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Quantum–Chemical Insight into the Reactivity of 5–Bromo–10,20–diarylporphyrins towards Nucleophiles

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Series of 5-bromo-15-R-10,20-diphenylporphyrins 1a-d, 2a-g (where R = CN, COOMe, Br, H, morpholinyl, NH_2, PrNH, ^{t}BuNH, Pr_2N, PhNH, Ph_2N) is investigated by means of density functional theory (DFT) in order to reveal their reactivity towards the nucleophilic substitution reaction. The influence of the electronic effects of the 15-substituent on the electrophilicity of the reaction centre was evaluated by the analysis of unoccupied molecular orbitals of the model porphyrins as well as the charge at the 5-carbon atom. The reactivity of the studied compounds is predicted by frontier orbitals calculation. The electron withdrawing porphyrins 1a-c (R = CN, COOMe, Br) are the most reactive compounds in the studied series. The steric demands of the 15-amino-substituent hugely affected its orientation with respect to the porphyrin macrocycle and the reactivity of 5-bromoporphyrins towards nucleophiles.

Keywords: Porphyrins, nucleophilic substitution, frontier orbitals, density functional theory.

Квантово–химическое исследование реакционной способности 5–бром–10,20–диарилпорфиринов в реакции нуклеофильного замещения

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Реакционная способность набора 5-бром-15-R-10,20-дифенилпорфиринов 1a-d, 2a-g (R = CN, COOMe, Br, H, морфолинил, NH_2, PrNH, ^{t}BuNH, Pr_2N, PhNH, Ph_2N) в реакции ароматического нуклеофильного замещения изучена с использованием теории функционала плотности (DFT). Влияние электронных характеристик заместителя в положении 15 макроцикла на электрофильность реакционного центра оценено на основе анализа граничных орбиталей модельных субстратов, а также заряда на атоме углерода в 5 положении порфирина. Показано, что электроноакцепторные заместители в порфиринах 1a-c (R = CN, COOMe, Br) повышают реакционную способность этих субстратов. В то же время стерические требования заместителей 15-амино-групп определяют их ориентацию относительно порфиринового макроцикла и реакционную способность субстратов 2a-g.

Ключевые слова: Порфирины, нуклеофильное замещение, граничные орбитали, теория функционала плотности.

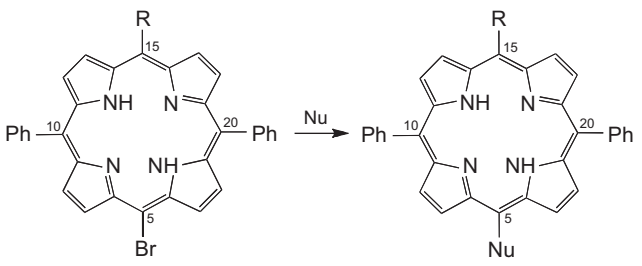
Introduction

Porphyrins and their metal complexes attract the interest of scientific community as promising compounds for multiple applications.[1-4] Various approaches are developed for the preparation of functionalized porphyrins by introduction of the desired substituents in the precursors or modification of the porphyrin core.[3-6] Transition metal-assisted cross-coupling reactions are widely used for porphyrin functionalization.[5,7-16] Notwithstanding their versatility, the palladium-mediated cross-coupling reactions require expensive catalysts and ligands that is a limiting factor for their industrial use, in particular in the medical pharmacology.

