Formation and Isolation of a Four-Electron Reduced Porphyrin Derivative via Further Reduction of a Stable 20π Isophlorin

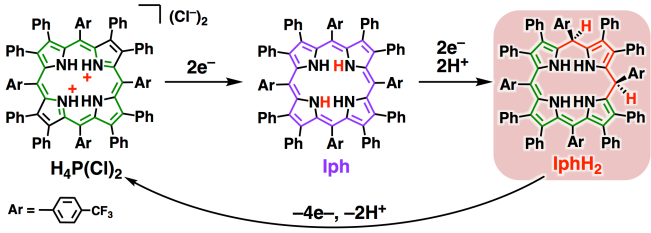
Wataru Suzuki,[a] Hiroaki Kotani,[a] Tomoya Ishizuka,[a] Yoshihito Shiota,[b] Kazunari Yoshizawa,[b] and Takahiko Kojima*[a]

Abstract: The two-electron reduction of a diprotonated dodecaphenylporphyrin derivative by $Na_2S_2O_4$ gave a corresponding isophlorin (**Iph**) selectively. Formation of **Iph** was confirmed by spectroscopic measurements and the isolation of tetra-methylated **Iph**. Further reduction of **Iph** proceeded to form an unprecedented four-electron reduced porphyrin (**IphH$_2$**), which is fully characterized by spectroscopic and X-ray crystallographic analysis. **IphH$_2$** with a unique conformation is capable of performing a reversibility to reproduce the starting porphyrin by the chemical oxidation, which acts as a proton-coupled four-electron reversible redox system.

Porphyrins are widely known to be 18π conjugated aromatic macrocycles and redox-active molecules showing reversible multi-redox processes. So far, the interesting redox properties of porphyrins have been investigated mainly through electrochemical measurements for several decades.[1] In addition, porphyrins with a phenolic moiety as a redox-active site at the periphery have been reported to show reversible multielectron redox behavior by external stimuli.[2] As an alternative candidate for a porphyrinoid showing multi-electron redox behavior without redox-active moieties at the periphery, is considered a multi-electron reduced porphyrin such as porphyrinogen and isophlorin, which have been proposed as intermediates in the synthetic pathway of porphyrins.[3] However, there is no report on the reversible redox system as a "multi-electron pool" based on the porphyrin framework without redox-active sites because of the instability of multi-electron reduced porphyrinoids.

Among various species of reduced porphyrinoids, isophlorin, which is one of the two-electron reduced form of a porphyrin in a 20π conjugated system, has attracted much attention due to the fact that isophlorin undergoes the two-electron oxidation to afford porphyrin.[3-7] So far, some isophlorin derivatives have been isolated through the reduction of corresponding porphyrins having highly positive central ions (Si(IV), Ge(IV))[4] or core modified porphyrins[5] such as tetraoxaporphyrin, showing 20π antiaromatic character. However, no investigation on further reduction of isophlorin has been reported, in spite of the fact that a porphyrin-based redox system is expected to act as a reversible multi-electron-redox system.

We have focused on a diprotonated saddle-distorted dodecaphenylporphyrin (**H$_4$DPP^{2+}**)[8] as an appropriate precursor for the formation of a corresponding isophlorin derivative, since **H$_4$DPP^{2+}** shows a high reduction potential to induce disproportionation of one-electron reduced species of **H$_4$DPP^{2+}** ($H_4DPP^{\bullet+}$), affording two-electron reduced species.[8b] Herein, we would like to report the selective formation of an isophlorin derivative (**Iph**) from **H$_4$DPP^{2+}** having electron-withdrawing trifluoromethyl (CF_3) groups at the *para*-position of *meso* phenyl groups (**H$_4$P(Cl)$_2$**). Interestingly, it was revealed that **Iph** could be further reduced to form a unique four-electron reduced porphyrin (**IphH$_2$**), which was fully characterized for the first time. In addition, **IphH$_2$** undergoes the four-electron oxidation to afford the starting porphyrin, which acts as a reversible multi-redox system (Scheme 1).



