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Selective Halogenation of C–H Bonds on Porphyrin Rings Using NaX/H_2O_2

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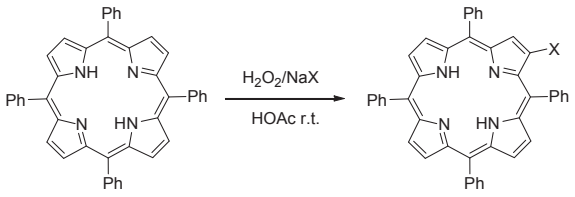
The selective oxidative halogenation of C–H bonds on porphyrins by halides/H_2O_2 is achieved. Different activities are observed for the three types of aromatic C–H bonds on porphyrin ring: *meso*-H is halogenated preferentially, the β-H could be substituted by Br or I, whereas *benzo*-C–H bonds remain intact. The reaction proceeds smoothly in a pseudo heterogeneous system and provides an alternative eco-friendly and efficient protocol for the synthesis of haloporphyrins.

Porphyrins, one type of important aromatic macrocycles, have been widely applied in catalysis, material sciences, and biology.[1] The performance of porphyrins in these fields generally depends on their peripheral substituents. Haloporphyrins are usually found to serve as the best organic synthetic intermediates for the synthesis of such substituted porphyrins, particularly unsymmetrical porphyrins, by aromatic nucleophilic substitution (SNAr) reactions and transition-metal-catalyzed cross-coupling reactions,[2] thus the selective direct halogenation of distinct C–H bonds on porphyrin ring have been widely investigated. Previous halogenation of porphyrin strongly depends on the toxic molecular halogen or organohalides generated from X_2. For example, Krishnan synthesized β-octabromotetraphenylporphyrin by reacting copper tetraphenylporphyrin with excess Br_2.[3] Burn achieved β-position chlorination of free-base porphyrins by pseudohalogens.[4] Nudy realized bromination of *meso*-C–H bonds of porphine by dibromoisocyanuric acid or PyHBr/Br_2.[5] Chen et al. also chlorinated porphyrins at *meso* positions using $PhICl_2$ as the halogen source.[6] In addition, halogenated amides were used widely to prepare *meso*-chloro/bromoporphyrins or β-bromotetraphenylporphyrins.[7]

The combination of $H_2O_2/X^-/H^+$ is a green oxidative halogenative system that is capable of selectively halogenating C–H bonds of simple arenes,[8] e.g. aniline and toluene were chlorinated at the *ortho* position of substituents by using an excess of HCl/H_2O_2 in hot alcohol.[9] The bromination at *ortho*-/*para*-positions of anilines and anisoles was achieved by using NH_4Br/H_2O_2/HOAc at room temperature.[10] *Ortho*-/*para*-C–H bonds of aniline were also iodinated quantitatively in a H_2SO_4/KI/H_2O_2 system.[11] Under microwave-assistant reaction conditions, the polycyclic aromatic hydrocarbons like anthraquinone also were halogenated by HX/H_2O_2.[12] However, to the best of our knowledge, the oxidative halogenation of macrocycle molecules has not been reported. Porphyrin is a special macrocycle with three types of special aromatic C–H bonds (*meso*-, β-, and potential *benzo*-). Herein, we report the selective oxidative halogenation of C–H bonds on porphyrin ring by using the combination of H_2O_2 and an inorganic halogen. It is shown that oxidative halogenation works smoothly and selectively: *meso*-H was substituted preferentially, when *meso*-H was not present, the β-H could be substituted by Br or I, whereas *benzo*-C–H bonds were unreactive. The substituent porphyrins or metal porphyrins showed similar reactivity.

Table 1. Halogenation of tetraphenylporphyrin



1 **2a** X = Br 28% **2b** X = I 11%

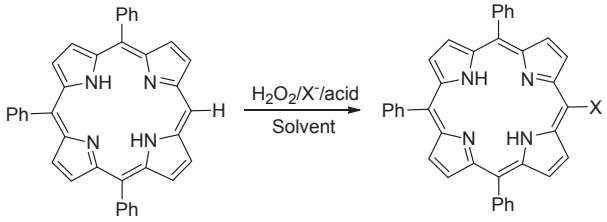
Entry[a]	Solvent	Halide (equiv)	Yield[b] /%
1	HOAc	NaCl (5)	—
2	HOAc	NaBr (5)	28
3	HOAc	NaI (5)	11

[a]2.5 mmol L^{-1} prophyrin, 5 equiv of 30% H_2O_2 stirred for 24 h at room temperature. [b]Measured by HPLC.

