substituents in a one-pot reaction.[9] When the in situ formed nickel(II) complex **28** is treated with excess butyl iodide at room temperature the brown solution turned deep red over the course of 2 h. In contrast, no color change was observed in experiments with the complex **31** derived from the free base **6**. After subsequent oxidation with atmospheric oxygen the porphyrins **30** and **8** were obtained from the two reactions, respectively. Similar experiments with 2,3,7,8,12,13,17,18-octaethylporphyrin derivatives gave the mono-butylated compound **17** as product of the reaction of the free base **16** with LiBu/BuI. The yield of this reaction does not change when the trapping electrophile is added after the hydrolysis step. This is further indication for the stability of intermediates such as **28**. (5,15-Dibutyl-2,3,7,8,12,13,17,18-octaethyl-*syn*-5,15-dihydroporphyrinato)nickel(II), a porphodimethene that could not be oxidized to the porphyrin was obtained from the reaction of **1** with LiBu/BuI.[15]

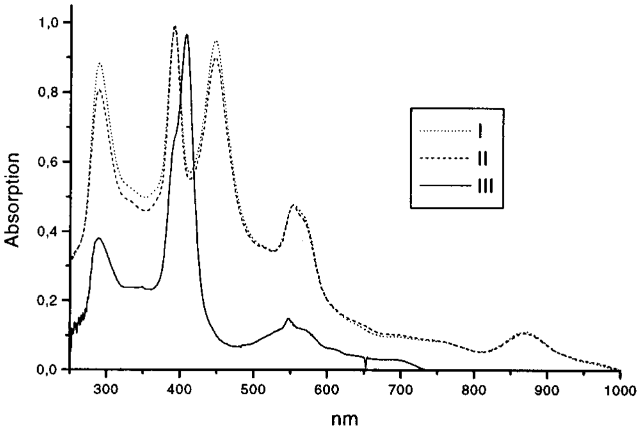
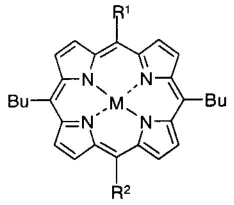


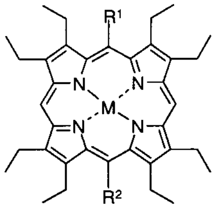
Figure 3. Electronic absorption spectra of the intermediates in the reaction of the nickel(II) complex **1** with butyllithium after addition of various reactants. (I) LiBu, (II) H_2O, (III) DDQ.

An explanation for the different reactivity of anionic intermediates derived from free base porphyrins and nickel(II) complexes with alkyl iodides goes back to Buchler's studies on the synthesis of porphodimethene, where he reacted metalloporphyrin dianions with alkyl iodides.[3] Generally the formation of 5,15-porphodimethenes is favored over the formation of 5,10-porphodimethenes.[16] This is due to steric considerations as the former can adopt a sterically relaxed roof-shaped conformation due to the small radius of the nickel(II) ion. This usually causes a higher degree of porphyrin macrocycle distortion in comparison to other metalloporphyrins (Zn^{II}, Pd^{II}, and Pt^{II}).[3a] Thus, the double bond in such strongly roof-shaped conformers is similar to a bridge-head double bond and shows a higher nucleophilic reactivity with alkyl iodide. On the other hand, this "roof effect" can favor a sp^3-hybridization and the localization of the negative charge at that *meso* position (like in **27**) which will facilitate a reaction with the electrophile. In contrast, the free base **6** is converted by addition of LiR to a lithium metal complex with two additional pairs of THF molecules as axial ligands above and below the macrocycle.[17] In contrast to the situation in the nickel(II) complex **28**, the $Li^I(THF)_2$ units located above and below the 4N core in the intermediate **31** prevent large macrocycle distortions. The relative planar conformation in the bilatriene unit obviously favors a double bond character and a location of the negative charge more on the nitrogen atom. Thus, the *meso* 10-position in phlorin **31** is more inert against electrophiles. The exact conformation of such lithium(I) phlorins is unknown. However, a relatively planar conformation of the bilatriene unit of in 5,10,15,20,21-pentaphenylphlorin has been described by Krattinger and Callot.[1e] To test this hypothesis, we used (5,15-diphenylporphyrinato)palladium(II) (large metal ion radius, weak deformation) and (5,15-diphenylporphyrinato)zinc(II) (with additional axial ligand, weak deformation) in similar experiments. As expected, reaction of the corresponding monoanionic (5-butyl-10,20-diphenylporphyrinato)palladium(II) and (5-butyl-10, 20-diphenylporphyrinato)zinc(II) intermediate with BuI did not yield a butylated product similar to **30**.

