nature portfolio

Peer Review File

Synthesis of nickel(II)-containing meso-edited phthalocyanine derivatives

Corresponding Author: Dr Naoyuki Toriumi

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
The authors have introduced noteworthy macrocyclic complexes structurally related to metallophthalocyanines. In analogy to contracted porphyrins, the coordinating macrocycles, reported in this work, can be readily recognized as contracted phthalocyanines. Importantly, Uchiyama and co-workers have elaborated the rational synthetic routes to the nickel(II) complexes of 16π-electron antiaromatic tetrabenzodiazanorcorrole, 17π-electron paramagnetic tetrabenzotriazacorrole, and tetrabenzodiazacorrole One can appreciate that the skillful synthesis allowed edition at selected meso position.
Thus, the synthetic methodology involves the formal meso-position editing of phthalocyanine derivatives via deprotonative macrocyclization of open-form acyclic phthalonitrile nickel(II) tetramer, prepared by thiolate-mediated reductive tetramerization of phthalonitrile followed by metalation. I am evaluating reported procedures as elegant and extremely useful. The fundamental conclusions of this report are well documented by spectroscopic (UV-Vis, NMR, EPR), electrochemical, and structural data. The essential DFT calculations accompanying the electronic structure analysis have also been reported.
This pioneering contribution may open a new promising avenue for creating the chemistry of contracted phthalocyanines, following the suit of contracted porphyrinoid chemistry. The degree of novelty meets the standards of Nature Communication. The publication in Nature Communication is recommended.
Before the subsequent submission, the authors are expected to address the following issues.
1.
In the title and the text, the authors promise to describe the synthesis of meso-edited phthalocyanine derivatives whereas, as a matter of fact, their report addresses nickel(II) complexes of meso-edited phthalocyanine derivatives. In my opinion, such statements are simply misleading and the precise terminology should be applied here. The syntheses of free base meso-edited phthalocyanine derivatives remain to be a challenge for the opening field. The newly reported molecules contain firmly coordinated nickel(II). Consequently, any attempt to replace nickel(II) with other metals or metalloids seems to be rather a difficult task to achieve. Appropriate modification, affording eventually the free base, would be highly appreciated in further research. The authors' comments addressing the generality of their methodology and feasible applicability to other metals are expected.
These issues should be directly addressed in the manuscript.
2.
In the introduction, the authors briefly presented the state of the art in the field of phthalocyanines and their complexes. Considering the general interest of this contribution including profoundly modified phthalocyanines the following references seem to be of importance.
Claessens, C. G.; Gonzalez-Rodriguez, D.; Torres, T.
Subphthalocyanines: Singular Nonplanar Aromatic Compounds-Synthesis, Reactivity, and Physical Properties.
Chem. Rev. 2002, 102, 835-853
Janczak, J. _Kubiak, R. Gadolinium(III) Bicyclic Phthalocyanine Acta Cryst. (1995). C51, 2039-2042
3. The EPR spectra should be measured in frozen frozen solutions. Such experiments seem to be necessary for the detailed discussion focusing on the electronic structure of paramagnetic nickel complexes.

Reviewer #2

(Remarks to the Author)

In this article, Toriumi, Uchiyama, and co-workers describe the systematic synthetic strategy for the meso-edited phthalocyanine derivatives. The successful synthesis of three different phthalocyanine derivatives, tetrabenzodiazanorcorrole, tetrabenzotriazacorrole, and tetrabenzodiazacorrole from a common precursor is impressive, which is otherwise difficult to achieve by conventional phthalocyanine synthesis. In particular, tetrabenzodiazanorcorrole 2 has been prepared, and its structure and distinct antiaromatic nature have been elucidated for the first time. The obtained products were carefully characterized by several analytical methods including X-ray diffraction analysis. Fundamental properties of the products were also investigated. The skeletal transformation of 2 is also interesting and would enable access to further elaborated phthalocyanine derivatives. The present manuscript demonstrates impressive advancement in the field of porphyrin and phthalocyanine chemistry. The quality of the present article would be further improved if the authors address the following issues.