Scheme 1. The multi-electron-redox cycle composed of a four-electron-reduced porphyrin (**IphH$_2$**) via the selective formation of **Iph** from **H$_4$P(Cl)$_2$**.

A diprotonated dodecaphenylporphyrin derivative with four CF_3 groups, **H$_4$P(Cl)$_2$**, was synthesized based on a literature method.[9] Characterization of **H$_4$P(Cl)$_2$** was conducted by spectroscopic measurements, elemental analysis, and X-ray crystallography. In the molecular structure of **H$_4$P(Cl)$_2$** (Figure S1), **H$_4$P(Cl)$_2$** shows a large saddle distortion (Δrms = 0.81 Å)[10], which is similar to that of **H$_4$DPP^{2+}** (Δrms = 0.87 Å).[8a] Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) of **H$_4$P(Cl)$_2$** showed reversible two-electron reduction waves of **H$_4$P(Cl)$_2$** at –0.67 V vs Fc/Fc$^+$ in DMSO at 298 K containing 0.1 M [N(*n*-butyl)$_4$]PF_6 ($TBAPF_6$) as an electrolyte (Figure S2a). The reduction potential of **H$_4$P(Cl)$_2$** (–0.67 V) is slightly more positive than that of **H$_4$DPP^{2+}** (–0.73 V) due to the electron-withdrawing CF_3 groups (Figure S2b).

Upon addition of 4 equiv. $Na_2S_2O_4$ in H_2O to a DMSO solution containing **H$_4$P(Cl)$_2$** under Ar, UV-Vis spectral changes were observed as shown in Figure S3. The Soret band at 495 nm and the Q band at 706 nm due to **H$_4$P(Cl)$_2$** disappeared completely with a concomitant appearance of new bands at 476 nm and 567 nm (Figure S3). When the reduction reaction of

[a] W. Suzuki, Dr. H. Kotani, Dr. T. Ishizuka, Prof. Dr. T. Kojima
Department of Chemistry
Graduate School of Pure and Applied Sciences
University of Tsukuba
1-1-1 Tennoudai Tsukuba, Ibaraki 305-8571 (Japan)
E-mail: kojima@chem.tsukuba.ac.jp
[b] Prof. Dr. Y. Shiota, Prof. Dr. K. Yoshizawa
Institute for Materials Chemistry and Engineering
Kyushu University
Motooka, Nishi-Ku, Fukuoka 819-0395 (Japan)

Supporting information for this article is given via a link at the end of the document.

$H_4P(Cl)_2$ by $Na_2S_2O_4$ in DMSO-d_6 was monitored by ^{1}H NMR spectroscopy, ^{1}H NMR signals due to **$H_4P(Cl)_2$** disappeared together with an appearance of new signals at 13.99 ppm and 7.1 – 6.5 ppm (Figure 1). The ^{1}H NMR signal at 13.99 ppm was assigned as N*H* protons of pyrrole rings, which is confirmed by the disappearance through H/D exchange in the presence of D_2O (Figure S4). The N*H* proton signal of the pyrrole rings at a low magnetic field indicates the loss of aromaticity of **$H_4P(Cl)_2$** by the chemical reduction. In addition, simple ^{1}H NMR signals due to the *β*-Ph and *meso*-Ph groups and one singlet signal in the ^{19}F NMR spectrum were indicative of the symmetrical structure due to the reduced derivative of **$H_4P(Cl)_2$**. Therefore, these spectroscopic data suggested the selective formation of **Iph** as the two-electron reduced product of **$H_4P(Cl)_2$** as seen in the previous report for the formation of an isophlorin derivative.[6] It should be noted that no formation of **Iph** isomers such as a phlorin derivative (**PhI**) and a 5,15-porphodimethene derivative (**Pdm**) was observed because of no singlet signals due to their methine protons around 6 ppm.[11]