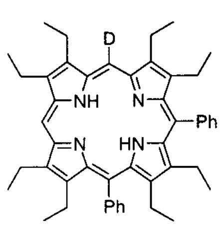
The stability of the intermediates under basic conditions prompted us to attempt labeling experiments under more acidic conditions. Thus, after formation of **31** from **6** the reaction mixture was treated with dilute DCl to a pH of 3−5 and the color changed to blue-green. After oxidation with DDQ and chromatographic workup, compound **8** was obtained as the sole, unlabeled product. When the same experiment was performed with **5** the solution became deep red at once upon addition of DCl and the monodeuterated porphyrin **9** (75% label based on ^1H NMR integration) was isolated after workup in 65% yield. Similar to the argumentation made above, a reaction with electrophiles (here D^+) is facilitated in the conformationally distorted nickel(II) complex intermediates and hindered in the more planar phlorin anions derived from the free base. This behavior is independent of the type of meso substituent present in the starting material. The (5,15-dibutylporphyrinato)nickel(II) **13** gave **14** upon treatment with $LiBu/D_2O/DDQ$ and yielded the deuterated derivative **15** when dilute DCl was used for hydrolysis.



13 M = Ni(II), R¹ = R²= H
14 M = Ni(II), R¹ = Bu, R² = H
15 M = Ni(II), R¹ = Bu, R² = D



16 M = 2H, R¹ = R²=H
17 M = 2H, R¹ = Bu, R²= H
18 M = 2H, R¹ = Bu, R²= D
19 M = Ni(II), R¹ = Bu, R²= D
20 M = Ni(II), R¹ = H, R²= Cl
21 M = 2H, R¹ = Ph, R² = H



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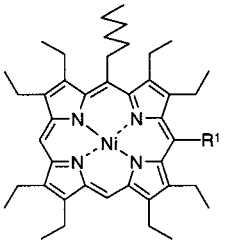

23 R¹ = H
24 R¹ = Ph

To distinguish the observed deuterium incorporation from the simple H/D exchange reported for porphyrins,[18,19] porphyrin **7** was treated with DCl under the experimental conditions used above ($3 < pH < 5$, 15 min, room temperature). No deuterated porphyrins were obtained, indicating that the observed deuteration must have occurred at the stage of the intermediate **28** and not by reaction with the porphyrin **7**. Having excluded a simple H/D exchange reaction, the deuteration experiments with DCl were repeated under even more acidic conditions ($pH < 2$). The intermediate obtained from the free base **6** after addition of LiBu and DCl exhibited a UV−vis spectrum typical for a phlorin cation with a broad absorption band at 755 nm (Figure 2), while the intermediate derived from the nickel(II) complex **5** gave a spectrum indicative for a porphodimethene with two broad absorption bands at 418 and 522 nm (Figure 1). Oxidation of the latter with DDQ resulted in the isolation of the pentadeuterated porphyrin **12** with deuterium labels at the 15-meso position and at four β-positions (3,7,13,17, see Figure 4) in a yield of 75%. To generalize these results, we performed this experiment with other porphyrins such as the nickel(II) complex **1** and obtained the deuterated porphyrin **19** in 68% yield (10% D label). Similarly, reaction of **21** with LiPh and DCl gave **22** in 88% yield and 100% D incorporation at the 5-position. A trapping of the nickel(II) monoanion **28** with electrophiles such as BuI was also attempted at low pH (<2). However, only the trisubstituted porphyrin **7** was isolated. These results are in agreement with the fact that alkyl iodides can react only with the intermediate **28** but not with the porphodimethene **29**.

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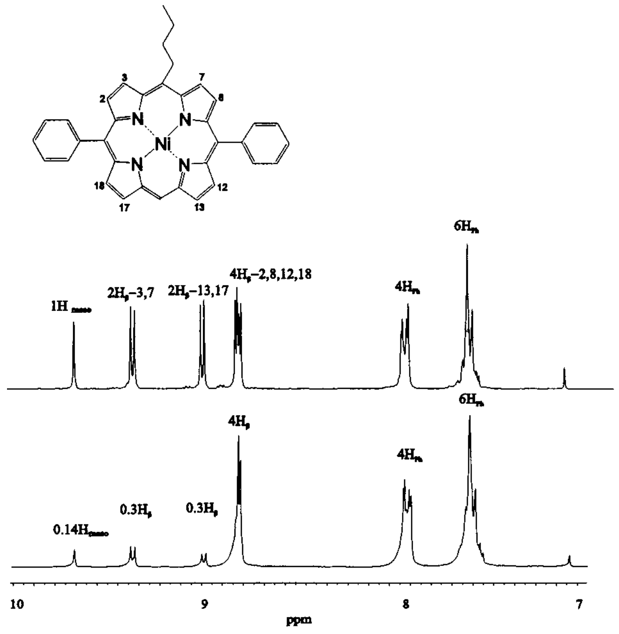

Figure 4. Low field region of the ^{1}N NMR spectra of the unlabeled **7** (top) and pentadeuterated **12** (5-butyl-10,20-diphenylporphyrinato)nickel(II).