How do the authors rationalize the preferential formation of compound 5 over the corresponding phthalocyanine, which would be considered to be the most stable product? In this regard, the information on the product distribution in Supplementary Table 1 is not enough. Other oligomeric products than 5 and S1 would probably exist in the reaction mixture. The authors should also include a discussion of the origin of the selectivity, in particular, on the effect of counterions of the bases.

The choice of a small Ni(II) ion is reasonable, but the effect of the template should be confirmed by experiments. Other central metals may serve as templates for cyclization. For example, the use of Cu(II) may provide Cu(II) tetrabenzodiazanorcorrole, Cu(III) tetrabenzotriazacorrole, and Cu(III) tetrabenzodiazacorrole.

A comparison of antiaromatic tetrabenzodiazanorcorrole 2 with tetrabenzonorcorrole would be intriguing. Tetrabenzonorcorrole was reported to exhibit singlet diradical character (Angew. Chem. Int. Ed. 2018, 57, 2209). The sharp signal in the 1H NMR spectrum of 2 suggests its dominant closed-shell character, but its possible open-shell nature should be investigated by DFT calculations. In addition, the reason for the distinctly different behavior of tetrabenzodiazanorcorrole 2 and tetrabenzonorcorrole should be provided.

For tetrabenzotriazacorroles, the authors cited a review paper, but original articles on seminal works should be referred.

Reviewer #3

(Remarks to the Author)
The manuscript describes the synthesis of meso-edited phthalocyanine derivatives. This work is very well documented and of very high quality, but I think it's too specific for a journal with a very wide audience like Nat. Commun. The proposed synthesis is not very versatile and the molecules described, although new, do not display remarkable properties. By way of example, analogues, reported by the Uchiyama's group, have shown intense absorption properties in the near infrared that make it possible to envisage multiple applications. See for instance:

Muranaka, A.; Kyotani, F.; Ouyang, X.; Hashizume, D.; Uchiyama, M. Synthesis and Properties of Palladium(II) Complexes of Aromatic Hemiporphyrazines. J. Porphyrins Phthalocyanines 2014, 18, 869–874.

Toriumi, N.; Muranaka, A.; Hirano, K.; Yoshida, K.; Hashizume, D.; Uchiyama, M. 18π-Electron Tautomeric Benziphthalocyanine: A Functional Near-Infrared Dye with Tunable Aromaticity. Angew. Chem.,Int. Ed. 2014, 53, 7814–7818.

I would therefore suggest publishing this nice work in a more specialized journal.

Here are a few points for discussion in the manuscript

1) Molecule 2 was investigated in basic medium with NaOH (10 equiv.) (formation of 7). Can the authors record absorption of 2 depending on the pH and the nature of the base and acid ? This experiment might give additional data on the stability of 2 and the basic character of the nitrogen bridge (for comparison with the parent phthalocyanine).

2) Although MeOH and THF are weakly coordinating solvents, they might coordinate the nickel center in 2 (Fig. 6). This effect would change its spin state and probably its reactivity. The use of non coordinating solvents to transform 2 would be relevant.

3) The reactivity of 2 has been investigated. What about 3 and 4 which, as radicals, should be very reactive ?

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

The change of title to "Synthesis of nickel(II)-containing meso-edited phthalocyanine derivatives" is essential.

One has to be very specific here and the title is expected to reflect the scientific reality. It will take some time to synthesize meso-edited phthalocyanine free bases.
After this crucial modification, the manuscript will be acceptable for publication.
Comment 1
The history of subporphyrins and boron(III) subporphyrins provides remarkable examples of similar distinctions.
See [1} and references cited therein.
[1] Liu, L.; Kim, J.; Xu, L.; Rao, Y. T.; Zhou, M. B.; Yin, B. S.; Oh, J.; Kim, D.; Osuka, A.; Song, J. X. Synthesis of Subporphyrin Free Bases. Angew. Chem. Int. Ed. 2022, 61.e202214342
https://doi.org/10.1002/anie.202214342

Comment 2
Supplementary Fig. 1. ESR spectrum of 3 in toluene at –150 °C
In fact, the ESR spectrum shown in ESI demonstrates the small and predictable anisotropy of the g tensor. The appropriate g1 and g2 values should be given in the caption.

