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Design Guidelines to Elongate Spin–Lattice Relaxation Times of Porphyrins with Large Triplet Electron Polarization

Akio Yamauchi,[§] Saiya Fujiwara,[§] Koki Nishimura, Yoichi Sasaki, Kenichiro Tateishi,* Tomohiro Uesaka, Nobuo Kimizuka,* and Nobuhiro Yanai*



atoms

free-base porphyrins as versatile and biocompatible polarizing agents for triplet-DNP. However, the electron polarization of freebase porphyrins is not very high, and the dilemma is that the high polarization of metalloporphyrins is accompanied by a too short spin–lattice relaxation time to be used for triplet-DNP. We report here that the introduction of electron-withdrawing fluorine groups into Zn porphyrins enables a long enough spin–lattice relaxation time (>1 μ s) while maintaining a high polarization ($P_x:P_y:P_z = 0:0:1.0$) at room temperature. Interestingly, the spin–lattice relaxation time of Zn porphyrin becomes much longer by

introducing fluorine substituents, whereas the spin-lattice relaxation time of free-base porphyrin becomes shorter by the fluorine substitution. Theoretical calculations suggest that this is because the introduction of the electron-withdrawing fluorine substituents reduces the spin density on Zn atoms and weakens the spin-orbit interaction.

1. INTRODUCTION

When there is a bias in the sublevel population, it is called spin polarization. Since the populations of each sublevel follow a Boltzmann distribution in thermal equilibrium, the electron spin polarization is very small under ambient conditions. Therefore, cryogenic conditions are required to obtain a large electron polarization in a thermal equilibrium state.^{1–7} As one of the solutions to this problem, the nonequilibrium and temperature-independent spin polarization of triplet electrons is widely used for applications such as quantum computing,^{8,9} room-temperature masers,^{10–12} and triplet dynamic nuclear polarization (triplet-DNP).^{13–17} The large polarization of a triplet state can be generated even at room temperature by sublevel-selective intersystem crossing from the photoexcited singlet state.

The properties of a polarized triplet state are evaluated by using two parameters, the population of the triplet sublevels in high fields P_{+1} , P_0 , P_{-1} and EPR decay time $T_{\rm EPR}$, which can be determined by time-resolved electron paramagnetic resonance (TR-EPR) measurements. The EPR signal intensity is proportional to the population difference P_{Δ} between the spin sublevels, and under the high field and the condition of fast relaxation, the decay of the signal intensity is expressed by the following equation:¹⁸

$$P_{\Delta} = \pm (P_0 - P_{\pm 1}) \exp\{-(1/T_1 + 1/T_{\text{tri}})t\}$$
(1)

where T_1 and T_{tri} denote the spin-lattice relaxation time and the triplet lifetime, respectively. The relationship among T_{EPR} , T_1 , and T_{tri} is expressed as follows:

spin density

$$1/T_{\rm EPR} = 1/T_{\rm 1} + 1/T_{\rm tri}$$
 (2)

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The derivation of this equation was based on a recent paper by Matsuoka et al.¹⁸ and is briefly summarized in the Supporting Information. In most of the previous works, pentacene has been commonly employed as the polarizing agent of triplet-DNP owing to its suitable electron polarization properties such as relatively large population differences in the zero field $(P_x:P_y:P_z = 0.76:0.16:0.08$ in the *p*-terphenyl crystal)¹⁹ and microsecond-scale long $T_{\rm EPR}$ at room temperature. Despite its potential, however, the applications of triplet-DNP have been mainly limited to molecular crystals that can be doped with pentacene due to pentacene's poor stability in air and very low solubility in solvents.

Therefore, we have focused on porphyrins as a new family of polarizing agents with good air stability and solubility and

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succeeded in triplet-DNP of biomolecules using porphyrins for the first time.²⁰ It had been known that porphyrins form a polarized triplet state,²¹⁻²³ but this had not been applied to triplet-DNP. In our previous report, we used a free-base porphyrin derivative as a polarizing agent for triplet-DNP, but its polarization $(P_v:P_v:P_z = 0.30:0.67:0.03)^{20}$ was not very high and there is room for improvement. Although metalloporphyrins such as Zn porphyrins are known to have very high polarization $(P_x:P_y:P_z = 0:0:1.0)$ ²³ they could not be used for triplet-DNP due to their too fast EPR decay (<1 μ s). Note that in the case of porphyrins, the spin-lattice relaxation time T_1 $(\sim \mu s)$ is much shorter than the triplet lifetime $T_{\rm tri}$ ($\sim ms$), and thus the inverse of the decay constant of the eq 1 $T_{\rm EPR}$ becomes nearly equal to T_1 . For simplicity, we refer to the decay time of the electron spin polarization of the porphyrin triplet as the spin-lattice relaxation time T_1 . From our previous studies, the microsecond-order EPR decay time is desired to gain a large enhancement by triplet-DNP.²⁴ Therefore, it is crucial to establish a design guideline to achieve metalloporphyrins with both high polarization and long T_1 in microseconds.

