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Opposing Influences of Ruffling and Doming Deformation on the 4-N Cavity Size of Porphyrin Macrocycles: The Role of Heme Deformations Revealed

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Nonplanar heme distortion has been recognized as a conserved structural feature of particular proteins.[1,2] Most recent computational study suggested that large-scale conformational change may play a more important role in the biomolecular function of the B_{12}-dependent enzyme than was previously thought.[3] Although such conformational changes are necessary for heme catalysis,[4,5] they are energetically unfavorable,[1,6] and can lead to changes in the oxygen affinity of heme proteins.[7,8] Furthermore, it can stabilize the unligated low-valent iron(II) oxidation state and generate a high-valent iron(V)–oxo complex,[9,10] which is a potent oxidant involved in the hydroxylation of inactivated C–H bonds.[11]

The role of heme distortion and its functional occurrence remains complicated and unclear. For this reason, significant attention has been focused on exploring the distortion properties of porphyrins, including their photophysical,[12–15] axial ligation,[16–18] electron transfer,[19,20] molecular stimulation,[4,21] redox potential,[22] and catalytic properties.[23] However, the impact of these deformations on the chemical properties of porphyrins remains unclear.

The size change of 4-N cavity in heme macrocycle may play a critical role in the functional occurrence. Several deformation modes of the heme macrocycle have been identified, including the dominant ruffling (*ruf*-), saddling (*sad*-), occasional waving (*wav*-), doming (*dom*-), and propeller-like (*pro*-) modes.[17,24] In all of these distortion modes, the distance among central four N atoms is inevitably changed due to the deviation of pyrrole rings from their original coplanarity. The *ruf*- and *sad*-deformation systems are commonly used as model ones to simulate the role of heme distortion and investigate spectral properties.[12,25,26] The *dom*-deformation, which is possibly short of a suitable sample with *dom*-feature, however, has rarely been studied.[27]

Nonplanar porphyrins show an observable out-of-plane feature, and the occurrence of the out-of-plane deformations is generally accompanied with the formation of in-plane components in the macrocycle.[27] The *ruf*- and *dom*-type porphyrins, taking on a typical out-of-plane deformation, will also induce an in-plane change. According to geometric analysis of the porphyrin macrocycle, the size of the 4-N cavity will be contracted in the ruffling system, as the degree of macrocyclic distortion increases (Figure 1). In contrast, the size of the cavity will be expanded in a doming deformation under the same increase of distortion degree.

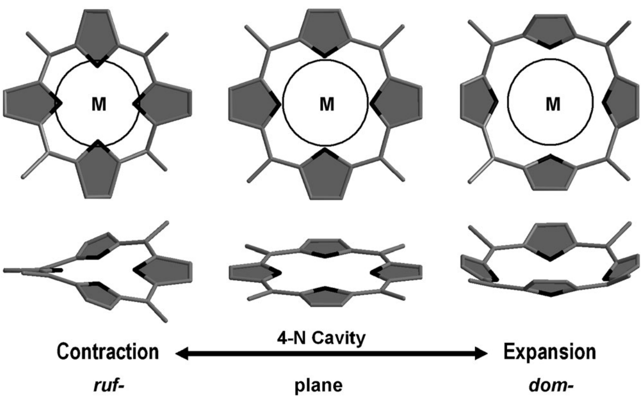

Figure 1. The influence of ruffling (*ruf*-) and doming (*dom*-) deformation modes on the 4-N cavity size in porphyrin macrocycles. The circle represents the free size of complexed metal ion.

The free M–N (M = Mn, Fe, Co, Ni, Cu, or Zn ion with a general valency) bond lengths were in the range of 1.97–2.06 Å,[28–30] providing a 4-N cavity of $L_{NN} = 3.94–4.12$ Å after complexation (L_{NN} = average length of diagonal N atoms in the porphyrin macrocycle). A planar porphyrin can readily complex a M ion because of its large cavity size ($L_{NN} \approx 4.10$ Å). However, the question is, whether can the cavity of a distorted porphyrin can be reduced to be smaller than the minimum size ($L_{NN} < 3.94$ Å) or enlarged to be larger than the maximum size ($L_{NN} > 4.12$ Å).