Reviewer #2

(Remarks to the Author)
In the revised manuscript, the authors have addressed my comments on the original version. I think that the stabilization of the HOMO level by electron-withdrawing sp2 nitrogen is essential to consider the electronic property and antiaromatic feature of tetrabenzodiazanorcorrole 2. Now the authors clearly discuss the effect on the meso-nitrogen atoms. The effect on cations during the oligomerization reaction to provide tetramer 5 is also mentioned. The publication in Nature Communication is recommended.

Reviewer #3

(Remarks to the Author)
My comments have been addressed in the revised manuscript. Taking into account the comments of the two other reviewers, I agree for publishing the work in Nat. Commun.

Reviewer 1

This pioneering contribution may open a new promising avenue for creating the chemistry of contracted phthalocyanines, following the suit of contracted porphyrinoid chemistry. The degree of novelty meets the standards of Nature Communication. The publication in Nature Communication is recommended.

Thank you for your positive evaluation of our work.

RE: 1) In the title and the text, the authors promise to describe the synthesis of meso-edited phthalocyanine derivatives whereas, as a matter of fact, their report addresses nickel(II) complexes of meso-edited phthalocyanine derivatives. In my opinion, such statements are simply misleading and the precise terminology should be applied here. The syntheses of free base meso-edited phthalocyanine derivatives remain to be a challenge for the opening field. The newly reported molecules contain firmly coordinated nickel(II). Consequently, any attempt to replace nickel(II) with other metals or metalloids seems to be rather a difficult task to achieve. Appropriate modification, affording eventually the free base, would be highly appreciated in further research. The authors' comments addressing the generality of their methodology and feasible applicability to other metals are expected.
These issues should be directly addressed in the manuscript.

Thank you for this important comment.
Firstly, we have included a statement in the abstract and also in the text (p. 2, 5) that the compounds were obtained as the Ni(II) complexes. We would prefer to retain the original title for brevity, as we think the word "derivatives" covers the presence of the metal. However, if the editor considers it necessary, we would be willing to change the title to "Synthesis of nickel(II)-containing *meso*-edited phthalocyanine derivatives".
Secondly, as you pointed out, removing Ni(II) from the centre of the macrocycles is not easy. Although we tried to remove Ni(II) from **2–4** under acidic (H_2SO_4) or reductive ($CoCp_2$) conditions, the corresponding free-base macrocycles were not obtained. We are now investigating metal complexes other than Ni(II), and have succeeded in obtaining **1**-Zn(II), **1**-Cu(II), **1**-Pd(II), and others. Cyclization using these metal complexes **1**-M(II) is currently under investigation (they do not cyclise under the conditions used in this work), and we plan to publish our findings in due course.

RE: 2) In the introduction, the authors briefly presented the state of the art in the field of phthalocyanines and their complexes.

Considering the general interest of this contribution including profoundly modified phthalocyanines the following references seem to be of importance.
Claessens, C. G.; Gonzalez-Rodriguez, D.; Torres, T.
Subphthalocyanines: Singular Nonplanar Aromatic Compounds-Synthesis, Reactivity, and Physical Properties.
Chem. Rev. 2002, 102, 835-853
Janczak, J. _Kubiak, R. Gadolinium(III) Bicyclic Phthalocyanine Acta Cryst. (1995). C51, 2039-2042

Thank you. We have added the above references as Refs. 2 and 3.

RE: 3) The EPR spectra should be measured in frozen solutions. Such experiments seem to be necessary for the detailed discussion focusing on the electronic structure of paramagnetic nickel complexes.

We have measured EPR spectra of **3** and **4** in frozen toluene at –150°C. However, hyperfine couplings were not observed, and anisotropic effects caused by restricted molecular motion were observed, leading to broadened spectra compared with those at room temperature. Therefore, we have decided to keep the EPR spectra measured at room temperature in the main text.

However, we have added the low-temperature EPR spectra in the SI (Supplementary Figs. 1, 3). We remeasured the EPR spectra at room temperature for comparison with those at –150 °C, and the spectra and the g values were slightly changed. Therefore, we have also updated the EPR data at room temperature in the manuscript (Fig. 4). These small changes have no effect on our conclusions.

