Catalytic Halogenation of Selected Organic Compounds Mimicking Vanadate-dependent Marine Metalloenzymes†

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The ammonium metavanadate, mimicking vanadate-dependent metalloenzymes, efficiently catalyses the halogenation of a variety of organic substrates in dilute conditions in moderate to good yields using dilute hydrogen peroxide (30%) as an oxidizing agent exhibiting remarkable *ortho* selectivity with electron-rich aromatics.

Marine natural products exhibit a considerable abundance of halogenated (Cl, Br, I) organic compounds, compared to the natural products from terrestrial species. While the catalytic oxyfunctionalization of relatively inert C–H bonds has attracted significant attention either by mimicking biocatalysts,[1] or *via* zeolites,[2] little attention has been given to catalytic halogenation studies mimicking marine metalloenzymes. The biogenesis of halogenated organic compounds is presumed to involve recently discovered vanadate-dependent non-haem marine metalloenzymes,[3] *e.g.* vanadium bromoperoxidase and iodoperoxidase, which catalyse the oxidation of chlorides, bromides and iodides by hydrogen peroxide (or peroxides) in the presence of their inorganic sodium or potassium salts[4–7] (Scheme 1). Here, we report ammonium metavanadate (AMV) catalysed halogenation of a variety of organic substrates from potassium halides and dilute hydrogen peroxide in moderate to good yields.

$$R\text{–}H + X^- + H_2O_2 + H^+ \rightarrow R\text{–}X + 2H_2O$$

Scheme 1

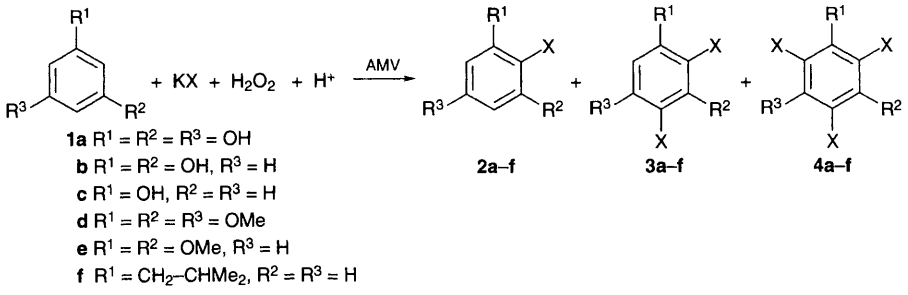
The substrates examined in our studies with AMV are phloroglucinol **1a**, resorcinol **1b**, phenol **1c**, 1,3,5-trimethoxybenzene **1d**, 1,3-dimethoxybenzene **1e**, isobutylbenzene **1f**, with various potassium salts (KX, X = Cl, Br, I and F), including TPAB (tetraisopropyl ammonium bromide) (see Table 1, Scheme 2). A typical experimental procedure (Table 1, entry 2) involves stirring of phloroglucinol (0.5 g, 3.96 mmol), KBr (0.944 g, 7.93 mmol) and AMV (46 mg, 0.39 mmol) in 50 ml of MeCN–H_2O (2 : 1), and the pH is adjusted to 5 by addition of dilute perchloric acid. Subsequently, 30% H_2O_2 (1.07 ml, 9.5 mmol) is added slowly over a period of 2 h during which time the reaction mixture changes from colourless to pale yellow to orange. The closed reaction mixture is stirred for 15 h at room temp., then saturated $NaHSO_3$ solution (10 ml) is added followed by brine. The mixture is then extracted with diethyl ether. Subsequently, drying of the diethyl ether layer, removal of solvent, separation, purification and characterization of organic compounds (**2a**, 24%; **3a**, 60%) is carried out in the usual way.

Several characteristic features from the Table 1 are summarized in the following. (*a*) A catalytic amount of AMV (0.03–0.1 equiv.) can halogenate electron-rich organic substrates from potassium halides (KBr and KCl, 1 equiv.) and H_2O_2 (1.1–1.2 equiv.) in moderate to good yields. (*b*) Unlike KBr and KCl, KI and KF fail to halogenate (entries 18 and 19). (*c*) Excess KBr, along with an appropriate amount of H_2O_2 leads to di- and tri-bromoproducts (entries 2 and 12). However, this pattern of reactivity is also a function of the nature of the substrates. (*d*) The presence of enzyme mimic, AMV, is essential for halogenation (entries 5 and 6). (*e*) The presence of H_2O_2 is also necessary for the success of halogenation (entry 7). (*f*) It is possible to perform the bromination only in H_2O (entry 13). (*g*) The nature of the counter ion is not relevant as TPAB could also lead to effective bromination even in CH_2Cl_2 (entry