The macrocyclic deformation modes and the degree of distortion in natural heme can be exactly adjusted with ease by the coordination of its prosthetic group[31] and the regulation of its side chains in proteins.[18,32] Whilst the development of artificial nonplanar systems, including the distorted

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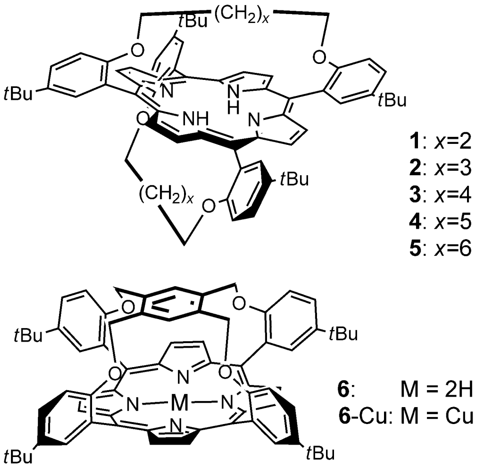
periphery-crowded porphyrins[33,34] and the strapped (or basketed) ones,[35,36] gave compounds with reliable deformation modes capable of producing enough distortion, they cannot meet the specificity of conformation and the invariability of distortion degree required in this field. This significantly limits a systematic investigation into the relationship of the unique functions of heme to the deformation modes and distortion degree.

In this paper, we clarify the role of macrocyclic deformation modes and distortion degree in heme for a series of 5,15-10,20-di-strapped free-base porphyrins **1**–**5** and a capped porphyrin **6** shown in Scheme 1, which have been developed as model compounds with the *ruf*- and *dom*-deformation modes, respectively, to investigate the influence of macrocyclic deformation on 4-N cavity size. Results indicated that the free cavity in the two types of nonplanar porphyrins showed an opposing trend, as the degree of distortion increased, implying a larger size range than that of the free-metal ions in the fourth period. Furthermore, we found that the spectral redshift of the nonplanar porphyrins was closely related to the size of the macrocyclic cavity for of the same deformation mode, providing an effective way to track changes in macrocyclic cavity in size.



Scheme 1. Model compounds 5,15-10,20-di-strapped free-base porphyrins **1**–**5** and the capped porphyrin **6** with its copper(II) complex **6**-Cu.

The crystal structures of the model compounds revealed that the di-strapped macrocycles adopt a typical *ruf*-deformation mode, whereas the capped examples adopt a typical *dom*-form (Figure 2). These structures effectively avoid disturbances due to substituent effects, and the exchange of conformations is similar to those reported for peripherally crowded porphyrins.[37] This represents a unique feature that makes these structures distinguishable from many previously reported artificial nonplanar systems.[12,38–40]

The 4-N-cavity size could be reduced in the *ruf*-type macrocycle and enlarged in the *dom*-type example by increasing the degree of distortion. Furthermore, the variable cavity size could completely exceed the free diameter of the central metal ions (for fourth-period metals). For the di-strapped porphyrins **1**–**5**, the shorter alkyl straps induced a greater degree of macrocyclic distortion. The length of the straps could be flexibly adjusted by changing the number of carbon atoms (N_C from 8 to 4) providing a variation in the L_{NN} of 3.87 to 4.10 Å (Table 1). A cavity size less than the minimum value ($L_{NN}=3.94$ Å) could be achieved in the di-strapped porphyrins **1** and **2**. For the capped porphyrin **6**, the L_{NN} was 4.17 Å, which is a larger cavity size than the maximum value ($L_{NN}=4.12$ Å).