Reviewer 2

The present manuscript demonstrates impressive advancement in the field of porphyrin and phthalocyanine chemistry.

Thank you for your positive evaluation of our work.

RE: 1) How do the authors rationalize the preferential formation of compound 5 over the corresponding phthalocyanine, which would be considered to be the most stable product? In this regard, the information on the product distribution in Supplementary Table 1 is not enough. Other oligomeric products than 5 and S1 would probably exist in the reaction mixture. The authors

should also include a discussion of the origin of the selectivity, in particular, on the effect of counterions of the bases.

Thank you for your comment. Indeed, another oligomeric product, phthalonitrile trimer **S2** was detected under the reaction conditions (2~6% yield), irrespective of the added bases. Other oligomers may be generated in the reaction mixture, but could not be separated or identified because they had very high polarity and seemed to be adsorbed and/or decomposed on silica gel.

Regarding the selectivity, the results of the screening of bases (Supplementary Table 1, entries 4–9) indicate that the selectivity for the tetramer **5** over phthalocyanine **S1** is increased by using bases with larger counter cations (Li~Na<K<Cs). We think this tendency is due to metal template effects on the formation of phthalocyanine. Small alkali metal ions such as Li and Na work well as templates for the phthalocyanine formation, as documented in the literature (Ref. 5). In contrast, the use of larger K and Cs atoms suppressed the formation of phthalocyanine, resulting in good selectivity for tetramer **5**.

We have added the discussion of the selective formation of **5** to the manuscript (p. 2). We have also updated the table in the SI (Supplementary Table 1), to include the yields of phthalonitrile trimer **S2** and the selectivity between **5** and **S1**.

RE: 2) The choice of a small Ni(II) ion is reasonable, but the effect of the template should be confirmed by experiments. Other central metals may serve as templates for cyclization. For example, the use of Cu(II) may provide Cu(II) tetrabenzodiazanorcorrole, Cu(III) tetrabenzotriazacorrole, and Cu(III) tetrabenzodiazacorrole.

We are also interested in the use of other central metals, and we have synthesized **1**-Zn(II), **1**-Cu(II), **1**-Pd(II), and others. However, these **1**-M(II) complexes including **1**-Cu(II) did not cyclize under the conditions employed for **1**-Ni(II). We are now investigating various other reaction conditions for the ring closure, and we plan to report the results in a future publication.

RE: 3) A comparison of antiaromatic tetrabenzodiazanorcorrole 2 with tetrabenzonorcorrole would be intriguing. Tetrabenzonorcorrole was reported to exhibit singlet diradical character (Angew. Chem. Int. Ed. 2018, 57, 2209). The sharp signal in the 1H NMR spectrum of 2 suggests its dominant closed-shell character, but its possible open-shell nature should be investigated by DFT calculations. In addition, the reason for the distinctly different behavior of tetrabenzodiazanorcorrole 2 and tetrabenzonorcorrole should be provided.

As you mentioned, **2** exhibited a closed-shell character judging from ^{1}H NMR spectroscopy, in contrast to the singlet diradical character of tetrabenzonorcorrole reported in the literature. According to your suggestion, we have tried to calculate open-shell singlet and triplet states of model compound **2'** using an unrestricted DFT method (UM06/6-31G*). However, the open-shell singlet state was not determined, probably due to the inherent closed-shell character, and the open-shell triplet state was much higher in energy (ΔE = 19.6 kcal/mol) than the closed-shell singlet state as computed by the restricted method (M06/6-31G*) (Supplementary Table 3). These results are all consistent with the closed-shell character of **2** observed experimentally. We think the difference that you refer to is due to the larger HOMO-LUMO energy gap of **2** (1.49 V, determined from the CV spectrum) than that of tetrabenzonorcorrole (0.75 V, reported in the literature), which is attributable to the stabilization of the HOMO of **2** by the *meso*-nitrogen atoms. Tetrabenzodiazanocorrole **2'** and tetrabenzonorcorrole show similar patterns of HOMOs and LUMOs, where the HOMOs show large orbital coefficients at the *meso*-positions. The HOMO energy of **2'** is significantly lowered by the two electronegative nitrogen atoms at the *meso*-positions (Supplementary Fig. 27). Thus, the larger HOMO-LUMO gap of tetrabenzodiazanorcorrole leads to its closed-shell character, in contrast to the reported tetrabenzonorcorrole.

