

Unexpected bromination ring-opening of tetraarylporphyrins†

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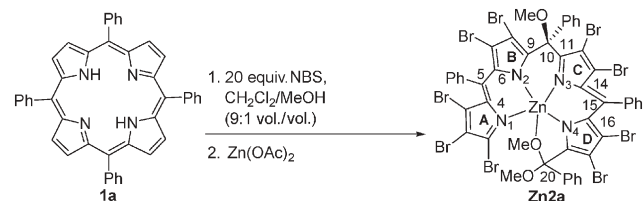
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An unexpected, mild, efficient bromination ring-opening method has been developed for convenient synthesis of various novel biladienes or brominated porphyrins by controlling the amounts of NBS used.

Open-chain tetrapyrrolic compounds are important natural products that are formed by the oxidative ring-opening of porphyrins *via* enzymatic heme oxygenase.¹ Reactions which accomplish a rupturing of the porphyrin macrocycle assume importance because this overall transformation can mimic the major biochemical processes of heme catabolism and chlorophyll degradation.¹ For example, coupled oxidation treatment of heme with dioxygen in the presence of a reducing agent has been used to mimic heme degradation in the presence of dioxygen.² On the other hand, a synthetic procedure for converting tetraarylporphyrins to these compounds should be a convenient and efficient route because various tetraarylporphyrins have been prepared as models for photosynthesis and redox enzymes. So far, synthetic routes to these compounds mainly include chemical oxidation,³ photooxygenation⁴ and those reactions of metalloporphyrin π -cation radicals with nucleophiles⁵. In general, these reactions will result in the formation of biliverdins. In the course of our ongoing efforts in the synthesis and application of perfluoroarylporphyrins,⁶ we have found an unexpectedly mild, efficient bromination ring-opening method for the convenient synthesis of various novel biladienes or brominated porphyrins. Here we present the results.

It is well known that *meso*-tetraphenylporphyrin H₂TPP (**1a**) is readily and regioselectively brominated using *N*-bromosuccinimide (NBS) under various conditions.^{6a,7} To our surprise, when 20 equivalents of NBS were added to a solution of **1a** in CH₂Cl₂/MeOH (9 : 1 vol./vol.), the color of the solution immediately changed from purple-red to blue (Scheme 1). However, the solution did not change at all in the absence of



Scheme 1 Bromination ring-opening reaction **1a**.

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MeOH. TLC of the blue solution revealed the complete loss of the starting porphyrin and the formation of a very complex product mixture. Relevant UV-visible spectra are shown in Fig. 1. The changes seen in Fig. 1, particularly the drop in the intensity of the Soret band at 418 nm, indicate that the porphyrin probably underwent a ring-opening reaction to produce an open-chain tetrapyrrole. After the addition of 5.0 equivalents of Zn(OAc)₂ to the reaction mixture and stirring for 30 minutes, a bright red solution developed. Its UV-visible spectrum displayed strong absorptions in the visible region (Fig. 1) and TLC indicated the formation of a main new red product, **Zn2a**, which partly decomposed during silica gel column purification. The ¹H NMR spectrum of **Zn2a** also revealed a non-aromatic conjugated system, with both pyrrolic and phenyl signals overlapping in the δ 7.15–7.45 range. Subsequently-obtained mass and UV-visible spectra suggested a more complex structure, and X-ray analysis was thought to be the only way to elucidate the structure unambiguously.

Fortunately, single crystals of **Zn2a** suitable for single crystal X-ray diffraction analysis were obtained by diffusion of petroleum ether into its dichloromethane solution. As shown in Fig. 2, the crystal structure† of **Zn2a** demonstrates that it is a novel biladiene resulting from the rupture of one of the *meso*-carbon–carbon bonds of **1a** and the addition of a methoxy group to the opposite *meso*-carbon. The pyrrolic periphery is perbrominated. The opening *meso*-carbon atom and adjacent phenyl group are transformed into a ketone acetal. One of the methoxy groups is coordinated to the zinc atom. The crystal structure of **Zn2a** also displays a helicoidal conformation. The dihedral angles of the exocyclic single and double bonds are: –2.4 (N1–C4–C5–C6),