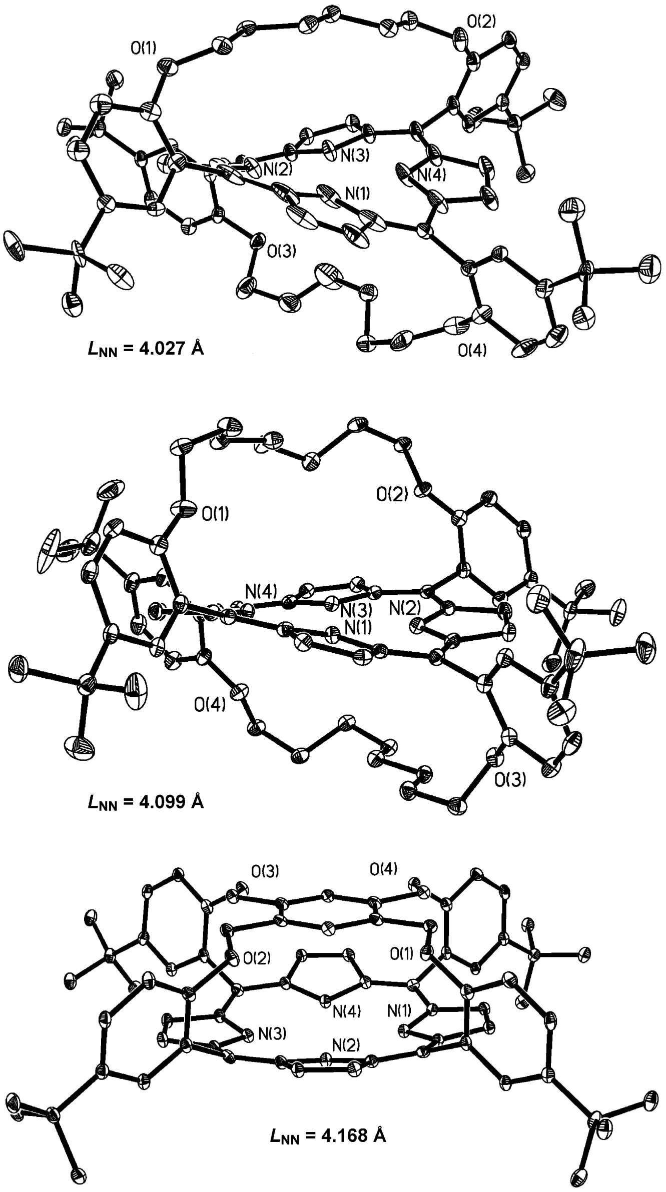


Figure 2. The crystal structures of compounds **3** (top), **5** (middle), and **6** (bottom).

The spectral redshift observed for the distorted porphyrin is believed to originate from the hybrid orbital-deformation effect.[12] The redshifts of the tetrapyrrole macrocycles are

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Table 1. The core size and the maxima of six model compounds.

Compound	**1**	**2**	**3**	**4**	**5**	**6**
L_{NN} [Å][a]	3.869[b]	3.929[b]	4.027	4.065[b]	4.099	4.168
λ_{max} [nm][c]	446.2	438.6	429.8	422.8	423.6	432.0

[a] L_{NN} is the averaged length between diagonal N atoms in the porphyrin center. [b] The values were acquired from DFT computation by applying the B3LYP hybrid functional with a 6-31G basis set (see the Supporting Information). [c] λ_{max} is the maxima at Soret band.

potentially useful indicators of ring nonplanarity. The electronic spectra of the model porphyrins **1**–**5** are significantly redshifted (Figure 3). Their maxima were observed to redshift over the range of $\lambda = 422.8$ to 446.2 nm (from **4**, **5**, **3**, **2** to **1**) at the Soret band, as the degree of distortion increased. A good linear correlation was found between the maxima and the L_{NN} values for the *ruf*-type compounds (see the Supporting Information). The maxima in the *dom*-type compound **6** was observed at $\lambda = 432.0$ nm, implying a degree of macrocyclic distortion between compounds **2** and **3** (Figure 3). The L_{NN} value of these compounds (4.17 Å), however, was much greater than the maximum value observed in the above described *ruf*-type compounds and other planer-type compounds reported in the literature.[41] Therefore, changing size of the 4-N cavity cannot be followed solely by the spectral redshift, and the deformation mode of the macrocycle must also be considered. These findings afford an indispensable additional tool in monitoring the degree of distortion in porphyrin macrocycles.

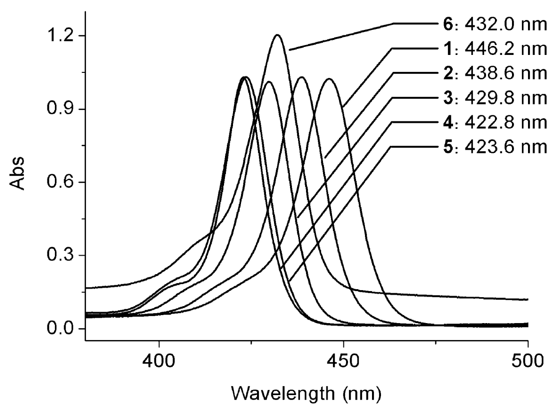

Figure 3. Comparison of absorption spectra of the di-strapped porphyrins **1**–**5** and the capped porphyrin **6** at the Soret band in a $CHCl_3$ solution ($\approx 2.0\times10^{-6}$ M) at 293 K.