The reactions of porphyrins with nucleophiles are still scarcely used for the functionalization of porphyrin macrocycle. Nevertheless, synthetically useful examples of the introduction of *meso*- and *β*-substituents into the porphyrin macrocycle by nucleophilic substitution are published. Non-catalytic nucleophilic substitution was used to prepare *meso*-amino derivatives from corresponding bromoporphyrins as alternative to Buchwald-Hartwig reaction. It was found that *meso*-monobromoporphyrins reacted with primary amines affording *meso*-monoaminoporphyrins with 50-95 % yields.[17,18] Although the electron-withdrawing substituents facilitate the substitution,[18] unactivated *meso*-mono- and dibromoporphyrins also can be used as substrates for this reaction.[17-19] The reaction of porphyrins with *O*- and *S*-nucleophiles allows preparation of aryloxy- and arylthia-substituted porphyrins with up to 70 % yield.[20-23]

Moreover, *meso*-functionalization of diarylporphyrins is possible also by the nucleophilic addition of alkyl- or aryllithium reagents to the porphyrins followed by the oxidation of the resulting porphyrinogens.[6,24,25]

In the present work we evaluated the reactivity of 5-bromoporphyrins towards the nucleophilic substitution reaction (Scheme 1) using the widely available level of DFT calculations. Analyzing the limited experimental data, it is possible to speculate that the electronic effects of a substituent at 15 position significantly influence the process.[17,18] Our objective was to find a rapid and reliable method for an estimation of the reactivity of 5-bromoporphyrins towards nucleophiles without carrying out complete DFT calculation of structural and energy characteristics of the reaction paths. We have demonstrated that DFT/6-31G* calculation of frontier orbital localization of the substrate molecule is sufficient for a reliable prediction of the reactivity.



Scheme 1. Nucleophilic substitution reaction of 5-bromoporphyrins.

Experimental

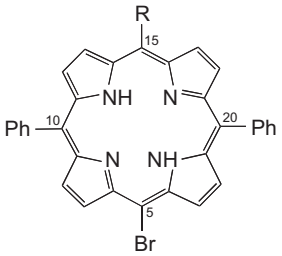
The quantum calculations were carried out with Spartan'10 software (build 1.1.0, Wavefunction Inc.) running on a desktop computer with the Windows operating system. The structures were found by convergence to equilibrium geometry at an energy minimum with default values of gradient tolerance ($4.5 \cdot 10^{-4}$ hartree. $bohr^{-1}$) and distance tolerance ($1.8 \cdot 10^{-3}$Å). The DFT calculations were performed at B3LYP level of theory with 6-31G* basis set. The starting structures for calculation were prepared by minimization with semi-empirical PM6 method. The vibrational frequencies were calculated to prove the found structures to be minimal and showed no imaginary frequencies. The details on the evaluation of the orientation of the amino-group nitrogen atom lone pair are provided in the supporting information (Figure S1).

Results and Discussion

Aromatic nucleophilic substitution reaction is widely used in the modern organic synthesis. However, a large number of systems exist, which undergo nucleophilic substitution and in which our current theoretic fundamentals provide vanishing insight. Density functional theory calculations are a powerful tool to get insight into such processes and have gained considerable attention at the present time.[24] This work is aimed at a different purpose, namely to application of the relatively simple level of DFT calculation, which is widely available in modern researches, as a guide for a synthetic work. As an example, we have chosen a nucleophilic substitution reaction of 5-bromoporphyrins, which is scarcely studied in the literature but has a significant synthetic potential. In this particular case, a valuable information on the substrate reactivity can be obtained by DFT calculation of the frontier orbitals in the ground state without time-consuming calculations of the reaction path.

A representative set of 5-bromo-10,20-diphenylporphyrins possessing a 15-substituent of different electronic character was selected for the evaluation of their reactivity towards the nucleophilic substitution reaction (Table 1). Thus, compounds **1a**,**b** possess strong π-electron-withdrawing groups, **1c** contains a weak σ-acceptor substituent and **1d** is an unsubstituted at 15-position compound. In contrast, the set of compounds **2a**-**g** includes the 15-amino-substituted derivatives, which differ in the steric and electronic

Table 1. Model compounds for the calculations.