Here, we show that the modification of Zn porphyrins with multiple electron-withdrawing fluorine groups leads to polarizing agents with long spin-lattice relaxation times T_1 while maintaining their high polarization. We have systematically studied the triplet polarization of Zn and free-base *meso*tetraphenylporphyrins with different numbers of fluorine substitutions by TR-EPR in a glass matrix at room temperature (Figure 1). Very interestingly, the introduction of fluorine



Figure 1. (a) Schematic illustration of the generation and relaxation of triplet polarization. (b) Chemical structures of *meso*-tetraphenyl-porphyrins MTPP, MF₈TPP, and MF₂₀TPP ($M = H_2$ and Zn).

substituents in the Zn porphyrins resulted in a significant increase in the T_1 , which was an opposite trend to that of the free-base porphyrins. Density functional theory (DFT) calculations suggest that the introduction of fluorine reduces the spin density around the Zn atom, which enables both high polarization and long T_1 .

2. METHODS

2.1. Experimental Details. Free-base tetraphenylporphyrin (H_2TPP) and free-base tetrakis(pentafluorophenyl)-porphyrin $(H_2F_{20}TPP)$ were purchased from TCI and used without further purifications. Zinc tetraphenylporphyrin

(ZnTPP) was purchased from Frontier Scientific and used without further purifications. Free-base tetrakis(2,6difluorophenyl)porphyrin (H₂F₈TPP), zinc tetrakis(2,6-difluorophenyl)porphyrin) (ZnF₈TPP), and zinc tetrakis-(pentafluorophenyl)porphyrin (ZnF₂₀TPP) were prepared by following the literature methods^{25,26} and characterized by ¹H NMR measurements and mass spectroscopy. The porphyrins were mixed with β -estradiol at a typical concentration of 0.1 mol %, heated at 300 °C, and then rapidly cooled with liquid N₂, giving porphyrin-doped β -estradiol glasses.

2.2. Synthesis of H_2F_8TPP .²⁵ Pyrrole (340 μ L, 4.04 mmol) and 2,6-diffuorobenzaldehyde (550 mg, 3.87 mmol) were dissolved in 80 mL of dry CH₂Cl₂ under N₂. BF₃·O(Et)₂ (60 μ L, 0.476 mmol) was then added and stirred at room temperature for 1 day. After adding *p*-chloronil (390 mg, 1.59 mmol), the reaction mixture was stirred at room temperature for 18 h. After the reaction, the product was washed with methanol. The residue was purified by silica gel column chromatography (eluent: chloroform/hexane (8/2 v/v)). Yield: 13%. ¹H NMR (400 MHz, CDCl₃, TMS): δ = 7.35–7.40 (t, 8H), 7.75–7.83 (quin, 4H), 8.86 (s, 8H), -2.77 (s, 2H). ¹⁹F NMR (376 MHz, CDCl₃) δ = -108.08 (s, 8F). MALDI-TOF-MAS (dithranol, *m/z*): calcd.: 758.17, found: 758.23.

2.3. Synthesis of ZnF_8TPP .²⁶ A saturated solution of zinc acetate in methanol (2 mL) was added to H_2F_8TPP (50 mg) in CHCl₃ (10 mL). The reaction mixture was refluxed for 7 h. The progress of the reaction was confirmed by the disappearance of the Q band in UV–vis absorption measurements. After the reaction, the obtained crude was filtered, washed with water, dried over anhydrous Na₂SO₄, and purified by silica gel column chromatography (eluent: chloroform). Yield: 54%. ¹H NMR (400 MHz, CDCl₃, TMS): δ = 7.36–7.41 (t, 8H), 7.76–7.84 (quin, 4H), 8.97 (s, 8H). ¹⁹F NMR (376 MHz, CDCl₃) δ = –108.40 (s, 8F). MALDI-TOF-MAS (dithranol, *m*/*z*): calcd.: 820.09, found: 820.17.