In general, the size of the 4-N cavity can change during complexation to match the ionic size of the metal. At the same time, the complexing metal ion changes (including compression or enlargement) to match the changed 4-N cavity size. Theoretically, the complexation of metal ions to the pressed cavity ($L_{NN} < 3.94$ Å) should become increasingly difficult, as the degree of distortion in a contraction-type (e.g., *ruf*-) macrocycle increases.

A larger cavity ($L_{NN} > 4.12$ Å) facilitates complexation in an expansion-type (e.g., *dom*-) system, but both the expanded cavity and the complexed metal ion tend to maintain their original size. The copper(II) complex **6**-Cu was prepared to assess changes in the 4-N cavity size of *dom*-type systems before and after complexation.[42] The crystal structure revealed contraction of the cavity ($L_{NN} = 4.01$ Å) after complexation, with a difference of 0.16 Å (Figures 2 and 4).

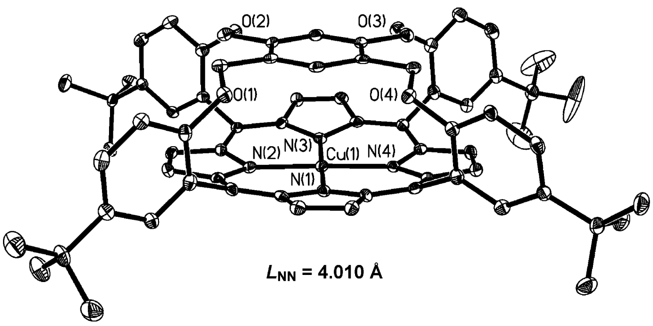

Figure 4. The crystal structure of compound **6**-Cu. L_{NN} is described in Figure 2.

In recent report, the cavity contraction of another in-plane type (*sad*-) copper(II) porphyrin complex ($L_{NN} = 3.96$ Å) revealed metal-ion shrinkage.[43] These facts illustrate that in compound **6**-Cu is a force balance between contraction of the 4-N cavity and expansion of the copper ion. The crystal structures of the synthetic porphyrins were further analyzed by using a normal structural decomposition method for quantifying their out-of-plane and in-plane distortions. (see Figure S3 in the Supporting Information).

Changes in the size of the 4-N cavity directly influence the electron cloud density of the complexed metal ion. The smaller cavity presses against the central metal ion leading to an increase in electron density (Figure 5 left), whereas an expanded cavity relaxes the central ion leading to a reduction in density (Figure 5 right). When the change in density reaches a certain level, an electron transfer including possible electronic rearrangement and transition in d orbitals, occurs. The change in the electron-cloud density is easily determined by DFT computation. As a consequence, the va-

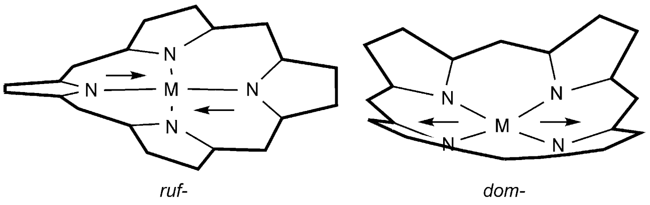

Figure 5. Stretching in the in-plane direction of the central metal ion (M of the fourth period) in differential nonplanar modes.

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lency of the central metal will increase (contraction-type deformation, e.g., *ruf*-) or descend (expansion-type form, e.g., *dom*-). Therefore, this model can satisfactorily explain, how the distortion of heme can regulate and stabilize its iron(II, III, IV, or V)-containing complexes by changing the deformation mode and degree of macrocyclic distortion.[9,10] That is, when the size of the macrocyclic cavity decreases, a d electron can leave forming a stable high-valent iron material. If the size of the cavity increases, the external electron can return to its valent orbit, and a low-valent state of the central ion occurs.