We have added a discussion of the comparison between **2** and tetrabenzonorcorrole to the manuscript (p. 4). The computational results on **2'** using the unrestricted method have been added to the SI (Supplementary Table 3).

RE: 4) For tetrabenzotriazacorroles, the authors cited a review paper, but original articles on seminal works should be referred.

We have added two original articles (*J. Am. Chem. Soc.* **108**, 1532–1536 (1986); *Chem. Commun.* 679–680 (1997)) on tetrabenzotriazacorroles as Refs. 23 and 24.

Reviewer 3

The manuscript describes the synthesis of meso-edited phthalocyanine derivatives. This work is very well documented and of very high quality, but I think it's too specific for a journal with a very wide audience like Nat. Commun. The proposed synthesis is not very versatile and the molecules described, although new, do not display remarkable properties. By way of example, analogues, reported by the Uchiyama's group, have shown intense absorption properties in the near infrared that make it possible to envisage multiple applications. See for instance:

Muranaka, A.; Kyotani, F.; Ouyang, X.; Hashizume, D.; Uchiyama, M. Synthesis and Properties of Palladium(II) Complexes of Aromatic Hemiporphyrazines. J. Porphyrins Phthalocyanines 2014, 18, 869−874.

Toriumi, N.; Muranaka, A.; Hirano, K.; Yoshida, K.; Hashizume, D.; Uchiyama, M. 18π-Electron Tautomeric Benziphthalocyanine: A Functional Near-Infrared Dye with Tunable Aromaticity. Angew. Chem.,Int. Ed. 2014, 53, 7814−7818.

I would therefore suggest publishing this nice work in a more specialized journal.

Thank you for your comments. We do think our work would be of interest to a broad readership for the following reasons. Firstly, as we noted in the manuscript, it is generally difficult to create diverse phthalocyanine derivatives, especially skeletal modification/editing. This is a major limitation in the chemistry of phthalocyanines, which have many advantages over porphyrins as functional molecules. Therefore, novel strategies to synthesise phthalocyanine derivatives are of great interest. Our dianion-mediated macrocyclization method should be useful for the construction of various types of *meso*-edited phthalocyanines.

Secondly, we respectfully disagree with your comment "the molecules do not display remarkable properties". We think the facile redox properties of 17π-electron radicals **3** and **4** are of great importance. They undergo single-electron oxidation and reduction to afford 16π-electron antiaromatic and 18π-electron aromatic species, respectively, with significant changes of absorption in the red-near-IR region (Supplementary Figs. 22, 23). In particular, the 18π-electron aromatic species displayed intense Q-bands derived from their phthalocyanine-like skeletons, and would be promising candidates for redox-switchable near-IR dyes for bioimaging.

Thirdly, in response to your constructive comments and suggestions, we have also been able to clarify some important physical properties of the *meso*-*N*-edited phthalocyanine derivatives through additional experiments, and have included these results in the revised manuscript.

Therefore, we believe our work represents a significant advance in the chemistry of phthalocyanine and related compounds, and would be suitable for *Nature Communications*. We hope you will agree, taking into account the opinions of the other reviewers as well.

RE: 1) Molecule 2 was investigated in basic medium with NaOH (10 equiv.) (formation of 7). Can the authors record absorption of 2 depending on the pH and the nature of the base and acid? This experiment might give additional data on the stability of 2 and the basic character of the nitrogen bridge (for comparison with the parent phthalocyanine).

Thank you for the suggestion. We have measured and compared the absorption spectra of **2** and Ni phthalocyanine **S1** in CH_2Cl_2 in the presence of a base and an acid. The results are summarized below.

・The addition of DBU or KO^{t}Bu (excess) as a base did not change the spectra of **2** or **S1** in CH_2Cl_2 at room temperature, indicating that these bases do not bind to or decompose the Ni complexes.