A mechanistic explanation for the pentadeuteration observed in **12** is more difficult. It may involve a reversible 1,3-hydrogen shift from the 5,15-position of **28**−**30** to the neighboring β-positions under formation of energetically favorable delocalization pathways. We obtained further evidence for a deprotonation of the porphodimethene intermediate during our study on the trapping of the carbanionic nickel(II) complex **28** with alkyl iodides.[12] Electrophiles such as methyl iodide resulted in the formation of a trimethylated porphodimethene **26** that can only be explained via the intermediate **25** and subsequent deprotonation/methylation sequences (Scheme 3).

Performing similar labeling experiments at low pH with free base porphyrins again gave results different from those with the respective nickel(II) complexes. Spectroscopic evidence indicated the predominant formation of an intermediary phlorin **32** which is protonated to the phlorin cation **33** (Scheme 4). Its formation is clearly evidenced by the broad and strong absorption band at 770 nm in the UV−vis spectra of the reaction mixture of **6** treated with butyllithium and HCl (Figure 2). As a result, treatment of **6** with LiBu, DCl (at pH < 2) followed by oxidation yielded the monodeuterated porphyrin **11** with 100% deuterium label at the 15 position in 33% yield.

The observation of a 100% deuterium label at the respective meso position in compounds **11** and **18** (prepared via a similar reaction from **16**) has to be attributed to the formation of phlorin intermediates such as **32**, where a fast H/D exchange is facilitated in strongly acidic deuterated media.[14,19] Unexpectedly, we also observed the formation of the meso chlorinated porphyrins **10** (from **6**) and **20** (from **1**) as byproducts (yields 20−30%) during deuteration experiments performed in the presence of DCl and DDQ at pH < 2. These results may be comparable to the radical meso chlorination of porphyrins with H_2O_2 and HCl described by Fischer and Woodward.[20]

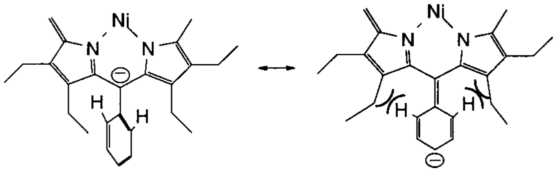

Figure 5. Illustration of the steric hindrance occurring in meso aryl and β-substituted porphyrins for benzylic anions.

The reactivity of the intermediates also accounts for the regioselectivity observed upon successive introduction of two meso substituents via a sequence of two LiR, H_2O, DDQ reaction sequences. Instead of the expected 2:1 ratio for the two possible regioisomers (with 5,10 and 5,15 substitution pattern) ratios of 4:1 or larger were observed.[8b] Sometimes, as in the reaction of **23** with LiPh to yield **24**, complete regioselectivity is observed. As similar results were also observed in reactions with porphyrin or 5-substituted porphyrins[8c] this effect is not due to steric or electronic effects of the β-substituents. Thus, the meso substituents introduced first govern the regioselectivity of subsequent S_NAr reactions.

Based on structural considerations for the identified intermediates a preferential location of the negative charge at the meso position opposite to that of the second LiR attack, i.e., giving a 5,15 disubstitution pattern, might be expected. However, this requires the anion to be located at a substituted position (from the first LiR reaction) where it would be destabilized compared to a 5,10 pattern. The typical mesomeric stabilization of benzylic anions is diminished in β-substituted porphyrins due to steric hindrance (Figure 5). This accounts for the generally higher regioselectivity for an attack of LiR at meso positions opposite to a meso alkyl residue compared to an attack at a meso position opposite to an aryl substituent. Additionally, it explains why β-substituted porphyrins with two meso aryl substituents in 5,10 arrangement are so far the only porphyrins that do not undergo S_NAr reactions with LiR.[8b]

Conclusions

The reaction of porphyrins with organolithium reagents proceeds via an addition-oxidation mechanism where the intermediates derived from free base porphyrins and metallo complexes have different electron distributions and conformations. These anionic intermediates are believed to possess a phlorin-like structure and the nickel(II) intermediates are stable against hydrolysis and exhibit a high degree of nucleophilic reactivity at the meso position opposite to the position of the nucleophilic attack of the organolithium reagent. Furthermore, the substituents at peripheral positions influence the chemical and structural properties of the intermediates and a protonation-deprotonation process in the hydrolysis step must exist for the nickel(II) intermediate. While several synthetic strategies have already been developed from these observations,[9,10] the present results indicate the possibility to synthesize phlorins in situ and we will now study the chemical and physicochemical properties of such reduced tetrapyrrole systems systematically.