We systematically investigated the influence of macrocyclic deformation modes on the size of the 4-N cavity. Two types of nonplanar porphyrins, including a *ruf*-type and a *dom*-type, were used as model compounds, taking on typical ruffling and doming deformation modes, respectively. The size of 4-N cavity was found to depend not only on the degree of distortion, but also on the deformation mode of the macrocycle. Furthermore, it was found that the 4-N cavity size could exceed the limit value (including the minimum and the maximum) of free metal ions from the fourth period. These observations are in line with the structural features of heme, providing a useful model for simulating its unique properties. These findings have methodically revealed the roles of the deformation mode and degree of macrocyclic distortion in heme. Moreover, the series of nonplanar porphyrins developed could be used as ideal model systems for exploring the characteristics of heme distortion and optimizing the biochemical functions of metalloporphyrins.

Experimental Section

Preparation of model compounds: The target materials, nonplanar porphyrins **1**–**6** were prepared according to our previous report[12] and deliberately characterized by MS, HRMS, NMR, UV/Vis, and X-ray methods to access their purity (see the Supporting Information).

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[1] J. A. Shelnutt, X.-Z. Song, J.-G. Ma, S.-L. Jia, W. Jentzen, C. J. Medforth, *Chem. Soc. Rev.* **1998**, *27*, 31–41.
[2] C. Colas, P. R. Ortiz de Montellano, *Chem. Rev.* **2003**, *103*, 2305–2332.
[3] J. Pang, X. Li, K. Morokuma, N. S. Scrutton, M. J. Sutcliffe, *J. Am. Chem. Soc.* **2012**, *134*, 2367–2377.
[4] Z. Shi, R. Franco, R. Haddad, J. A. Shelnutt, G. C. Ferreira, *Biochemistry* **2006**, *45*, 2904–2912.
[5] J. Yin, S. E. Andryski, A. E. Beuscher, R. C. Stevens, P. G. Schultz, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 856–861.
[6] D. Li, D. J. Stuehr, S. R. Yeh, D. L. Rousseau, *J. Biol. Chem.* **2004**, *279*, 26489–26499.
[7] D. E. Bikiel, F. Forti, L. Boechi, M. Nardini, F. J. Luque, M. A. Martí, D. A. Estrin, *J. Phys. Chem. B* **2010**, *114*, 8536–8543.
[8] X. Ma, N. Sayed, A. Beuve, F. van den Akker, *EMBO J.* **2007**, *26*, 578–588.
[9] P. Pellicena, D. S. Karow, E. M. Boon, M. A. Marletta, J. Kuriyan, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 12854–12859.
[10] C. Olea, Jr., E. M. Boon, P. Pellicena, J. Kuriyan, M. A. Marletta, *ACS Chem. Biol.* **2008**, *3*, 703–710.
[11] P. R. Ortiz de Montellano, J. De Voss, *Nat. Prod. Rep.* **2002**, *19*, 477–493.
[12] Z. C. Zhou, C. Z. Cao, Q. H. Liu, R. Q. Jiang, *Org. Lett.* **2010**, *12*, 1780–1783.
[13] C. M. Drain, C. Kirmaier, C. J. Medforth, D. J. Nurco, K. M. Smith, D. Holten, *J. Phys. Chem.* **1996**, *100*, 11984–11993.
[14] R. E. Haddad, S. Gazeau, J. Pécaut, J. C. Marchon, C. J. Medforth, J. A. Shelnutt, *J. Am. Chem. Soc.* **2003**, *125*, 1253–1268.
[15] H. Ryeng, A. Ghosh, *J. Am. Chem. Soc.* **2002**, *124*, 8099–8103.
[16] A. B. Cowley, D. R. Benson, *Inorg. Chem.* **2007**, *46*, 48–59.
[17] S. Neya, M. Suzuki, T. Hoshino, H. Ode, K. Imai, T. Komatsu, A. Ikezaki, M. Nakamura, Y. Furutani, H. Kandori, *Biochemistry* **2010**, *49*, 5642–5650.