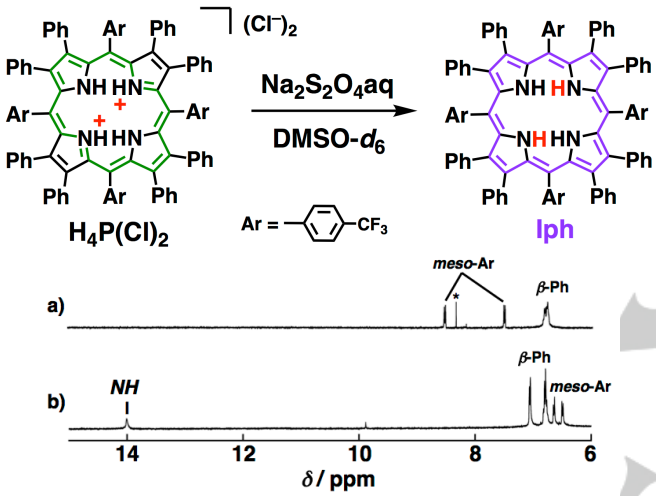
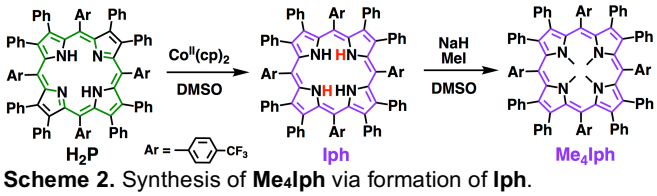


Figure 1. ^{1}H NMR spectra of a) **$H_4P(Cl)_2$**, and b) **$H_4P(Cl)_2$** in the presence of 4 equiv $Na_2S_2O_4$aq in DMSO-d_6 at 298 K. *:$CHCl_3$ in crystals of **$H_4P(Cl)_2$**.

To evaluate the aromaticity of **Iph**, the nucleus independent chemical shift (NICS(0))[12] was calculated at the B3LYP/6-31G** level of theory (Figure S5). The estimated NICS(0) value (+2.97 ppm) at the ring center of **Iph** was comparable with that of the previously reported non-aromatic isophlorin (+2.25 ppm).[6] In the case of planar antiaromatic isophlorins, the estimated NICS(0) values were estimated to be above +20 ppm due to the paratropic ring current effect of a 4nπ macrocycle.[4,5] Thus, the aromaticity of **Iph** is interpreted as a non-aromatic character.

The requirements for reaction conditions to form **Iph** were investigated by changing reductants and solvents (Table S1). Formation of **Iph** was also confirmed by using cobaltocene ($Co^{II}(cp)_2$) or zinc powder (Zn) as an electron donor instead of $Na_2S_2O_4$, whereas the reduction of **$H_4P(Cl)_2$** by $NaBH_4$ unsuccessfully afforded unidentified species. In addition, the formation of **Iph** was confirmed in polar aprotic solvents such as DMSO and DMF (Figure S6): **Iph** is stable in these solvents for several days under deaerated conditions at room temperature. In contrast, mixtures of reduced products were produced in other solvents such as methanol, acetone, and acetonitrile, although the formation of **Iph** was detected at the beginning of the reaction by ^{1}H NMR measurements in each solvent. In the case of methanol, formation of **Pdm** as one of the reduced products was confirmed by X-ray crystallography (Figure S7). To compare the thermodynamic stability of **Iph**, **PhI**, and **Pdm**, DFT calculations were conducted. As a result, **Iph** was thermodynamically disfavored rather than **PhI** (–6.3 kcal mol^{-1} relative to **Iph**) and **Pdm** (–15.3 kcal mol^{-1} relative to **Iph**), respectively (Figure S8). However, the similarity of saddle-distorted structures between **$H_4P(Cl)_2$** and **Iph** is assumed to induce kinetically favorable formation of **Iph** as described above. In the case of DMSO, **Iph** was stabilized by the formation of hydrogen bonding with DMSO molecules rather than **PhI** or **Pdm**.[13,14] Therefore, the electron-transfer reduction of **$H_4P(Cl)_2$** in polar aprotic solvents is essential for the selective formation of **Iph**.