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(20) (a) Fischer, H.; Lautsch, W. *Liebigs Ann. Chem.* **1937**, *528*, 247. (b) Woodward, R. B. *Ind. Chim. Belge* **1962**, 1293. Senge, M.; Senger, H. *Photochem. Photobiol.* **1988**, *48*, 711.

Experimental Section

General Methods. All chemicals used were of analytical grade and purified before use by distillation. THF was dried before use by distillation with sodium. To remove oxygen from the solvent, argon (99.999999%) was bubbled through absolute THF with a Teflon capillary for 1 h or more. Deuterated water (99.8% D) and hydrochlorid acid (37%, 99% D) were obtained from Merck; DCl used for reactions was diluted with D_2O under an argon atmosphere. All reactions with organolithium reagents were performed under a purified argon atmosphere using Schlenk techniques. Melting points were measured on a Büchi melting point apparatus and are uncorrected. Neutral or basic alumna (Alfa) (usually Brockmann Grade III, i.e., deactivated with 7% water) was used for column chromatography. Analytical thin-layer chromatography (TLC) was carried out using Merck silica gel 60 plates or alumina 60 (neutral, fluorescence indicator F_{254}) plates. ^1H and ^2H NMR spectra were recorded at frequency of 270 MHz (AC 270) and 500 MHz (AMX 500). All chemical shifts are given in ppm, referenced on the δ scale downfield from the TMS signal used as internal standard. Electronic absorption spectra were recorded with a Speccord S10 (Carl Zeiss) spectrophotometer using dichloromethane as solvent. Absorption spectra of the reactive intermediates were measured by transferring 10 μL aliquots from the reaction mixture under argon to a modified closed cell compartment filled with 2.5 mL degassed THF (abs). pH-Values were determined with a pH-Meter E603 (Metrohm Herisan). Mass spectra were recorded with a Varian MAT 711 mass spectrometer using EI technique with a direct insertion probe and an excitation energy of 80 eV.

General Procedure for the Deuteration Experiments with Butyllithium. A Schlenk flask was charged with 0.1 mmol of the porphyrin (ca. 50 mg) dissolved in 40 mL THF under an argon atmosphere and the solution was cooled to −70 °C. Within 15 min, butyllithium (0.75 mmol, 0.3 mL of a 2.5 M solution in cyclohexane) was added dropwise. After removal of the cold bath, the reaction mixture was stirred for 30 min and 1 mL deuterated water or dilute deuterated hydrochloric acid in an appropriate concentration was added. After 15 min, 4−6 equiv of DDQ in dry THF were added and stirring continued for 20 min. Finally, the mixture was filtered through neutral alumina and subjected to column chromatography on neutral alumina (Alfa) followed by recrystallization from CH_2Cl_2/methanol.

(5-Butyl-15-deutero-10,20-diphenylporphyrinato)-nickel(II) (9). A Schlenk flask was charged with 0.1 mmol of the porphyrin **5** (50 mg) dissolved in 40 mL THF under an argon atmosphere and the solution was cooled to −70 °C. Within 15 min, butyllithium (0.75 mmol, 0.3 mL of a 2.5 M solution in cyclohexane) was added dropwise. After removal of the cold bath, the reaction mixture was stirred for 30 min and 1 mL DCl (2 N) was added (pH ∼3−5) and the color of the reaction solvent changed to red at once. After 15 min, 6 equiv of DDQ (0.06 M) in dry THF were added and stirring continued for 20 min. Finally, the mixture was filtered through neutral alumina and subjected to column chromatography on neutral alumina (Alfa) eluting with ethyl acetate/*n*-hexane (1:100, v/v); yield 37 mg (0.064 mmol, 65%) as purple crystals, mp 230 °C (CH_2Cl_2/CH_3OH). UV−vis: λ_{max} (CH_2Cl_2)/nm 408 (log ϵ/dm^3 mol^{-1} cm^{-1} 5.18), 523 (4.03), 556 (3.20). ^1H NMR ($CDCl_3$): δ 1.15 (t, J = 7.6 Hz, 3H), 1.60−1.75 (m, 2H), 2.25−2.45 (m, 2H), 4.60 (t, J = 7.8 Hz, 2H), 7.55−7.65, 7.95−8.05 (each m,10H), 8.85 (m, 4H), 9.05, 9.35, (each d, J = 4.9 Hz, 4H), 9.70 (s, 0.25H). MS (EI, 80 eV): *m/z* 575 (M$^+$, 100%), 532 (M$^+$ − $CH_2CH_2CH_3$, 76), 288 (M^{2+}, 5). Anal. Calcd for $C_{36}H_{27.25}D_{0.75}N_4Ni \cdot 0.7\ CH_2Cl_2$: C, 69.50; H, 4.56; N, 8.84. Found: C, 69.46; H, 4.35; N, 8.73. HRMS: calcd for $C_{36}H_{27}DN_4Ni$ 575.1730, found 575.1763.