[18] T. Shokhireva, R. E. Berry, E. Uno, C. A. Balfour, H. Zhang, F. A. Walker, *Proc. Natl. Acad. Sci. USA* **2003**, *100*, 3778–3783.
[19] J. Haggin, *Chem. Eng. News* **1991**, *69*, 23–24.
[20] G. Simonneaux, A. Bondon, *Chem. Rev.* **2005**, *105*, 2627–2646.
[21] E. Sigfridsson, U. Ryde, *J. Biol. Inorg. Chem.* **2003**, *8*, 273–282.
[22] C. Olea, J. Kuriyan, M. A. Marletta, *J. Am. Chem. Soc.* **2010**, *132*, 12794–12795.
[23] E. M. Maes, S. A. Roberts, A. Weichsel, W. R. Montfort, *Biochemistry* **2005**, *44*, 12690–12699.
[24] M. O. Senge in *The Porphyrin Handbook, Vol. 1* (Eds.: K. M. Kadish, K. M. Smith, R. Guilard), Academic Press, Boston, **2000**, p. 239.
[25] Q. Huang, C. J. Medforth, R. Schweitzer-Stenner, *J. Phys. Chem. A* **2005**, *109*, 10493–10502.
[26] M. Veyrat, O. Maury, F. Faverjon, D. E. Over, R. Ramasseul, J.-C. Marchon, I. Turowska-Tyrk, W. R. Scheidt, *Angew. Chem.* **1994**, *106*, 200–203; *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 220–223.
[27] W. Jentzen, J.-G. Ma, J. A. Shelnutt, *Biophys. J.* **1998**, *74*, 753–763.
[28] W. M. Haynes in *Handbook of Chemistry and Physics*, 91st ed., CRC, Boca Raton, London, New York, Section 9, p. 18, and Section 12, p. 11.
[29] J. A. Dean in *Lange's Handbook of Chemistry*, 15th ed., McGraw-Hill Book, New York, Section 4, p. 34
[30] A. M. Rich, R. S. Armstrong, P. J. Ellis, H. C. Freeman, P. A. Lay, *Inorg. Chem.* **1998**, *37*, 5743–5753.
[31] W. Gong, B. Hao, S. S. Mansy, G. Gonzalez, M. A. Gilles-Gonzalez, M. K. Chan, *Proc. Natl. Acad. Sci. USA* **1998**, *95*, 15177–15182.
[32] S. A. Roberts, A. Weichsel, Y. Qiu, J. A. Shelnutt, F. A. Walker, W. R. Montfort, *Biochemistry* **2001**, *40*, 11327–11337.
[33] C. J. Medforth, R. E. Haddad, C. M. Muzzi, N. R. Dooley, L. Jaquinod, D. C. Shyr, D. J. Nurco, M. M. Olmstead, K. M. Smith, J.-G. Ma, J. A. Shelnutt, *Inorg. Chem.* **2003**, *42*, 2227–2241.
[34] M. K. Ellison, C. E. Schulz, W. R. Scheidt, *J. Am. Chem. Soc.* **2002**, *124*, 13833–13841.
[35] T. Picaud, C. Le Moigne, B. Loock, M. Momenteau, A. Desbois, *J. Am. Chem. Soc.* **2003**, *125*, 11616–11625.
[36] B. Morgan, D. Dolphin, R. H. Jones, T. Jones, F. W. B. Einstein, *J. Org. Chem.* **1987**, *52*, 4628–4631.
[37] Y. J. Song, R. E. Haddad, S. L. Jia, S. Hok, M. M. Olmstead, D. J. Nurco, N. E. Schore, J. Zhang, J. G. Ma, K. M. Smith, S. Gazeau, J. Pécaut, J. C. Marchon, C. J. Medforth, J. A. Shelnutt, *J. Am. Chem. Soc.* **2005**, *127*, 1179–1192.

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[38] K. M. Mullen, M. J. Gunter, *J. Org. Chem.* **2008**, *73*, 3336–3350.

[39] S. Fantauzzi, E. Gallo, E. Rose, N. Raoul, A. Caselli, S. Issa, F. Ragaini, S. Cenini, *Organometallics* **2008**, *27*, 6143–6152.

[40] H. Miyaji, H. K. Kim, E. K. Sim, C. K. Lee, W. S. Cho, J. L. Sessler, C. H. Lee, *J. Am. Chem. Soc.* **2005**, *127*, 12510–12512.

[41] M. O. Senge, C. J. Medforth, T. P. Forsyth, D. A. Lee, M. M. Olmstead, W. Jentzen, R. K. Pandey, J. A. Shelnutt, K. M. Smith, *Inorg. Chem.*, **1997**, *36*, 1149–1163.

[42] The di-strapped porphyrins **1**–**5** cannot be complexed with the copper(II) ion under the existing conditions metalated.

[43] W. Chen, M. E. El-Khouly, S. Fukuzumi, *Inorg. Chem.* **2011**, *50*, 671–678.

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