Unfortunately, crystallization of **Iph** was not achieved due to the limitation of reaction conditions described above. As an alternative way for characterization of **Iph**, methylation of inner-pyrrole nitrogen atoms was employed to characterize **Iph** derivatives by X-ray crystallography. As shown in Scheme 2, tetra-methylation of **Iph** was accomplished sequentially in a one-pot reaction in DMSO by two-electron reduction of **H_2P** with $Co^{II}(cp)_2$ and methylation by iodomethane (MeI) in the presence of sodium hydride (NaH) as a base. The tetra-methylated **Iph** derivative (**Me_4Iph**) was characterized by MALDI-TOF-MS and ^{1}H NMR (Figure S10). The observed ^{1}H NMR signal at 5.24 ppm due to an inner methyl group under air suggested the formation of non-aromatic air-stable **Me_4Iph** (Figure S10b). The UV-vis spectrum of **Me_4Iph** in acetone shows a characteristic absorption band at 475 nm due to **Me_4Iph**, which is similar to that of non-aromatic **Iph** (Figure S11).[6,7a] Then, a molecular structure of **Me_4Iph** was revealed as shown in Figure 2 by X-ray crystallography. Single crystals of **Me_4Iph** were obtained by vapor diffusion of 2-propanol to a CH_2Cl_2 solution containing **Me_4Iph**. As shown in Figure 2, **Me_4Iph** shows a large saddle distortion (Δrms = 0.83 Å), which is comparable with that of **Iph** (Δrms = 0.96 Å) estimated by DFT calculations. No inclusion of counter anions in the structure indicates that the macrocycle should be chargeless and maintains the two-electron-reduced form after methylation of **Iph**, in contrast to the case of **$H_4P(Cl)_2$** that includes two chloride ions as the counter anions (Figure S1).[15]



Scheme 2. Synthesis of **Me_4Iph** via formation of **Iph**.

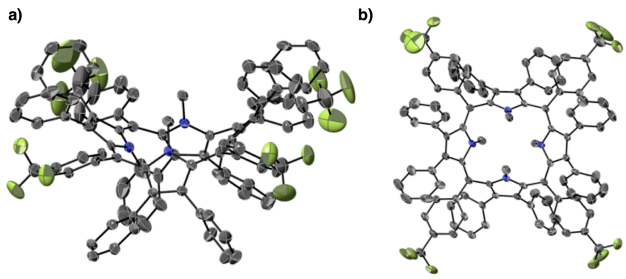


Figure 2. ORTEP drawings of **Me_4Iph** a) side view, and b) top view. Hydrogen atoms were omitted for clarity.

Next, we investigated the reductive transformation of **Iph** in the presence of excess $Na_2S_2O_4$ in DMSO. It was revealed that

Iph was further reduced to form a four-electron reduced porphyrin (**IphH$_2$**) as seen in Figure 3. The ^{1}H NMR signals due to **Iph** were completely converted to those due to **IphH$_2$** with lower symmetry as seen in three kinds of *NH* protons around 10 ppm. A characteristic singlet signal was also observed at 5.99 ppm due to the two protons attached to the *meso* carbons in the reduced porphyrin ring. MALDI-TOF-MS showed a peak cluster at *m*/*z* = 1499.67, which was assigned to [**IphH$_2$** + H]$^+$ as a four-electron reduced **H$_4$P(Cl)$_2$** (Figure S13). UV-Vis spectral changes from **Iph** to **IphH$_2$** were observed with isosbestic points (519 nm, and 580 nm) as shown in Figure S3b. The single crystals of **IphH$_2$** were successfully obtained by vapor diffusion of EtOH to a DMF solution containing **IphH$_2$**. Then, the molecular structure of **IphH$_2$** was unambiguously revealed by X-ray crystallography as shown in Figure 4. In the structure, the 5,10-*meso*-carbons were reduced to be sp^3 configurations in a "*syn*" geometry for the two adjacent 4-CF$_3$-phenyl groups attached to the carbon atoms, forming a unique conformation of the porphyrinoid core: The left half part shows an isophlorin-like conformation and the right half part shows a porphodimethene-like conformation. As shown in Figure 4c, the C-C bond-length alternation was observed in the left part (green colored) of **IphH$_2$**, as seen in the case of **Me$_4$Iph**;[15] in the right part (red colored), the C-C bond lengths around the *meso*-carbons were determined to be 1.508(5) Å, 1.507(5) Å, 1.495(5) Å and 1.500(5) Å. This C-C bond elongation and the detection of methine protons in ^{1}H NMR measurements clearly indicate that the further reduction and protonation occur at the *meso*-carbons.