5-Butyl-15-chloro-10,20-diphenylporphyrin (10). This compound was isolated first as a byproduct of the synthesis of **11**. Chromatography eluting with ethyl acetate/*n*-hexane (1:100, v/v); yield 15 mg (0.027 mmol, 27%) as purple crystals, mp >300 °C (CH_2Cl_2/CH_3OH). UV−vis: λ_{max}(CH_2Cl_2)/nm 418 (log ϵ/dm^3 mol^{-1} cm^{-1} 5.24), 518 (3.99), 551 (3.76), 601 (3.52), 655 (3.68). ^1H NMR ($CDCl_3$): δ −2.60 (s, 2H), 1.15 (t, J = 7.6, 3H), 1.60−1.75 (m, 2H), 2.45−2.55 (m, 2H), 4.85 (t, J = 7.7, 2H), 7.75−7.85, 8.15−8.25 (each m, 10H), 8.85 (m, 4H), 9.45, 9.60, (each d, J = 4.8, 4H). MS (EI, 80 eV): *m/z* 552 (M$^+$, 100%), 509 (M$^+$ − $CH_2CH_2CH_3$, 94), 276 (M^{2+}, 16). HRMS: calcd for $C_{36}H_{29}ClN_4$ 552.2081, found 552.2067.

5-Butyl-15-deutero-10,20-diphenylporphyrin (11). A Schlenk flask was charged with 0.1 mmol of the porphyrin **6** (47 mg) dissolved in 40 mL THF under an argon atmosphere and the solution was cooled to −70 °C. Within 15 min, butyllithium (0.75 mmol, 0.3 mL of a 2.5 M solution in cyclohexane) was added dropwise. After removal of the cold bath, the reaction mixture was stirred for 30 min and 1 mL DCl (4 N) was added and the color of the reaction solvent (pH < 2) changed to blue at once. After 15 min, 6 equiv of DDQ (0.06 M) in dry THF were added and stirring continued for 20 min. Finally, the mixture was filtered through neutral alumina and subjected to column chromatography on neutral alumina (Alfa), eluting with ethyl acetate/*n*-hexane (1:100, v/v) The first fraction contained a chloro derivative **10** in 27% yield, while the second fraction gave 17 mg of **11** (0.033 mmol, 33%) as purple crystals, mp 250 °C (CH_2Cl_2/CH_3OH). UV−vis: λ_{max}(CH_2Cl_2)/nm 411 (log ϵ/dm^3 mol^{-1} cm^{-1} 5.14), 509 (3.84), 543 (3.28), 584 (3.35), 641 (3.01). ^1H NMR ($CDCl_3$): δ −3.02 (s, 2H), 1.15 (t, J = 7.5, 3H), 1.78−1.90 (m, 3H), 2.55−2.60 (m, 2H), 5.05 (t, J = 7.8, 2H), 7.75−7.85, 8.25−8.32 (each m, 10H), 8.95 (m, 4H), 9.25 (d, J = 4.9, 2H) 9.55 (d, J = 4.9, 2H). MS (EI, 80 eV): *m/z* 519 (M$^+$, 100%), 476 (M$^+$ − $CH_2CH_2CH_3$, 87), 260 (M^{2+}, 11). Anal. Calcd for $C_{36}H_{29}DN_4 \cdot 0.5\ H_2O$: C, 81.78; H, 5.72; N, 10.60. Found: C, 82.00; H, 5.59; N, 10.43. HRMS: calcd for $C_{36}H_{29}DN_4$ 519.2533, found 519.2536.