1a, R = CN	**2a**, R = morpholinyl
1b, R = COOMe	**2b**, R = NH_2
1c, R = Br	**2c**, R = PrNH
1d, R = H	**2d**, R = ^{t}BuNH
	2e, R = Pr_2N
	2f, R = PhNH
	2g, R = Ph_2N

character. Some of these compounds were already studied in the nucleophilic substitution reaction, namely **1a**, **1d** and **2a**[17,18] while others were chosen for the prediction of the scope of the reaction. In this regards, the amino substituted derivatives are the most interesting substrates due to their donor character and expected low reactivity in the studied reaction.

The B3LYP/6-31G* level of theory was selected for the calculation of the molecular characteristics in the ground state. The B3LYP functional is a common method for the calculation of the parameters of the tetrapyrrolic macrocycles. While the extension of basis set with the polarizing and diffuse functions may increase the quantitative accuracy of the obtained data, the 6-31G* basis set provides compensated compromise between the accuracy and time-consuming characteristics of the calculation. The B3LYP/6-31G* level of theory is widely applied for the calculation of the characteristics of porphyrins and their metal complexes, such as structural parameters,[26-30] electronic coupling,[26] energy profiles,[27,30] electron transfer and charge separation,[31,32] molecular orbitals localization,[28,29,31-33] spectral properties.[29,30]

We attempted to evaluate the reactivity of bromoporphyrins **2a-g** towards nucleophiles using the value of a skew angle between the nitrogen atom lone pair and the porphyrin plane. The energy-minimized structures of the model compounds **2a-g** were calculated to estimate whether the steric factors are important for the reactivity of 5-center. It was found that the increase of substituent bulkiness results in a variation of the skew angle between the nitrogen atom lone pair and the porphyrin plane (Figures 1 and S1). Thus, this angle is *ca*. 90° for 15-aminoporphyrin **2b**, while in the case of morpholinyl substituted compound **2a** the nitrogen lone pair is located virtually in the plane of the porphyrin macrocycle. According to these data the reactivity of the compounds **2a** and **2b** in the nucleophilic substitution reaction should be significantly different. Indeed, the conjugation of the nitrogen lone pair with the porphyrin macrocycle should decrease the electrophilicity of the reaction centre. 5-Bromo-15-morpholinyl-10,20-diphenylporphyrin **2a** should be more reactive in comparison with **2b** that is proved by the experimental data.[18] The compounds **2c-g** with less bulky substituents should be less reactive in the investigated process.

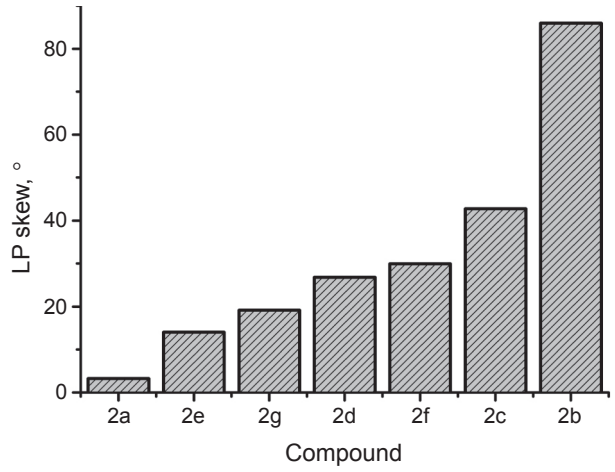


Figure 1. Skew angle of the nitrogen lone pair (LP) for **2a-g**.

Selectivity of the nucleophilic substitution reactions is well described by the concept of the charge- or frontier-controlled reactions.[34] In the former case the reaction path is determined by the charge at the reaction centre, while in the latter case the frontier orbital localization is the key factor of the process. Both charge- and frontier-controlled reactions are known for porphyrin derivatives.[20-22] Thus, the solvent-dependent ambident nucleophilicity of phenoxide anion is known.[21] Moreover, the different selectivity of the substitution was observed for the reaction of *meso*- and *β*-nitroporphyrins with aryloxide and alkoxide anions.[20,22] To evaluate the reactivity of 5-bromoporphyrins **1a-d** and **2a-g** towards nucleophiles the factors determining the reaction course should be found. Therefore, the charge at the 5-carbon atom was analysed for all studied compounds. Interestingly, this charge was found to be slightly negative and virtually independent from the electronic characteristics of the 15-substituent. This observation indicates that the studied reaction is frontier controlled rather than charge controlled.