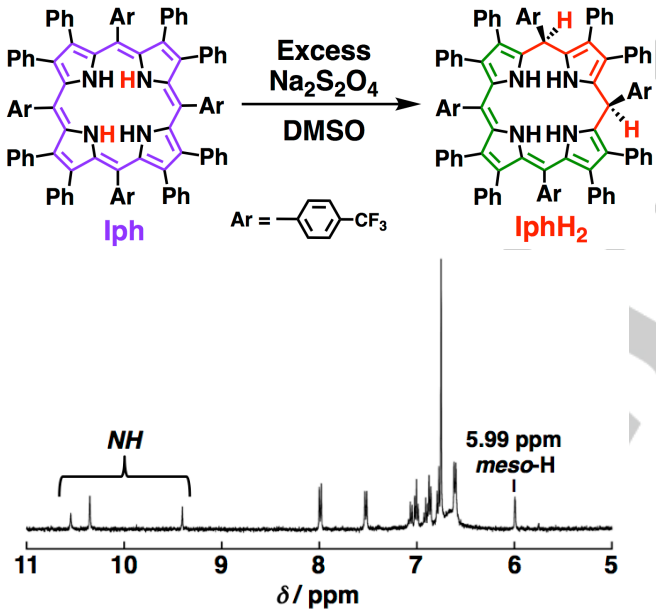


Figure 3. ^{1}H NMR spectrum of **IphH$_2$** in DMSO-d_6 at 298 K.

To compare the thermodynamic stability of **IphH$_2$** with other structural isomers, DFT optimized structures of three possible isomers of four-electron reduced porphyrins were calculated at the B3LYP/6-31G** level of theory. We considered **5,10-*Anti*** and **5,15-*Syn*** of a triplet biradical form as the structural isomers of **IphH$_2$** (**5,10-*Syn*,** Figure 5, S14). As shown in Figure 5, the stability of **5,15-*Syn*** is thermodynamically disfavored compared with that of **5,10-*Syn*** (+20.7 kcal mol^{-1} relative to **5,10-*Syn***) due to the unstable open-shell structure. **5,10-*Anti*** was destabilized by 7.2 kcal mol^{-1} in comparison to **5,10-*Syn*** because of steric repulsion between a *meso*-aryl group and a *β*-phenyl group. Therefore, it was clarified that **5,10-*Syn*** should be the most stable isomer of the four-electron-reduced species.

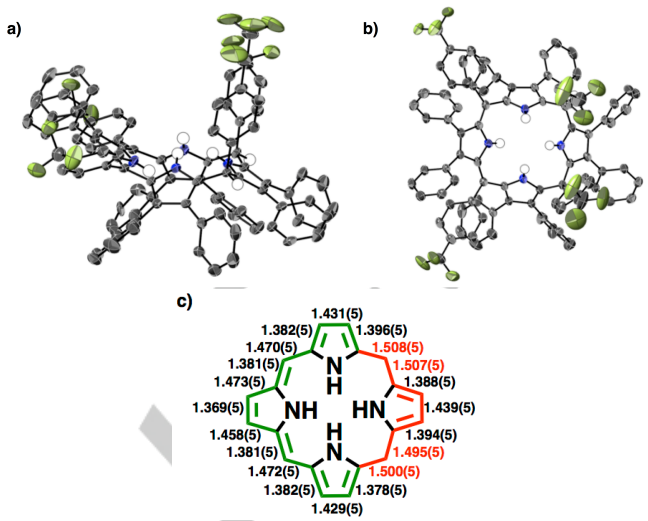


Figure 4. ORTEP drawings of **IphH$_2$** a) side view, and b) top view. Hydrogen atoms were omitted for clarity except for protons of nitrogen atoms and protons attached to the *meso* carbons. c) The C-C bond lengths (Å) of the macrocycle in **IphH$_2$**.