Initially, 5,10,15,20-tetraphenylporphyrin (**1**) was selected as the model substrate to react with NaX/H_2O_2 (Table 1).[13] Although the chlorination of **1** failed, the bromination and iodination afforded the corresponding β-halogenated products selectively in 28% and 11% yields, respectively, indicating that the β-C–H bonds on a porphyrin ring can be halogenated by such a system and the C–H bonds on the benzene ring are unreactive. Obviously, the activity of halogens increased as $Cl^- < Br^- < I^-$. However, the lower yield of iodoporphyrin was unexpected. This is probably ascribed to the formation of the labile hypoiodous which easily decomposes to unreactive I_2.[7a] This hypothesis was proved by heating the reaction mixture and recovering 72% sublimated I_2.

Subsequently, 5,10,15-triphenylporphyrin (**3**) was synthesized following a literature method[14] to investigate the reactivity of *meso*-C–H bonds and β-C–H bonds. The results summarized in Table 2 showed that the halogenation of *meso*-C–H bonds proceeded preferentially. All the chlorination reactions were successful, and the *meso*-chloroporphyrins were obtained regioselectively. The Lewis acids, $TiCl_4$ and AlX_3, which were first used as the halogen source, afforded chloroporphyrin in 99% and 38% yields, respectively (Entries 1 and 2). Considering the generation of HCl from the hydrolysis of Lewis acids in the presence of water, equivalent HCl was loaded as the chlorinated reagent and also gave **4a** in a moderate yield under similar conditions (68%, Entry 3). The excellent reactivity of $TiCl_4$ may be partially ascribed to the catalytic capability of Ti cation.[15] Using the combination of $NaCl/H_2SO_4$ instead of HCl solution, this chlorination also proceeded smoothly (65%, Entry 4). The

Table 2. Halogenation of 5,10,15-triphenylporphyrin



3 **4a** X = Cl, **4b** X = Br

Entry	Solvent	Prophyrin /mmol L^{-1}	H_2O_2 (equiv)	Halide (equiv)	Temp. /°C	Time /h	Yield[a] /%
1	CH_2Cl_2	2.5	H_2O_2 (5)	$TiCl_4$ (0.5)	25	24	99
2	CH_2Cl_2	2.5	H_2O_2 (5)	$AlCl_3$ (0.66)	25	24	38
3	CH_2Cl_2	2.5	H_2O_2 (5)	HCl (2)[b]	25	24	68
4	CH_2Cl_2	2.5	H_2O_2 (5)	H_2SO_4 (2.5); NaCl (2)[b]	25	24	65
5	HOAc	1	H_2O_2 (5)	NaCl (2)	25	24	74
6	HOAc	1	H_2O_2 (5)	NaCl (5)	25	24	99
7	HOAc	10	H_2O_2 (10)	NaCl (2)	60	4	99
8	CH_2Cl_2	1	H_2O_2 (5)	$AlBr_3$ (2)	25	24	99
9	HOAc	1	H_2O_2 (5)	NaBr (2)	25	24	99
10	HOAc	10	H_2O_2 (10)	NaBr (2)	60	4	99
11	HOAc	1	H_2O_2 (5)	NaI (2)	25	24	complicated

[a]Measured by HPLC. [b]Dissolved in 1:5 H_2O–MeOH.

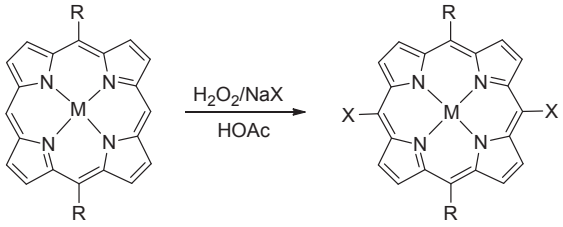
present oxidative halogenation was also achieved in the weak acidic system (HOAc/NaCl) to give the desired product **4a** in good yield (74%, Entry 5). Interestingly, almost quantitative yield was obtained under similar reaction conditions when the concentration was increased to 10 mmol L^{-1} (Entry 7).[16] This result probably was attributed to the poor solubility of haloporphyrin in HOAc, which precipitated during the reaction. This result also indicated more amount of substrate could be employed under the reaction conditions.