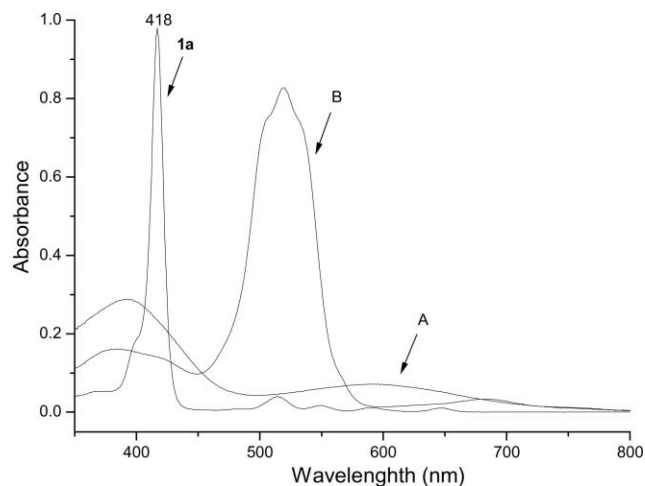


Fig. 1 The UV-visible spectrum of H₂TPP (**1a**) and the reaction system before (A) and after (B) the addition of Zn(OAc)₂.

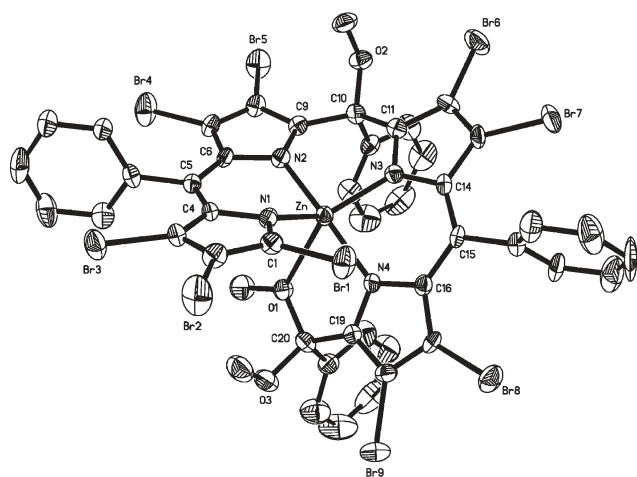


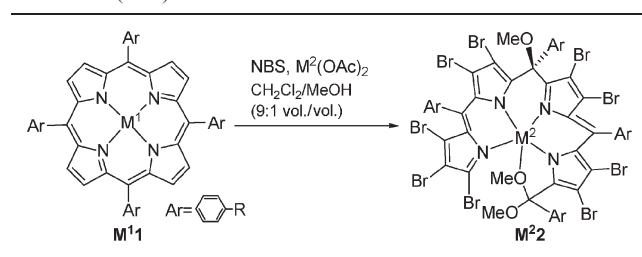
Fig. 2 Top view of the X-ray crystal structure of **Zn2a** (hydrogen atoms are omitted for clarity).

4.1 (C4–C5–C6–N2), -15.4 (N2–C9–C10–C11), 39.3 (C9–C10–C11–N3), 4.5 (N3–C14–C15–C16) and 0.6° (C14–C15–C16–N4). The bond angles of N1–Zn–N3 and N2–Zn–N3 are 133.8 and 156.8° , respectively. The Zn–N2 (1.990 Å) and Zn–N4 (1.988 Å) bond lengths are shorter than those of Zn–N1 (2.031 Å) and Zn–N3 (2.021 Å). One of the ketone acetal oxygen atoms forms a longer intramolecular distance of 2.409 Å to the zinc atom. All these data indicate that the A-ring pyrrole is distorted from coplanarity with the D-ring pyrrole, which is clearly reflected in the dihedral angle between them (57.8°). This can probably be attributed to the coordinated configuration around the zinc ion and the interactions of the ketone acetal group and bromine atom.