(5-Butyl-3,7,13,15,17-pentadeutero-10,20-diphenylporphyrinato)nickel(II) (12). A Schlenk flask was charged with 0.1 mmol of the porphyrin **6** (50 mg) dissolved in 50 mL THF under an argon atmosphere and the solution was cooled to −70 °C. Within 15 min, butyllithium (0.75 mmol, 0.3 mL of a 2.5 M solution in cyclohexane) was added dropwise. After removal of the cold bath, the reaction mixture was stirred for 30 min and 1 mL DCl (4 N) was added and the color of the reaction solution (pH < 2) changed to red at once. After 15 min, 6 equiv of DDQ (0.06 M) in dry THF were added and stirring continued for 20 min. Finally, the mixture was filtered through neutral alumina and subjected to column chromatography on neutral alumina (Alfa), eluting with ethyl acetate/*n*-hexane (1:100, v/v). Besides several green and blue polar fractions, the first fraction gave 43 mg (0.75 mmol, 75%) as purple crystals, mp 232 °C (CH_2Cl_2/CH_3OH). UV−vis: λ_{max}(CH_2Cl_2)/nm 408 (log ϵ/dm^3 mol^{-1} cm^{-1} 5.16), 523 (4.00), 556 (3.17). ^1H NMR ($CDCl_3$): δ 1.15 (t, J = 7.6, 3H), 1.60−1.75 (m, 2H), 2.25−2.45 (m, 2H), 4.60 (t, J = 7.8, 2H), 7.55−7.65, 7.95−8.05 (each m, 10H), 8.85 (m, 4H), 9.05, (d, J = 4.9, 0.3H), 9.35 (d, J = 4.9, 0.3H), 9.70 (s, 0.14H).^2H NMR ($CDCl_3$): δ 9.05 (d, br. 2D), 9.35 (d, br. 2D), 9.65 (s, br, 1D). MS (EI, 80 eV): *m/z* 579 (M$^+$, 100%), 536 (M$^+$ − $CH_2CH_2CH_3$, 92), 290 (M^{2+}, 2). Anal. Calcd for $C_{36}H_{23.75}D_{4.25}N_4Ni$: C, 74.69; H, 4.14; N, 9.68. Found: C, 74.27; H, 4.49; N, 9.74. HRMS: calcd for $C_{36}H_{23}D_5N_4Ni$ 579.1981, found 579.1985.

(5,10,15-Tributylporphyrinato)nickel(II) (14). A Schlenk flask was charged with 0.1 mmol of the porphyrin **13** (47 mg) dissolved in 40 mL THF under an argon atmosphere and the solution was cooled to −70 °C. Within 15 min, butyllithium (0.75 mmol, 0.3 mL of a 2.5 M solution in cyclohexane) was added dropwise. After removal of the cold bath, the reaction mixture was stirred for 30 min and 1 mL deuterated water was added. After 15 min, 6 equiv of DDQ (0.06 M) in dry THF were added and stirring continued for 20 min. Finally, the mixture was filtered through neutral alumina and subjected to column chromatography on neutral alumina (Alfa) eluting with ethyl acetate/*n*-hexane (1:100, v/v); yield 42 mg of **14** (0.08 mmol, 79%) as purple crystals, mp > 300 °C (CH_2Cl_2/CH_3OH). UV−vis: λ_{max}(CH_2Cl_2)/nm 410 (log ϵ/dm^3 mol^{-1} cm^{-1} 5.12), 528 (4.04). ^1H NMR ($CDCl_3$): 1.10−1.15 (m, 9H), 1.60−1.75 (m, 6H), 2.25−2.45 (m, 6H), 4.55−4.60 (m, 6H), 9.00−9.05 (d, J = 4.7, 2H), 9.25−9.35 (m, 6H), 9.45 (s, 1H). MS (EI, 80 eV): *m/z* 534 (M$^+$, 100%), 491 (M$^+$ − $CH_2CH_2CH_3$, 50), 448 (M$^+$ − 2 ×

$CH_2CH_2CH_3$, 7), 405 ($M^+ - 3 \times CH_2CH_2CH_3$, 14), 267 ($M^{2+}$, 6). HRMS: calcd for $C_{32}H_{36}N_4Ni$ 534.2293, found 534.2298.

(5,10,15-Tributyl-20-deuterioporphyrinato)nickel(II) 15. The synthesis followed the procedure given for compound **9**. Chromatography eluting with ethyl acetate/*n*-hexane (1:100, v/v); yielded 29 mg of **15** (0.055 mmol, 55%) as purple crystals from porphyrin **13** (47 mg, 0.1 mmol), mp >300 °C (CH_2Cl_2/CH_3OH). UV−vis: λ_{max}(CH_2Cl_2)/nm 410 (log ϵ/dm^3 mol^{-1} cm^{-1} 5.14), 528 (4.06). ^{1}H NMR ($CDCl_3$): δ 1.10−1.15 (m, 9H), 1.60−1.75 (m, 6H), 2.25−2.45 (m, 6H), 4.55−4.60 (m, 6H), 9.00−9.05 (d, *J* = 4.7, 2H), 9.25−9.35 (m, 6H), 9.45 (s, 0.4H). MS (EI, 80 eV): *m*/*z* 535 (M^+, 100%), 492 ($M^+ - CH_2CH_2CH_3$, 51), 449 ($M^+ - 2 \times CH_2CH_2CH_3$, 9), 406 ($M^+ - 3 \times CH_2CH_2CH_3$, 17), 268 ($M^{2+}$, 6). HRMS: calcd for $C_{32}H_{35}DN_4Ni$ 535.2356), found 535.2396.