2.4. Synthesis of $ZnF_{20}TPP$.²⁶ A saturated solution of zinc acetate in methanol (2 mL) was added to $H_2F_{20}TPP$ (50 mg) in CHCl₃ (10 mL). The reaction mixture was refluxed for 12 h. The progress of the reaction was confirmed by the disappearance of the Q band in UV–vis absorption measurements. After the reaction, the obtained crude was filtered, washed with water, dried over anhydrous Na₂SO₄, and purified by silica gel column chromatography (eluent: chloroform/hexane (2/1 v/v)). Several reprecipitations (methanol/water) were performed to obtain the final compound. Yield: 68%. ¹H NMR (400 MHz, CDCl₃, TMS): δ = 9.00 (s, 8H). ¹⁹F NMR (376 MHz, CDCl₃) δ = -136.63 to -136.70 (d, 8F), -151.66 to -151.72 (d, 4F), -161.48 to -161.70 (t, 8F). MALDI-TOF-MAS (dithranol, *m*/*z*): calcd.: 1035.97, found: 1035.87.

2.5. General Characterizations. ¹H NMR (400 MHz) spectra were measured on a JEOL JNM-ECZ400 spectrometer using TMS as the internal standard. UV–vis absorption spectra were recorded on a JASCO V-670 spectrophotometer. Fluorescence and phosphorescence spectra were measured by using a JASCO FP-8700 fluorescence spectrometer. Powder X-ray diffraction (PXRD) patterns were measured on a Bruker D2 Phaser (Cu-K α , 30 kV, 10 mA). Transient absorption measurements were conducted by using a UNISOKU TSP-2000 system.

Time-resolved EPR measurements were carried out using a homebuilt \sim 9 GHz dielectric resonator with a window for laser irradiation at a magnetic field generated using an electro-

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Figure 2. UV-vis absorption (black) and fluorescence (red) spectra at room temperature and phosphorescence spectra at 77 K (blue) of (a) H_2 TPP, H_2F_8 TPP, and H_2F_{20} TPP (top to bottom) and (b) ZnTPP, ZnF₈TPP, and ZnF₂₀TPP (top to bottom) in toluene (20 μ M for UV-vis absorption and fluorescence, 1 mM for phosphorescence). The shoulders on the short wavelength side of the phosphorescence spectra of free-base porphyrins are due to fluorescence.

magnet. A Spectra Physics Quanta-Lay Nd:YAG laser was used for excitation. The wavelength, repetition rate, pulse width, and pulse energy were 532 nm, 10 Hz, ~8 ns, and ~12 mJ/pulse, respectively. The electromagnet was purchased from Takano (MC160A-16). The gap and the pole size were 50 and 120 mm, respectively. A power supply PAG60-55 (Kikusui) with a stability of 10⁻⁴ was used. A microwave was generated from an SG22000Pro (DS instruments) with a power of ~10 μ W. The EPR signal was converted to DC using a diode detector, amplified with a low noise amplifier (ALN0905-12-3010, Dynamic RF Inc.), and detected using an oscilloscope (DSOX3024T, Keysight). The samples were put into capillaries and were measured at room temperature. The zero-field populations and zero-field splitting parameters were determined by the fitting of spectra by using the EasySpin toolbox²⁷ in MATLAB.²⁸

2.6. Computational Details. The optimized structures of porphyrins in the ground state and the lowest triplet state were obtained with the B3LYP exchange–correlation functional as implemented in the Gaussian 16 software²⁹ using the 6-31G* basis set. Time-dependent DFT for the calculation of the energies and the configurations was employed with B3LYP/SDD for Zn and EPR-II for others. Molecular orbitals and spin densities were visualized by GaussView 6.0.³⁰

3. RESULTS AND DISCUSSION

The electronic structures of porphyrins were characterized in toluene by measuring absorption and fluorescence spectra at room temperature and phosphorescence spectra at 77 K (Figure 2). It is well documented that Zn porphyrins have an approximate D_{4h} symmetry, with two highest occupied molecular orbitals (HOMOs) and two lowest unoccupied molecular orbitals (LUMOs) degenerated, but in free-base porphyrins, the symmetry drops to D_{2h} , and the HOMO and LUMO degenerations are resolved. Accordingly, ZnTPP showed one prominent absorption peak in the Q-band region, whereas H_2 TPP showed separated peaks due to the symmetry breaking. The absorption and fluorescence peaks of free-base and Zn porphyrins in toluene were slightly blueshifted by introducing the fluorine substituents due to the stabilization of HOMOs by fluorine substitution via an inductive effect (Table S1).^{31,32} A similar substituent effect was also observed in the triplet state, where the phosphorescence peak positions of freebase and Zn porphyrins were blueshifted by the fluorine substitution.