Under similar conditions, the procedure could be applied to a variety of *meso*-tetraarylporphyrins, affording a series of novel biladienes, as shown in Table 1. Various free base porphyrins with different substituents could all be subjected to smooth bromination ring-opening to provide the corresponding **Zn2** products in acceptable yields (Table 1, entries 1–5). When $\text{Cu}(\text{OAc})_2$ was used instead of $\text{Zn}(\text{OAc})_2$, the reaction proceeded for a longer time (2 hours) to afford the desired product **Cu2a** in a lower yield (Table 1, entry 6). No desired **Ni2a** product was obtained, even after 12 hours, when using $\text{Ni}(\text{OAc})_2$ instead of $\text{Zn}(\text{OAc})_2$; only an inseparable, complex reaction mixture resulted (Table 1, entry 7). The central metal ions of the starting porphyrins were also important in the reaction. The use of Zn(II) or free base porphyrin as a substrate resulted in smooth reactions, yielding the corresponding product **Zn2** (Table 1, entries 1–5 and 8). When using Cu(II) or Ni(II) as the central metal ions, various β -brominated porphyrin mixtures, instead of the desired products **Cu2a** or **Ni2a**, were obtained (Table 1, entries 9 and 10).

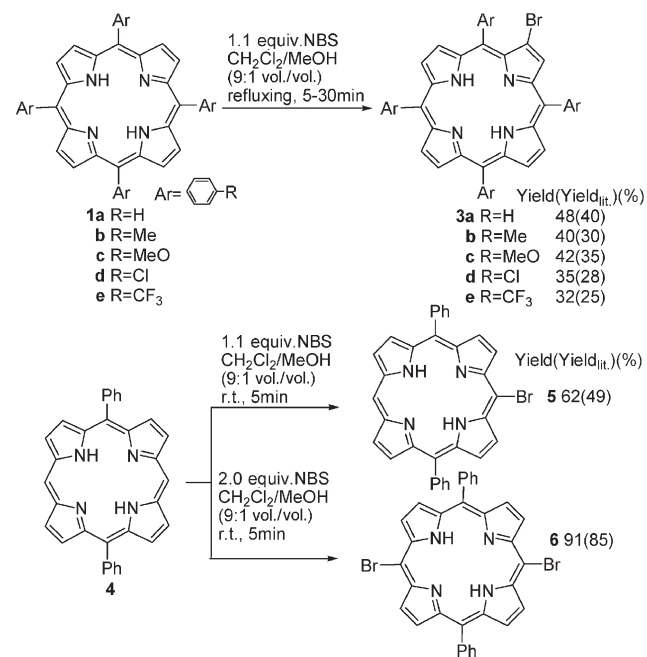
Realization of the powerful bromination ability of the system led us to explore its application in the synthesis of various brominated porphyrins. Under the above similar conditions, *i.e.*, using methanol as a co-solvent, when the amount of NBS was reduced to 1.1 equivalents, **1** could be smoothly brominated to provide the corresponding β -monobrominated porphyrins $\text{H}_2\text{TAP}(\text{Br})$ (**3**) in somewhat higher yields compared to the reported method (without methanol, 25–40%) (Scheme 2).^{6d,7a} Similarly, 5,10-diphenylporphyrin H_2DPP (**4**) could be efficiently monobrominated or dibrominated in better yields than the

Table 1 Bromination ring-opening of various *meso*-tetraarylporphyrins $\text{M}^1\text{TAP}(\text{M}^1)^a$



Entry	M ¹	R	Reactant	M ²	Product	Time/min	Yield (%) ^b
1	2H	H	1a	Zn	Zn2a	30	32
2	2H	Me	1b	Zn	Zn2b	30	46
3	2H	MeO	1c	Zn	Zn2c	30	40
4	2H	Cl	1d	Zn	Zn2d	30	38
5	2H	CF ₃	1e	Zn	Zn2e	30	25
6	2H	H	1a	Cu	Cu2a	120	11
7	2H	H	1a	Ni	— ^c	720	— ^c
8	Zn	H	Zn1a	— ^d	Zn2a	30	34
9	Cu	H	Cu1a	— ^d	— ^e	30	— ^e
10	Ni	H	Ni1a	— ^d	— ^e	30	— ^e