The reactivity of the substrate towards the nucleophilic substitution depends on the energy of LUMO and its localization at the 5-carbon reaction centre. Therefore, the localization (Figures 2, S2, S3) and energy (Figure 3) of LUMO and LUMO+1 of the model compounds **1a-d** and **2a-g** were analysed in order to evaluate their relative reactivity towards the nucleophiles.

In the case of substrates **1** the localization of LUMO is similar to each other and the contribution of atomic orbitals of the 5-carbon is non-zero. In contrast, LUMO+1 possesses no localization at the reaction centre. The energy levels of the LUMO and LUMO+1 are dependent from the electronic characteristics of the 15-substituent (Figure 3). The less electron-withdrawing is the group, the higher is the energy of the substrate LUMO. Nevertheless, despite the difference of the LUMO energies, all substrates **1a-d** possess non-zero contribution of atomic orbitals of the 5-carbon. In contrast, variations of the contribution of atomic orbitals of the porphyrin core to LUMO and LUMO+1 are observed for the set of compound **2a-g**. The representative diagrams of LUMO and LUMO+1 of the substrates are shown in Figure 2. The conjugation of nitrogen lone pair with the porphyrin π-system results in an increase of the LUMO energy and simultaneous decrease of the contribution of atomic orbitals of the 5-carbon reaction centre. However, this influence is significant only for NH_2- and NHPr-substituted derivatives **2b** and **2c**. There is no contribution of the 5-carbon atom to LUMO of these porphyrins and thus, the nucleophilic substitution should be prohibited. It is important that the energy and the localization of LUMO for compounds **2a,d-g** resemble that of 15-unsubstituted bromoporphyrin **1d**. It is remarkable, that **1d** undergoes nucleophilic substitution reaction with various primary amines with 52-89 % yields.[17] In this respect we expect that all these compounds could react with the nucleophiles.

It should be noted, that the influence of the amino substituent on the reactivity of the compound **2d, 2f** and **2g** towards nucleophiles cannot be predicted taking into consideration only the value of a skew angle of the lone pair of the nitrogen atom. It is noteworthy, that these angles are similar for these three compounds. Nevertheless, LUMO