To characterize the room-temperature polarization properties, all the porphyrins were dispersed in a β -estradiol glass matrix at room temperature (Figure 3a). We employed β estradiol since its rigid room-temperature glass has an excellent ability to disperse various dyes and to avoid the oxygen quenching of the photoexcited triplet state,^{33,34} although its short ¹H spin–lattice relaxation time (\sim 3 s at 0.6 T) makes it difficult to be directly used for triplet-DNP. Then, 0.1 mol % porphyrins were dissolved in a β -estradiol melt at 300 °C above the melting point of β -estradiol ($T_{\rm m}$ = 176 °C) and then quenched with liquid nitrogen. This process provided roomtemperature glass with high transparency doped with porphyrins (Figure 3b). Powder X-ray diffraction (PXRD) measurements of the porphyrin-doped β -estradiol samples did not show any sharp crystalline peaks, confirming the amorphous structure of the glass matrix (Figure S1).

The dispersibility of the porphyrins in the β -estradiol glass matrix was examined by comparing the absorption and fluorescence spectra of the porphyrins in toluene solution, β estradiol glass, and neat solid at room temperature. The absorption spectra of all the porphyrins were redshifted and broadened in the neat state compared to the solution state, suggesting the presence of interchromophore interactions in the neat sample (Figure S2). The absorption spectra of the three free-base porphyrins in β -estradiol glass did not change from the solution state, suggesting that they are in the molecularly dispersed state. The three Zn porphyrins showed a change in the shape of their spectra in β -estradiol glass compared to the solution state, but the broadening did not occur in β -estradiol glass as much as in the neat state. We measured the concentration dependence of the absorption spectra of $\rm ZnF_{20}TPP$ in $\beta\text{-estradiol}$ glass and found that there was no change in the spectral shape up to 0.1 mol %, but above 0.5 mol %, the spectra gradually broadened and became closer to the neat state (Figure S3). This result suggests that the Zn porphyrins are not aggregated in β -estradiol glass at 0.1 mol %, and the change of the absorption spectra would be due to the slight structural distortion in β -estradiol glass. In the



Figure 3. (a) Chemical structure of β -estradiol. (b) Picture of β -estradiol glass doped with 0.1 mol % ZnF₂₀TPP. (c, e) Time-resolved EPR spectra and (d, f) decays of the EPR peaks of the free-base porphyrins and Zn porphyrins. Black lines are experimental data, and red lines are fitting results. The EPR decays were recorded at 328, 332, 338, 354, 356, and 335 mT for H₂TPP, H₂F₈TPP, H₂F₂₀TPP, ZnTPP, ZnF₈TPP, and ZnF₂₀TPP, respectively.

fluorescence spectra, all the porphyrins showed a redshift in the neat state compared to the solution state, but the shape of the spectra in the β -estradiol glass was similar to that in the solution state, supporting their molecularly dispersed state in the glass (Figure S4).

The TR-EPR spectra and fitting results of the porphyrins doped in β -estradiol glass at room temperature are shown in Figure 3. The relative population, zero-field splitting parameters, and spin-lattice relaxation time T_1 are summarized in Table 1. It has been known that in-plane sublevels are dominantly populated for free-base porphyrins due to the inplane components of spin-orbit coupling (SOC).³⁵ We also observed the in-plane (P_x and P_y) selective population for H₂TPP and H₂F₈TPP. For H₂F₂₀TPP, some population of the out-of-plane (P_z) sublevel was also generated. Since the *n* and σ orbitals of the F atoms are oriented in various directions, they can also contribute to the production of the P_z population.^{32,36} Due to the strong interaction between the d orbital of the central Zn ion and the π^* orbital of the porphyrin ligand, the strong out-of-plane component of SOC is generated

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Table 1. Relative Zero-Field Populations, Zero-Field Splitting Parameters, and Spin-Lattice Relaxation Times T_1 ($\approx T_{\text{EPR}}$) of the Free-Base and Zn Porphyrins

compound	$P_x:P_y:P_z$	D (MHz)	E (MHz)	T_1 (μ s)
H_2TPP	0.29:0.71:0	1125	221	9.3
H_2F_8TPP	0.18:0.82:0	1219	147	6.3
$H_2F_{20}TPP$	0:0.75:0.25	1292	93	4.9
ZnTPP	0:0:1.00	955	316	0.30
ZnF ₈ TPP	0:0:1.00	1046	352	0.17
$ZnF_{20}TPP$	0:0:1.00	961	121	1.7

 $(P_x:P_y:P_z = 0:0:1.0)$.³⁷ Importantly, this highly selective population of the out-of-plane sublevel was maintained in the fluorinated Zn porphyrins.