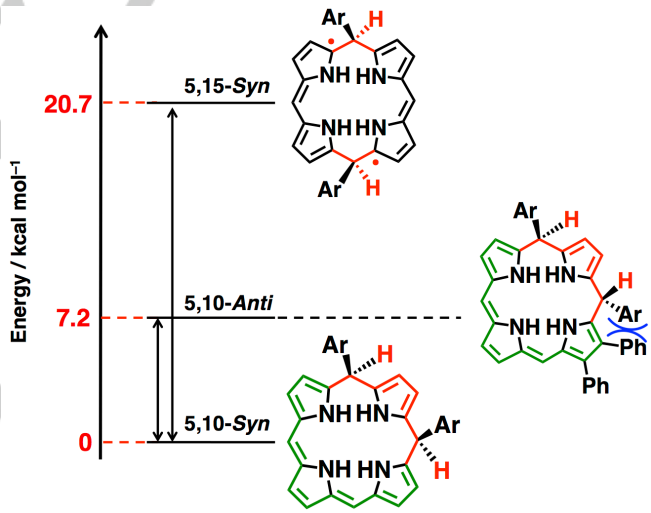


Figure 5. Comparison of thermodynamic stability of **5,10-*Syn*** (**IphH$_2$**) with structural isomers (**5,10-*Anti*** and **5,15-*Syn***) based on DFT calculations.

Finally, the thermodynamic stability and redox behavior of **IphH$_2$** were investigated to ascertain that **IphH$_2$** could act as a reversible multi-redox system. Since no ^{1}H NMR spectral change was observed for **IphH$_2$** in DMSO-d_6 under deaerated conditions at 353 K for two days (Figure S15), the compound should be thermodynamically stable. In contrast, **IphH$_2$** was smoothly oxidized by excess amount of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) to produce **H$_4$P(Cl)$_2$** (Figure S16), which should be derived from protonation of **H$_2$P** formed as the oxidized product. The yield of **H$_4$P(Cl)$_2$** was determined to be 96% by ^{1}H NMR measurements. This result clearly indicates that the reversible four-electron redox cycle between **H$_4$P(Cl)$_2$** and **IphH$_2$** was established (Scheme 1).

In summary, we have established a methodology for the selective formation of an isophlorin derivative (**Iph**) by using a

saddle-distorted diprotonated dodecaphenylporphyrin derivative through the reduction with electron donors in polar aprotic solvents (such as DMSO or DMF). Surprisingly, further two-electron reduction of **Iph** by $Na_2S_2O_4$ afforded a novel four-electron reduced porphyrinoid (**IphH$_2$**), showing a unique conformation. Finally, we have demonstrated a four-electron reversible redox system by re-oxidation of **IphH$_2$** to reproduce the starting diprotonated dodecaphenylporphyrin, **H$_4$P(Cl)$_2$.**

Acknowledgements

This work was supported by Grants-in-Aid (Nos 24245011 and 17H03027) from the Japan Society of Promotion of Science (JSPS, MEXT) of Japan and a grant from Yazaki Memorial Foundation for Science and Technology. We also appreciate Dr. Tatsuhiro Kojima (Osaka University) for helpful guidance in X-ray crystallography.