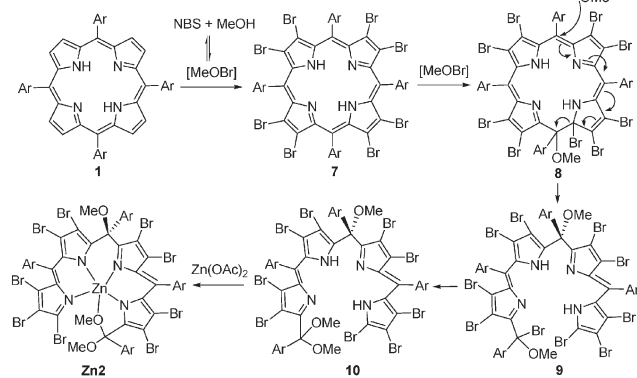
^a Reactions were carried out in $\text{CH}_2\text{Cl}_2/\text{MeOH}$ (9 : 1 vol./vol.) (20 mL) under air with $\text{M}^1\text{TAP}(\text{M}^1)$ (100 mg, 1.0 equiv.) and $\text{M}^2(\text{OAc})_2$ (5.0 equiv.) at room temperature. ^b Isolated yields. ^c None of the desired product **Ni2a** was formed, but instead an inseparable complex mixture was obtained. ^d No $\text{M}^2(\text{OAc})_2$ was used. ^e Various β -brominated porphyrin mixtures were obtained instead of the desired biladienes.



Scheme 2 Bromination of various porphyrins by controlling the amounts of NBS used.

literature method (49% for **5**, 85% for **6**) by controlling the amounts of NBS used (Scheme 2). In addition, it is worth mentioning that our method is more convenient because neither solvent purification nor a low reaction temperature (0°C) are needed.

As for the reaction mechanism, involvement of radical species in the reaction is ruled out because the reaction proceeds smoothly in



Scheme 3 Proposed reaction mechanism for the bromination ring-opening reaction.

the presence of an electron transfer scavenger, *i.e.*, *para*-dinitrobenzene (p-DNB) or a radical inhibitor, *i.e.*, hydroquinone (HQ). A possible reaction pathway for the bromination ring-opening process is shown in Scheme 3. Based on the literature,¹⁰ an active species [MeOBr] is proposed for the reaction process, which can be observed by ¹H NMR spectroscopy.† Firstly, porphyrin **1** is perbrominated by [MeOBr] to provide octabromoporphyrin H₂TAP(Br)₈ (**7**), which is a highly congested dodecasubstituted porphyrin macrocycle possessing a highly non-planar conformation.¹¹ Addition of [MeOBr] to one of the *meso*-carbon-carbon double bonds leads to the formation of intermediate **8** and subsequent nucleophilic attack of MeO[−] on the opposite *meso*-carbon, resulting in the formation of intermediates **9** and **10**, which can dramatically relieve the high steric congestion present in the non-planar porphyrin **7**. This might be the driving force for these bromination ring-opening reactions.¹² All of these intermediates are too unstable to be isolated by silica gel column chromatography; only the intermediate **10** can be transformed into the stable separable product **Zn2a** in the presence of Zn(OAc)₂.

In summary, an unexpected mild, efficient bromination ring-opening method has been developed for the convenient synthesis of various novel biladienes or brominated porphyrins by controlling the amounts of NBS used. Due to its efficiency and convenience, this method might find applications in other areas.

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† Crystal data. C₄₉H₃₄N₄Br₉O_{3.5}Zn, *M* = 1519.36, monoclinic, space group C2/c, *a* = 28.0250 (16), *b* = 14.0764 (8), *c* = 26.7094 (15) Å, α = 90,

β = 102.3100 (10), γ = 90°, *V* = 10294.4 (10) Å³, *T* = 293(2) K, *Z* = 8, *D_c* = 1.961 g cm^{−3}, μ(moKα) = 7.510 mm^{−1}, 26535 reflections measured, 9547 unique which were used in all calculations. *R*_{int} = 0.1362. *R*₁ = 0.1088. The final *wR*(*F*²) was 0.0548 (all data). CCDC 286156. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b514767k

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