The spin-lattice relaxation time T_1 was obtained by single exponential fitting of the EPR decays. As the number of fluorine substitution increased, T_1 of free-base porphyrins became shorter from 9.3 to 4.9 μ s. This trend is consistent with the change of the D value that became larger from 1125 to 1292 MHz with the increase in the number of fluorine atoms. A similar trend, a shorter T_1 and a larger D value by fluorine substitution, was also observed for ZnTPP and ZnF₈TPP. It has been reported that the modulation of the electron spin dipolar interaction is mainly responsible for the spin-lattice relaxation of photoexcited triplets of organic molecules without any heavy atoms, and the spin-lattice relaxation rate is proportional to the square of zero-field splitting parameters.^{38,39} Interestingly, a totally different behavior was observed for $ZnF_{20}TPP$ that showed a much longer T_1 of 1.7 μ s than ZnTPP (0.30 μ s) and ZnF₈TPP (0.17 μ s). This unexpected result cannot be explained by the D value since the D value of ZnF₂₀TPP (961 MHz) was close to that of ZnTPP (955 MHz). Rather, this behavior can be explained by changes in the spin-orbit interaction, as discussed later. Note that the lifetime of the triplet excited state $T_{\rm tri}$ of all the examined porphyrins was in the millisecond-scale from transient absorption measurements (Figure S5), which does not limit the EPR decay time $T_{\rm EPR}$ ($T_{\rm EPR} \approx T_1$). It is remarkable that ZnF₂₀TPP achieves both of the high polarization and the long T_1 over 1 μ s.

The stronger dipole-dipole interactions between electrons in the fluorinated free-base porphyrins, which is indicated by the larger D value,^{40,41} would result in the shorter spin-lattice relaxation time T_1 . It has been reported that the larger D value in the fluorinated Mg porphyrins is due to the enhanced mixing of ${}^{3}(a_{2u}e_{g})$ and ${}^{3}(a_{1u}e_{g})$ configurations by the fluorine substitution.³² We performed DFT calculations for free-base porphyrins using B3LYP/6-31G* for geometry optimizations, and we used B3LYP/EPR-II⁴² for time-dependent DFT calculations.⁴³ The four frontier orbitals in the lowest triplet state are shown in Figure S6. In the triplet state, both the HOMO and LUMO are singly occupied molecular orbitals (SOMOs), but we retain the ground state labeling for clarity. The fluorine substituents largely increased the excitation energy to the lowest triplet state (Table S2). The main configuration of the lowest triplet state of H₂TPP was (LUMO \leftarrow HOMO), but the contribution of the (LUMO+1 \leftarrow HOMO-1) configuration (HOMO-1: the second highest molecular orbital, LUMO+1: the second lowest unoccupied molecular orbital) was increased with fluorination. The increased excitation energy to the triplet state and the enhanced contribution of the (LUMO+1 \leftarrow HOMO-1)

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Figure 4. Spin densities (isovalue = 0.00015) of (a) H_2TPP , (b) H_2F_8TPP , (c) $H_2F_{20}TPP$, (d) ZnTPP, (e) ZnF_8TPP , and (f) $ZnF_{20}TPP$ in the lowest triplet state calculated by B3LYP/6-31G*.

configuration by the fluorine substitutions are consistent with the observed blueshift of the phosphorescence peaks (Figure 2).³² Therefore, we expect that the larger D value by the fluorine substitutions of the free-base porphyrins is derived from the mixing of the configurations.

A much shorter T_1 of 0.30 μ s was observed for ZnTPP compared with H₂TPP (9.3 μ s). Since the *D* value of ZnTPP was smaller than that of H₂TPP, another relaxation mechanism that is not dipole–dipole interaction should be occurring to Zn porphyrins. In the case of organic molecules without heavy atoms, the effect of the spin–orbit interaction on spin–lattice relaxation is known to be insignificant.^{39,44} On the other hand, in the case of Zn porphyrins, the large spin–orbit interaction between the electrons and the heavy Zn atom may have a significant effect on spin–lattice relaxation. The T_1 of ZnF₈TPP (0.17 μ s) was shorter than that of ZnTPP (0.30 μ s). The DFT calculation results show that the mixing of the configurations were done by fluorine substitution, which may result in the increase in the *D* value and the shortening of T_1 , similar to the case of free-base porphyrins.