Keywords: Saddle-distorted porphyrin · Porphyrinoids · Isophlorin · Electron-transfer reduction · Electron pool

[1] a) K. M Kadish, M. M. Morrison, *J. Am. Chem. Soc.* **1976**, *98*, 3326-3328. b) Y. Fang, P. Bhyrappa, Z. Ou, K. M. Kadish, *Chem. Eur. J.* **2014**, *20*, 524-532. c) Y. Fang, Y. G. Gorbunova, P. Chen, X. Jiang, M. Manowong, A. A. Sinelshchikova, Y. Y. Enakieva, A. G. Martynov, A. Y. Tsivadze, A. Bessmertnykh-Lemeune, C. Stern, R. Guilard, K. M. Kadish, *Inorg. Chem.* **2015**, *54*, 3501-3512. d) X. Ke, P. Yadav, L. Cong, R. Kumar, M. Sankar, K. M. Kadish, *Inorg. Chem.* **2017**, *56*, 8527-8537. e) K. Rybicka-Jasińska, W. Shan, K. Zawada, K. M. Kadish, D. Gryko, *J. Am. Chem. Soc.* **2016**, *138*, 15451-15458.

[2] a) K. M. Kadish, W. E, R. Zhan, T. Khoury, L. J. Govenlock, J. K. Prashar, P. J. Sintic, K. Ohkubo, S. Fukuzumi, M. J. Crossley, *J. Am. Chem. Soc.* **2007**, *129*, 6576-6588. b) S. Hayashi, J. Sung, Y. M. Sung, Y. Inokuma, D. Kim, A. Osuka, *Angew. Chem. Int. Ed.* **2011**, *50*, 3253-3256. c) S. Ishihara, J. P. Hill, A. Shundo, G. J. Richards, J. Labuta, K. Ohkubo, S. Fukuzumi, A. Sato, M. R. J. Elsegood, S. J. Teat, K. Ariga, *J. Am. Chem. Soc.* **2011**, *133*, 16119-16126.

[3] B. K. Reddy, A. Basavarajappa, M. D. Ambhore, V. G. Anand, *Chem. Rev.* **2017**, *117*, 3420-3443.

[4] a) J. A. Cissell, T. P. Vaid, A. L. Rheingold, *J. Am. Chem. Soc.* **2005**, *127*, 12212-12213. b) J. A. Cissell, T. P. Vaid, G. P. A Yap, *J. Am. Chem. Soc.* **2007**, *129*, 7841-7847. c) H. Song, J. A. Cissell, T. P. Vaid, D. Holten, *J. Phys. Chem. B* **2007**, *111*, 2138-2142.

[5] a) R. Bachmann, F. Gerson, G. Gescheidt, E. Vogel, *J. Am. Chem. Soc.* **1992**, *114*, 10855-10860. b) E. Vogel, M. Pohl, A. Herrmann, T. Wiss, C. Königm J. Lex, M. Gross, J. P. Gisselbrecht, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1520-1524. c) A. Weiss, M. C. Hodgson, P. D. W. Boyd, W. Siebert, P. J. Brothers, *Chem. Eur. J.* **2007**, *13*, 5982-5993. d) J. S. Reddy, V. G. Anand, *J. Am. Chem. Soc.* **2008**, *130*, 3718-3719. e) Y. Matano, T. Nakabuchi, S. Fujishige, H. Nakano, H. Imahori, *J. Am. Chem. Soc.* **2008**, 1*30*, 16446-16447. f) P. J. Brothers, *Chem. Commun.* **2008**, 2090-2102. g) J. Yan, M. Takakusaki, Y. Yang, S. Mori, B. Zhang, Y. Feng, M. Ishida, H. Furuta, *Chem. Commun.* **2014**, *50*, 14593-14596. h) B. K. Reddy, S. C. Gadekar, V. G. Anand, *Chem. Commun.* **2015**, *51*, 8276-8279. i) S. P. Panchal, S. C. Gadekar, V. G. Anand, *Angew. Chem. Int. Ed.* **2016**, *55*, 7797-7800. j) A. Yamaji, H. Tsurugi, Y. Miyake, K. Mashima, H. Shinokubo, *Chem. Eur. J.* **2016**, *22*, 3956-3961.

[6] C. Liu, D.-M. Shen, Q.-Y. Chen, *J. Am. Chem. Soc.* **2007**, *129*, 5814-5815.