Similar results were obtained in the bromination of **3**. Although Br can substitute the β-H on porphyrin, no β-bromoporphyrin was detected under the reaction conditions indicating much higher reactivity of *meso*-C–H bonds than β-C–H bonds (Entries 8–10). Unfortunately, the iodination failed and a mixture was afforded. As indicated from the MS and ^{1}H NMR spectrum, both β-iodinated porphyrins and *meso*-iodinated porphyrins were generated. (Entry 11, for MS and ^{1}H NMR spectrum, see pages 4–6 in SI).

Then, 5,15-diphenylporphyrin bearing two *meso*-C–H bonds was synthesized[17] and treated with NaX/H_2O_2 under the optimal conditions. Both of *meso*-C–H bonds on porphyrin ring were chlorinated or brominated regioselectively to produce the dihalogenated products **6a** and **6b** in high yields (Table 3, Entries 1 and 2). Other selected 5,15-diaryl-substituted porphyrins with electron-withdrawing group or electron-donating groups on the benzene rings, 5,15-dialkyl-substituted porphrins and metal prophyrins were tested under the same conditions and gave similar results (Table 3, Entries 3–8).

In an effort to get some information on the mechanism, several control experiments were performed (Table 4). In the absence of chlorinated reagent, **3** did not decompose and was recovered quantitatively (Entry 1). This chlorination also occurred when 2 equiv NaClO was employed as the chlorinated reagent replacing the combination of H_2O_2/NaCl, indicating that NaClO would be the active intermediate (Entry 2). In the presence of radical scavenger 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) or 2,6-dibutylhydroxyltoluene (BHT), **3** could also be chlorinated readily, implying that this reaction would not be a radical process (Entries 3 and 4). Thus, this reaction probably takes place via a reaction path involving the oxidation of X^- by H_2O_2 to generate hypohalous species, which subsequently

Table 3. Halogenation of 5,15-disubstituted porphyrin[a]



5 **6**

Entry	R	M	Halide (equiv)	Isolated yield /%
1	Ph	2H	NaCl (5)	**6a**, 96
2	Ph	2H	NaBr (5)	**6b**, 97
3	*p*-ClC_6H_4	2H	NaCl (5)	**6c**, 97
4	*p*-MeC_6H_4	2H	NaCl (5)	**6d**, 96
5	*p*-$MeOC_6H_4$	2H	NaCl (5)	**6e**, 94
6	*n*-C_6H_{13}	2H	NaCl (5)	**6f**, 91
7	Ph	Ni	NaCl (5)	**6g**, 93
8	Ph	Cu	NaCl (5)	**6h**, 86

[a]10 mmol L^{-1} porphyrin, 10 equiv of 30 wt % H_2O_2, 60 °C stirred for 5.5 h.

Table 4. Control experiments[a]

3 ⟶ 4a

Entry	H_2O_2 /equiv	Halide (equiv)	Yield[b] /%
1	10	—	—
2[c]	5	NaClO (2)	66
3	10	NaCl (2) BHT (11)	95
4	10	NaCl (2) TEMPO (11)	89

[a]10 mmol L^{-1} porphyrin, 10 equiv 30 wt % H_2O_2, 60 °C stirred for 4 h. [b]Measured by HPLC. [c]1 mmol L^{-1} porphyrin, 5 equiv 30 wt % H_2O_2, 25 °C stirred for 24 h.

reacts with porphyrins to produce the corresponding haloporphyrins.[18]

In summary, C–H bonds on porphyrin ring can be selectively halogenated by using the combination of $H^+/X^-/H_2O_2$. The chlorination and bromination reactions of porphyrin exhibited the regioselectivity to *meso*-C–H bond, the bromination and iodination reactions also occurred at the β-position when the *meso*-C–H was absent. This transformation represents the first selective oxidative halogenation of aromatic macrocyclic compounds in the green $H^+/X^-/H_2O_2$ system, and also provides an alternative eco-friendly and efficient strategy for the synthesis of haloporphyrins under mild reaction conditions.

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Supporting Information is available electronically on J-STAGE.

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13 Typical procedure: 30.7 mg of **1** was dissolved in 50 mL of acetic acid, and then 5 equiv of H_2O_2 and sodium halide were added. The mixture was stirred at room temperature for 24 h and then neutralized with a sodium carbonate solution and extracted with dichloromethane. The crude product was purified by flash column chromatography on silica gel eluted with methylene chloride/hexane (1:3) to give the product.

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