On the other hand, by increasing the number of fluorine atoms, a significantly longer T_1 of 1.7 μ s was observed for ZnF_{20} TPP than ZnTPP and ZnF₈TPP, which cannot be explained by the change of the *D* value. To understand the observed large elongation of T_1 by the fluorine substitutions on Zn porphyrins, we estimated their spin density in the lowest triplet state. The spin density of Zn atoms in ZnF₂₀TPP was significantly reduced compared to other Zn porphyrins (Figure 4 and Table S3). Therefore, the long T_1 of ZnF₂₀TPP can be attributed to the electron-withdrawing fluorine substituents that reduce the spin density on Zn atoms and weaken the spin—orbit interaction. In free-base porphyrins, no large change in spin density was observed due to fluorine substitution, suggesting that the mixing of configurations does not affect the spin density significantly.

4. CONCLUSIONS

We have found a design guideline to extend the spin-lattice relaxation time T_1 , which was previously very short, to longer than 1 μ s at room temperature while maintaining the high polarization $(P_x:P_y:P_z = 0:0:1.0)$ of metalloporphyrins. In addition to generating a strong out-of-plane spin-orbit coupling by using a central metal ion with d orbitals, it is important to weaken the spin-orbit interaction by introducing electron-withdrawing substituents to reduce the spin density at the metal atom. In our previous work, we have reported that an EPR decay time of a few microseconds is sufficient for the polarization transfer to nuclear spins.²⁴ Therefore, the achievement of a spin-lattice relaxation time exceeding 1 μ s in the current work is a critical milestone, while the further elongation of the spin-lattice relaxation time by optimizing molecular structures is an important future task. The current strategy is expected to lead to the creation of a variety of biocompatible polarizing agents with both high polarization and long spin-lattice relaxation time, which allows the hyperpolarization of various biomolecules at room temperature for NMR and MRI applications.

ASSOCIATED CONTENT

③ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpca.1c01839.

PXRD patterns, absorption and fluorescence spectra, absorption/fluorescence/phosphorescence peak positions, transient absorption decays, shapes of frontier orbitals, main configurations, and spin densities of porphyrin triplets (PDF)

AUTHOR INFORMATION

Corresponding Authors

- Kenichiro Tateishi Cluster for Pioneering Research, RIKEN, RIKEN Nishina Center for Accelerator-Based Science, Wako, Saitama 351-0198, Japan; o orcid.org/0000-0001-5566-526X; Email: kenichiro.tateishi@riken.jp
- Nobuo Kimizuka Department of Chemistry and Biochemistry, Graduate School of Engineering, Center for Molecular Systems (CMS), Kyushu University, Fukuoka 819-0395, Japan; orcid.org/0000-0001-8527-151X; Email: n-kimi@mail.cstm.kyushu-u.ac.jp
- Nobuhiro Yanai Department of Chemistry and Biochemistry, Graduate School of Engineering, Center for Molecular Systems (CMS), Kyushu University, Fukuoka 819-0395, Japan; JST-PRESTO, Kawaguchi, Saitama 332-0012, Japan; orcid.org/0000-0003-0297-6544; Email: yanai@ mail.cstm.kyushu-u.ac.jp

Authors

Akio Yamauchi – Department of Chemistry and Biochemistry, Graduate School of Engineering, Center for Molecular Systems (CMS), Kyushu University, Fukuoka 819-0395, Japan

Saiya Fujiwara – Department of Chemistry and Biochemistry, Graduate School of Engineering, Center for Molecular Systems (CMS), Kyushu University, Fukuoka 819-0395, Japan

Koki Nishimura – Department of Chemistry and Biochemistry, Graduate School of Engineering, Center for Molecular Systems (CMS), Kyushu University, Fukuoka 819-0395, Japan

- Yoichi Sasaki Department of Chemistry and Biochemistry, Graduate School of Engineering, Center for Molecular Systems (CMS), Kyushu University, Fukuoka 819-0395, Japan
- **Tomohiro Uesaka** Cluster for Pioneering Research, RIKEN, RIKEN Nishina Center for Accelerator-Based Science, Wako, Saitama 351-0198, Japan

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jpca.1c01839

Author Contributions

⁸A.Y. and S.F. contributed equally.

Notes

The authors declare no competing financial interest.

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