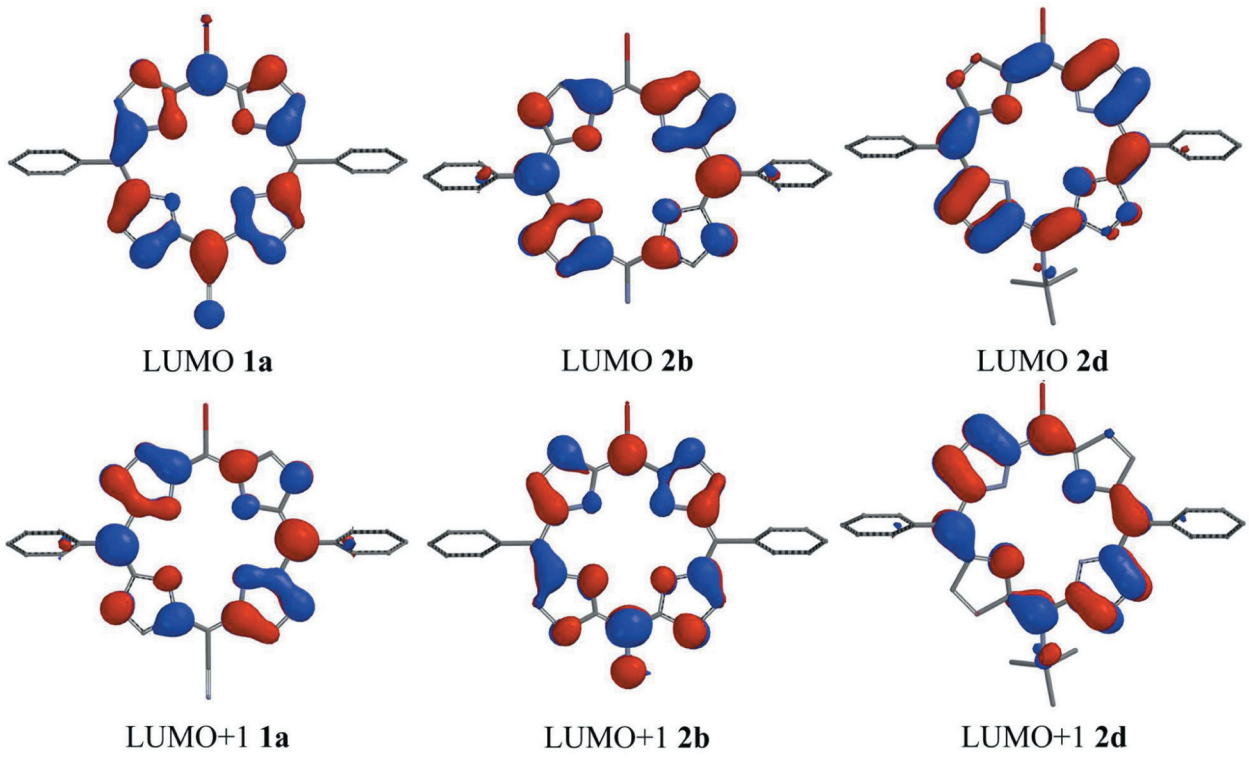


Figure 2. The representative diagrams of molecular orbitals of the 15-substituted 5-bromoporphyrins. Red and blue regions of the diagrams demonstrate the opposite sign of the orbitals.

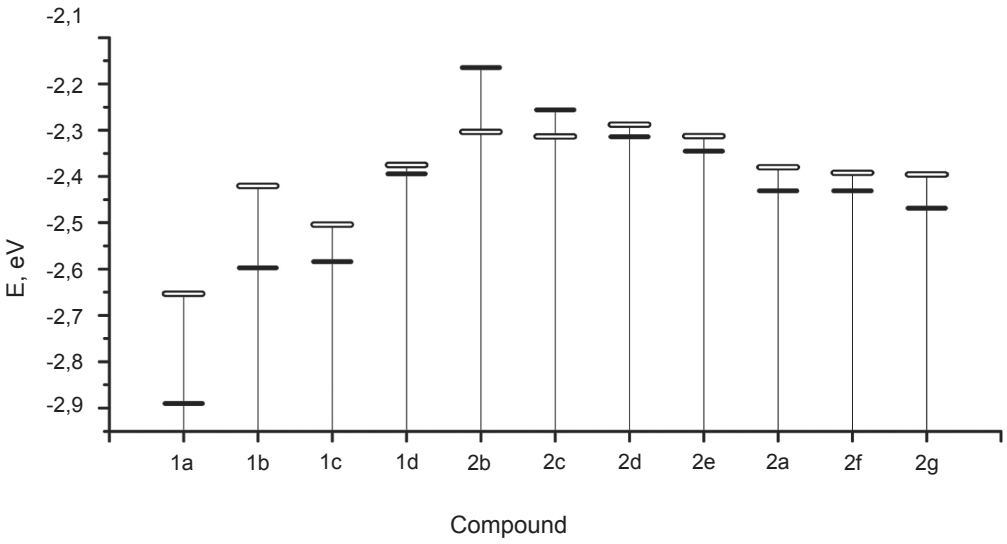


Figure 3. The energy levels of LUMO and LUMO+1 and the contribution of atomic orbitals of the 5-carbon (white bars represent zero contribution and black bars – non-zero contribution of the 5-carbon atomic orbitals).