5-Butyl-15-deutero-2,3,7,8,12,13,17,18-octaethylporphyrin (18). Free base 2,3,7,8,12,13,17,18-octaethylporphyrin **16** (100 mg, 0.19 mmol) was dissolved in 50 mL THF and cooled to −70 °C. Butyllithium (0.5 mL, 1 mmol of the 2 M stock solution) was added dropwise and the mixture stirred for 15 min. DCl (1 mL of a 4% deuterated hydrochloride solution) was added and stirring continued for 20 min. This was followed by addition of 10 mL of a 0.06 M DDQ solution in dry THF to the cold reaction mixture. The cold bath was removed and after stirring for another 20 min the reaction mixture was filtered through alumina (grade I) and chromatographed on neutral alumina (grade III) with hexane/dichloromethane (1:1, v/v). The deuterated compound **18** was obtained in 43% yield (49 mg, 0.082 mmol) as purple crystals, besides 18% of educt, mp 213 °C (CH_2Cl_2/CH_3OH). UV−vis: λ_{max}(CH_2Cl_2 + 1% NEt_3)/nm 407 (log ϵ/dm^3 mol^{-1} cm^{-1} 5.43), 508 (4.37), 543 (4.04), 625 (3.58). ^{1}H NMR ($CDCl_3$): δ −2.80, −2.72 (s, br, 2H), 0.89 (m, 3H), 1.59 (m, 4H), 1.88 (m, 24H), 4.10 (m, 16H), 5.12 (m, 2H), 10.11 (s, 2H). MS (EI, 80 eV): *m*/*z* 591 (M^+, 100%), 548 ($M^+ - C_3H_7$, 25), 533 ($M^+ - C_3H_7 - CH_3$, 7), 518 ($M^+ - C_3H_7 - CH_3 - CH_3$, 7), 295 ($M^{2+}$, 15). Anal. Calcd for $C_{40}H_{55}N_4$: C, 80.35; H, 9.38; N, 9.37. Found: C, 80.09: H, 9.17; N, 9.26. HRMS: calcd for $C_{40}H_{53}DN_4$ 591.4411, found 591.4443.

(5-Butyl-15-deutero-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) (19). Porphyrin **5** (100 mg, 0.17 mmol) was placed in a Schlenk flask and 60 mL THF and 0.3 mL of the butyllithium stock solution were added at − 70 °C. After 10 min the cold bath was removed and the reaction mixture was treated with 1 mL D_2O (containing 2% DCl). After stirring for 30 min the solution was treated with 10 mL of a 0.06 M solution of DDQ in dry THF. Column chromatography on neutral alumina (grade III), eluting with dichlormethane/hexane (1:6, v/v), yielded three fractions. The first, major red band was (5-butyl-2,3,7,8,12,13,17,18-octaethyl-15-deuterioporphyrinato)nickel(II) **19**, only partially labeled with deuterium (75 mg, 0.11 mmol, 68%, purple crystals, 10% deuterium labeled) the third band contained 13% educt, and the second fraction yielded 24 mg (0.038 mmol, 23%) of the chlorinated byproduct **20** (see below). Data for **18**: mp 242 °C (CH_2Cl_2/CH_3OH). UV−vis: λ_{max}(CH_2Cl_2)/nm 410 (log ϵ/dm^3 mol^{-1} cm^{-1} 5.20), 534 (3.93), 573 (4.00). ^{1}H NMR: ($CDCl_3$): δ 0.44 (t, *J* = 7.18, 3H), 0.75−0.83 (m, 4H), 1.60 (t, *J* = 7.54, 6H), 1.67 (m, 12H), 1.75 (t, *J* = 7.45, 6H), 3.71 (s, br, 16H), 4.34 (t, *J* = 7.63, 2H), 9.25 (s, 2H), 9.26 (s, 0.9H, 10% deuterium label). MS (EI, 80 eV): 647 (M^+, 47%), 602 (M^+, $C_{40}H_{52}N_4Ni$, − C_3H_7, 11), 323 (M^{2+}, 16). HRMS: calcd for $C_{40}H_{51}DN_4Ni$ 647.3608, found 647.3611.