・The addition of CF_3COOH changed the absorption spectra of both **2** and **S1** in CH_2Cl_2, suggesting that protonation of the *meso*-nitrogen atoms occurred (Supplementary Figs. 18, 19). In contrast, the addition of CH_3COOH did not change the absorption spectra of **2** or **S1** in CH_2Cl_2. These experimental results suggest that the *meso*-nitrogen atoms of **2** have similar basicity to those of NiPc **S1**.

We have added absorption spectra of **2** and **S1** in the presence of CF_3COOH to the SI (Supplementary Figs. 18, 19).

RE: 2) Although MeOH and THF are weakly coordinating solvents, they might coordinate the nickel center in 2 (Fig. 6). This effect would change its spin state and probably its reactivity. The use of non coordinating solvents to transform 2 would be relevant.

We think the coordination of solvents to the Ni centre of **2** is unlikely, based on the following experimental results.

・As you suggested, we examined the transformation of **2** in a non-coordinating solvent. The reaction of **2** with hydrazine in toluene proceeded to yield **8** with full conversion of **2** in 19 h at room temperature, similarly to the reaction in THF. This result suggests that the coordination ability of solvents does not influence the reactivity. The reaction with NaOH in non-coordinating solvents was not investigated due to insufficient solubility.

・We measured the ^{1}H NMR spectrum of **2** in pyridine-d_5 as a representative coordinating solvent. Sharp signals were observed, indicating little contribution of 5- or 6-coordinated Ni(II) species with a paramagnetic, high-spin state.

We have added the ^{1}H NMR spectrum of **2** in pyridine-d_5 to the SI.

RE: 3) The reactivity of 2 has been investigated. What about 3 and 4 which, as radicals, should be very reactive?

According to your suggestion, we have investigated the reactivities of radicals **3** and **4**. As we wrote in the manuscript, the addition of $CoCp_2$ as a reductant led to the formation of 18π-electron aromatic anionic species $\mathbf{3}^-$ and $\mathbf{4}^-$, judging from the ^{1}H NMR and UV-vis-NIR spectra. On the other hand, the addition of $NOBF_4$ generated 16π-electron antiaromatic cationic species $\mathbf{3}^+$ and $\mathbf{4}^+$. These facile redox behaviours are consistent with the extremely narrow redox potential gaps obtained in the CV measurements (Fig. 5b).

We also compared the reactivities of **3** and **4** with that of **2**. The reactions of **3** and **4** with hydrazine or NaOH as a nucleophile seemed to afford 18π-electron aromatic compounds via single-electron reduction, similarly to the reactions with $CoCp_2$. We think the narrow redox potentials of **3** and **4** are responsible for their susceptibility to electron transfer with multiple reagents.

We have added a discussion of the redox reactions of radical species **3** and **4** to the manuscript (p. 4) and the SI (Supplementary Information Section 2-4).

Response to Reviewer 1

The change of title to "Synthesis of nickel(II)-containing meso-edited phthalocyanine derivatives" is essential.

One has to be very specific here and the title is expected to reflect the scientific reality. It will take some time to synthesize meso-edited phthalocyanine free bases.

After this crucial modification, the manuscript will be acceptable for publication.

Thank you for this important comment. We have changed the title to "Synthesis of nickel(II)-containing *meso*-edited phthalocyanine derivatives".

RE: 1) The history of subporphyrins and boron(III) subporphyrins provides remarkable examples of similar distinctions.

See [1} and references cited therein.

[1] Liu, L.; Kim, J.; Xu, L.; Rao, Y. T.; Zhou, M. B.; Yin, B. S.; Oh, J.; Kim, D.; Osuka, A.; Song, J. X. Synthesis of Subporphyrin Free Bases. Angew. Chem. Int. Ed. 2022, 61.e202214342

Thank you for the comment. We have added the above reference as Ref. 44.

RE: 2) Supplementary Fig. 1. ESR spectrum of 3 in toluene at –150 °C

In fact, the ESR spectrum shown in ESI demonstrates the small and predictable anisotropy of the g tensor. The appropriate g1 and g2 values should be given in the caption.

We have added g_1, g_2, and g_3 values to the captions of Supplementary Fig. 1 and 3.