and LUMO+1 localization for **2d** significantly differs from that of **2f** and **2g**. Moreover, the similarity of LUMO and LUMO+1 localization was observed in the series **2a**, **2g** and **2f**, despite the difference in the orientation of the amino-group lone pair. This observation can be explained by an efficient conjugation of the lone pair of the nitrogen atom with phenyl groups in the case of **2g** and **2f**, that decreases its electronic influence on the porphyrin π-system. Thus, both steric and electronic effects of the substituents of the 15-amino-group are important for efficient nucleophilic substitution at the 5-carbon reaction centre and compounds **2a**, **2f** and **2g** are expected to be reactive towards nucleophiles.

Conclusions

In conclusion, DFT/B3LYP calculations provide a fast and reliable qualitative evaluation of the reactivity of 5-bromo-10,20-diphenylporphyrins towards nucleophiles. The aromatic nucleophilic substitution reaction of 5-bromoporphyrins is shown to be a frontier-controlled reaction. The analysis of the calculated LUMO orbitals is in

a good agreement with the experimental data and is useful for the prediction of the reactivity of new substrates.

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References

1. Chou J.H., Kosal M.E., Nalwa H.S., Rakow N.A. In: *The Porphyrin Handbook,* Vol. 6 [Kadish K.M., Smith K.M., Guilard R., Eds.] **2000**, p. 43-131.
2. Suslick K.S. In: *The Porphyrin Handbook,* Vol. 4 [Kadish K.M., Smith K.M., Guilard R., Eds.] **2000**, p. 41-62.
3. Rose E., Andrioletti B., Zrig S., Quelquejeu-Ethève M. *Chem. Soc. Rev.* **2005**, *34*, 573.
4. Intrieri D., Caselli A., Gallo E. *Eur. J. Inorg. Chem.* **2011**, *2011*, 5071-5081.
5. Beletskaya I.P., Tyurin V.S., Uglov A., Stern C., Guilard R. In: *Handbook of Porphyrin Science,* Vol. 23 [Kadish K.M., Smith K.M., Guilard R., Eds.] **2012**, p. 82-281.
6. Senge M.O. *Chem. Commun.* 2011, *47*, 1943-1960.
7. Liu C., Shen D.M., Chen Q.Y. *J. Org. Chem.* **2007**, *72*, 2732-2736.
8. Takanami T., Hayashi M., Hino F., Suda K. *Tetrahedron Lett.* **2003**, *44*, 7353-7357.
9. Chen Y., Zhang X.P. *J. Org. Chem.* **2003**, *68*, 4432-4438.
10. Warnan J., Favereau L., Meslin F., Severac M., Blart E., Pellegrin Y., Jacquemin D., Odobel F. *Chem. Sus. Chem.* **2012**, *5*, 1568-1577.
11. Liu Y., Lin H., Dy J.T., Tamaki K., Nakazaki J., Nakayama D., Uchida S., Kubo T., Segawa H. *Chem. Commun.* **2011**, *47*, 4010-4012.
12. Pereira A.M.V.M., Neves M.G.P.M.S., Cavaleiro J.A.S., Jeandon C., Gisselbrecht J.-P., Choua S., Ruppert R. *Org. Lett.* **2011**, *13*, 4742-4745.
13. Lee C.W., Lu H.P., Reddy N.M., Lee H.W., Diau E.W.G., Yeh C.Y. *Dyes Pigm.* **2011**, *91*, 317-323.