(5-Chloro-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) (20). This compound was obtained as a byproduct of the synthesis of **19**, mp 258 °C (CH_2Cl_2/CH_3OH). UV−vis: λ_{max}(CH_2Cl_2)/nm 407 (log ϵ/dm^3 mol^{-1} cm^{-1} 5.42), 530 (4.17), 566 (4.27). ^{1}H NMR ($CDCl_3$): δ 0.81 (m, 16H), 1.73 (m, 6H), 3.78 (m, 12H), 3.99 (q, *J* = 4.5, 4H), 9.37 (s, 1H), 9.40 (s, 2H). MS: (EI, 80 eV): *m*/*z* 624 (M^+, 100%), 609 ($M^+ - CH_3$, 5), 590 ($M^+ - Cl + H$, 32), 312 (M^{2+}, 8). HRMS: calcd for $C_{36}H_{43}ClN_4Ni$ 624.2530, found 624. 2578.

5-Deutero-2,3,7,8,12,13,17,18-octaethyl-10,15-diphenylporphyrin (22). 2,3,7,8,12,13,17,18-Octaethyl-5-phenylporphyrin **21** (100 mg, 0.16 mmol) was dissolved in 40 mL THF and treated with 1 mL (1.8 mmol) phenyllithium. After heating to 40 °C and stirring for 15 min the mixture was cooled to 0 °C and 1 mL deuterated hydrochloride (4%) was added. Subsequently, a solution of 10 mL DDQ in dry THF (0.06 M) was added and the reaction mixture was stirred for another 20 min at room temperature. Column chromatography on neutral alumina (grade III) eluting with dichloromethane/*n*-hexane (1:4, v/v) gave a major red fraction yielding 97 mg (88%, 0.14 mmol) of purple crystals of the title compound, mp 243 °C (CH_2Cl_2/CH_3OH). UV−vis: λ_{max}(CH_2Cl_2 + 1% NEt_3)/nm 424 (log ϵ/dm^3 mol^{-1} cm^{-1} 5.19), 520 (3.98), 592 (3.71), 655 (2.97). ^{1}H NMR ($CDCl_3$): δ −2.63 (s, br, 2H), 0.46, 0.65, 1.57, 1.84 (each t, *J* = 7,5 Hz, 24H), 2.24, 2.71 (each m, 8H), 3.84, 3.96 (each m, 8H), 7.86 (m, 6H), 8.38 (d, *J* = 4.3 Hz, 4H), 9.67 (s, 1H). MS (EI, 80 eV): *m*/*z* 687 (M^+, 100%), 658 ($M^+ - C_2H_5$, 7), 610 ($M^+ - C_6H_5$, 5), 344 (M^{2+}, 8). HRMS: calcd for $C_{48}H_{53}DN_4$ 687.4411, found 687.4432.

(5-Hexyl-10-phenyl-2,3,7,8,12,13,17,18-octaethylporphyrinato)nickel(II) (24). A solution of 100 mg (0.15 mmol) (2,3,7,8,12,13,17,18-octaethyl-5-hexylporphyrinato)nickel(II) **23** in dry THF was treated at room temperature with 1 mL phenyllithium (1.8 mmol). The mixture was heated to 40 °C and stirred for 15 min. Subsequently, the solution was cooled to 0 °C followed by treatment with 1 mL water and stirring was continued for 5 min. 10 mL DDQ in methylene chloride (0.06 M) was added and the reaction mixture was stirred for another 20 min at room temperature. The mixture was filtered through a short plug of alumina (grade I). After evaporation of the solvent, the final purification involved column chromatography on alumina (grade III) with dichloromethane/*n*-hexane (1:8, v/v) as eluent. Besides 11% of educt the second, slower running brown band gave 71 mg (0.095 mmol, 63%) of purple crystals after recrystallization, mp 248 °C (CH_2Cl_2/CH_3OH). UV−vis: λ_{max}(CH_2Cl_2)/nm 420 (log ϵ/dm^3 mol^{-1} cm^{-1} 5.15), 546 (4.95), 585 (3.95). ^{1}H NMR ($CDCl_3$): δ 0.49 (t, *J* = 7.3, 3H), 0.55−1.05 (m, 14H), 1.60−1.92 (m, 18H), 2.49 (m, 4H), 3.70 (m, 12H), 4.23 (m, 2H), 7.52 (s, br, 1H), 7.52 (m, 2H), 7.64 (m, 2H), 9.10, 9.23 (each s, 2H). MS (EI, 80 eV): *m*/*z* 750 (M^+, 55%), 679 ($M^+ - C_5H_{11}$, 11). HRMS: calcd for $C_{48}H_{60}N_4Ni$ 750.4172, found 750.4138.

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Supporting Information Available: ^{1}H NMR spectra of **9**, **10**, **11**, **14**, **15**, **18**, **19**, **20**, and **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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