[7] a) M. Pohl, H. Schmickler, J. Lex, E. Vogel, *Angew. Chem. Int. Ed.* **1991**, *30*, 1693-1697. b) J. Setsune, K. Kashihara, K. Wada, H. Shinozaki, *Chem. Lett.* **1999**, 847-848. c) J. Setsune, K. Kashihara, K. Wada, *Chem. Lett.* **2001**, 72-73. d) T. P. Vaid, *J. Am. Chem. Soc.* **2011**, *133*, 15838-15841. e) M. Umetani, T. Tanaka, T. Kim. D. Kim, A. Osuka, *Angew. Chem. Int. Ed.* **2016**, *55*, 8095-8099.

[8] a) R. Harada, T. Kojima, *Chem. Commun.* **2005**, 716-718. b) T. Kojima, T. Nakanishi, R. Harada, K. Ohkubo, S. Yamauchi, S. Fukuzumi, *Chem. Eur. J.* **2007**, *13*, 8714-8725.

[9] C.-J. Liu, W.-Y. Yu, S.-M. Peng, T. C. W. Mak, C.-M. Che, *J. Chem. Soc., Dalton Trans.* **1998**, 1805-1812.

[10] W. Jentzen, I. Turowska-Tyrk, W. R. Scheidt, J. A. Shelnutt, *Inorg. Chem.* **1996**, *35*, 3559-3567.

[11] a) T. Kojima, K. Hanabusa, K. Ohkubo, M. Shiro, S. Fukuzumi, *Chem. Commun.* **2008**, 6513-6515. b) B. Liu, X. Li, X. Xu, M. Stępień, P. Chmielewski, *J. Org. Chem.* **2013**, *78*, 1354-1364.

[12] a) Z. Chen, C. S. Wannere, C. Corminboeuf, R. Puchta, P. v. R. Schleyer, *Chem. Rev.* **2005**, *105*, 3842-3888. b) P. v. R. Schleyer, C. Maerker, A. Dransfeld, H. Jiao, N. J. R. v. E. Hommes, *J. Am. Chem. Soc.* **1996**, *118*, 6317-6318.

[13] a) P. Bhyrappa, P. Bhavana, *Chem. Phys. Lett.* **2001**, *342*, 39-44. b) J. Tanaka, M. Sato, *Chem. Lett.* **1995**, 971-972.

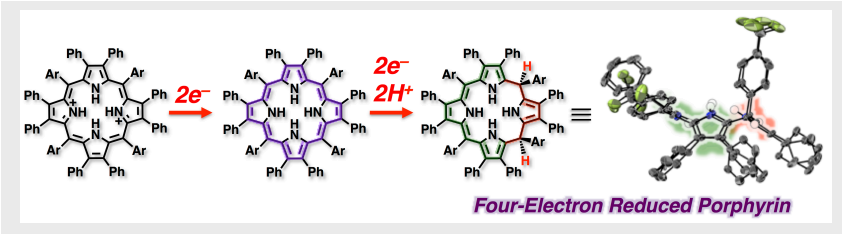
[14] We conducted DFT calculations of **Iph** and other isomers in the presence of two DMSO molecules. As a result, the difference of energy between **Iph** and **PhI** or **Pdm** decreased to 1.2 kcal mol^{-1} and 1.7 kcal mol^{-1}, respectively as shown in Figure S9. This result suggested the stabilization of **Iph** through hydrogen bonds with a polar solvent such as DMSO.

[15] The core structure of **Me$_4$Iph** (Figure S12) also suggests the preservation of a 20π-conjugated isophlorin skeleton (see ref 6).

Entry for the Table of Contents

Layout 2:

COMMUNICATION



A four-electron reduced porphyrin (**IphH$_2$**) was fully characterized by X-ray crystallography for the first time. **IphH$_2$** shows a unique conformation. Additionally, **IphH$_2$** was oxidized to afford the starting porphyrin, which acts as a proton-coupled four-electron reversible redox system.

*Wataru Suzuki, Hiroaki Kotani, Tomoya Ishizuka, Yoshihito Shiota, Kazunari Yoshizawa, and Takahiko Kojima**

Page No. – Page No.

Formation and Isolation of a Four-Electron Reduced Porphyrin Derivative via Further Reduction of a Stable 20π Isophlorin