14. Lee C.-W., Lu H.-P., Lan C.-M., Huang Y.-L., Liang Y.-R., Yen W.-N., Liu Y.-C., Lin Y.-S., Diau E.W.-G., Yeh C.-Y. *Chem. Eur. J.* **2009**, *15*, 1403-1412.
15. Vinogradova E.V., Enakieva Y.Y., Nefedov S.E., Birin K.P., Tsivadze A.Y., Gorbunova Y.G., Bessmertnykh-Lemeune A.G., Stern C., Guilard R. *Chem. Eur. J.* **2012**, *18*, 15092-15104.
16. Enakieva Y.Y., Bessmertnykh A.G., Gorbunova Y.G., Stern C., Rousselin Y., Tsivadze A.Y., Guilard R. *Org. Lett.* **2009**, *11*, 3842-3845.
17. Balaban M.C., Chappaz-Gillot C., Canard G., Fuhr O., Roussel C., Balaban T.S. *Tetrahedron* **2009**, *65*, 3733-3739.
18. Balaban M., Eichhöfer A., Buth G., Hauschild R., Szmytkowski J., Kalt H., Balaban T. *J. Phys. Chem. B* **2008**, *112*, 5512-5521.
19. Chappaz-Gillot C., Canard G., Andreoli F., Vanthuyne N., Giorgi M., Naubron J.-V., Monnier V., Rosas R., Roussel C., Balaban T.S. *Eur. J. Org. Chem.* **2012**, 6526-6536.
20. Crossley M.J., King L., Pyke S., Tansey C. *J. Porphyrins Phthalocyanines* **2002**, *6*, 685-694.
21. Crossley M.J., King L.G., Simpson J.L. *J. Chem. Soc., Perkin Trans. 1* **1997**, 3087-3096.
22. Crossley M.J., King L.G. *J. Chem. Soc., Perkin Trans. 1* **1996**, 1251-1260.
23. Hombrecher H.K., Gherdan V.M., Ohm S., Cavaleiro J.A.S., Graça M., Neves P., Fátima Condesso M. *Tetrahedron* **1993**, *49*, 8569-8578.
24. Senge M.O., Shaker Y.M., Pintea M., Ryppa C., Hatscher S.S., Ryan A., Sergeeva Y. *Eur. J. Org. Chem.* **2010**, *2010*, 237-258.
25. Fazekas M., Pintea M., Senge M.O., Zawadzka M. *Tetrahedron Lett.* **2008**, *49*, 2236-2239.
26. Zhu P., Zhang X., Wang H., Zhang Y., Jaworski J., Jiang J. *Inorg. Chem.* **2012**, *51*, 5651-5659.
27. Li Y., Xiao J., Shubina T.E., Chen M., Shi Z., Schmid M., Steinrück H.-P., Gottfried J.M., Lin N. *J. Am. Chem. Soc.* **2012**, *134*, 6401-6408.
28. Chokbunpiam T., Thamyongkit P., Saengsawang O., Hannongbua S. *Int. J. Photoenergy* **2010**, *2010*, 1-9.
29. Liu C.-G., Guan W., Song P., Yan L.-K., Su Z.-M. *Inorg. Chem.* **2009**, *48*, 6548-6554.
30. Yao P., Han S., Zhang Y., Zhang X., Jiang J. *Vib. Spectrosc.* **2009**, *50*, 169-177.
31. Pasunooti K.K., Song J.-L., Chai H., Amaladass P., Deng W.-Q., Liu X.-W. *J. Photochem. Photobiol. A* **2011**, *218*, 219-225.
32. Honda T., Nakanishi T., Ohkubo K., Kojima T., Fukuzumi S. *J. Am. Chem. Soc.* **2010**, *132*, 10155-10163.
33. Hsieh C.-P., Lu H.-P., Chiu C.-L., Lee C.-W., Chuang S.-H., Mai C.-L., Yen W.-N., Hsu S.-J., Diau E.W.-G., Yeh C.-Y. *J. Mater. Chem.* **2010**, *20*, 1127.
34. Klopman G. *J. Am. Chem. Soc.* **1968**, *90*, 223-234.

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