Table 1 Catalytic halogenation mimicking marine metalloenzymes

Entry No.	Substrate	Halide source	Molar ratio[a] Sub.	KX	H_2O_2	Cat.	Solvent[b]	*t*[c]/*h*	Convn.[d](%)	Product(s)(%)[e]
1	**1a**	KBr	1	1	1.2	0.05	A	15	90	**2a**(75)
2	**1a**	KBr	1	2	2.4	0.1	A	15	92	**2a**(24), **3a**(60)
3	**1a**	KBr	1	3	3.6	0.15	A	15	95	**3a**(75)
4	**1a**	KBr	1	6	7.2	0.3	A	15	96	**3a**(80)
5	**1a**	KBr	1	1	1.2	0.0	A	15	0	**1a**(90)[f]
6	**1a**	KBr	1	3	3.6	0.0	A	15	0	**1a**(85)[f]
7	**1a**	KBr	1	3	0.0	0.1	A	15	0	**1a**(92)[f]
8	**1b**	KBr	1	1	1.2	0.05	A	20	40	**2b**(32)
9	**1b**	KBr	1	2	2.2	0.1	A	20	45	**2b**(37)
10	**1c**	KBr	1	2	2.4	0.1	A	20	0	**1c**(90)[f]
11	**1d**	KBr	1	1	1.2	0.05	B	24	95	**2d**(90)
12	**1d**	KBr	1	3	3.6	0.1	B	24	98	**2d**(43), **3d**(20), **4d**(13)[g]
13	**1d**	KBr	1	1	1.2	0.1	H_2O	24	20	**2d**(10)
14	**1d**	KBr	1	3	3.6	0.1	B	24	55	**2d**(40)
15	**1e**	KBr	1	2	2.4	0.05	A	24	73	**2e**(65)
16	**1e**	KCl	1	2	2.4	0.1	A	24	65	**2e**(45)
17	**1e**	TPAB[h]	1	2	2.4	0.1	CH_2Cl_2	24	30	**2e**(23)
18	**1e**	KI	1	2	2.4	0.1	A	24	0	**1e**(90)[i]
19	**1e**	KF	1	2	2.4	0.1	A	24	0	**1e**(92)
20	**1f**	KBr	1	2	2.4	0.1	A	24	20	**2f**(15)
21	**1f**	KBr	1	5	6.2	0.2	A	24	50	**2f**(18)[j]

[a] Molar ratio of substrates : halide source (KX) : 30% H_2O_2 : ammonium metavanadate (catalyst and enzyme mimic) at pH = 4–5 in indicated solvents is shown. Usually 10–20% excess of H_2O_2 with respect to KX was utilized. [b] Normally a 50 ml batch of 2 : 1 mixture of either MeCN : H_2O (A) or MeOH : H_2O (B) was stirred at room temperature. [c] Number of hours stirred at room temperature. [d] % Conversion of starting materials determined by capillary GC. [e] The % product(s) formation, as isolated by column chromatography, after appropriate work-up. Complementary observations were made by GC of reaction mixtures as well. [f] Usually in control experiments, >90% of substratate was recovered. [g] The products are confirmed by GC–MS as well. [h] Tetraisopropyl ammonium bromide was used. [i] Only iodine (I_2) was isolated. [j] Other side products were isopropylphenyl ketone (19%) and its reduced form (3%).



1a $R^1 = R^2 = R^3 = OH$
b $R^1 = R^2 = OH$, $R^3 = H$
c $R^1 = OH$, $R^2 = R^3 = H$
d $R^1 = R^2 = R^3 = OMe$
e $R^1 = R^2 = OMe$, $R^3 = H$
f $R^1 = CH_2–CHMe_2$, $R^2 = R^3 = H$

Scheme 2

17). The purpose of choosing TPAB and CH_2Cl_2 was to enhance miscibility of reaction mixture. (*h*) The *ortho* halogenation in all these studies is indeed unique and unprecedented (entries 8, 9, 15–17, 20–21). (*i*) Additionally, other probable VPO mimics, *e.g.* $VO(SO_4)$, V_2O_5, *etc.* failed to halogenate selected substrates in the studies outlined above.

The probable mechanism can be visualized as oxidation of X^- to X^0 (may dimerize to X_2), which may be further oxidized to X^+ (as XOH). Although liberation of Br_2 is observed in the absence of organic substrates and I_2 could be isolated (entry 18), the absence of benzylic bromination rules out the intermediacy of long-lived radicals. The various oxidizing species involved during oxidation could be oxyperoxides or oxovanadium (VO_2^+, **5**), peroxovanadium [$VO(O_2)^+$, **6**], diperoxovanadium [$VO(O_2)_2^-$, **7**] and/or hydroxyperoxides (HO-V-O-O-H, **8**). Indeed, ^{51}V NMR studies indicate the presence of resonances at δ −540.13 (for **5**), −468.6, −486.7 (for **6**) and −654.8 (for **7**)[8] relative to $VOCl_3$ (δ = 0) and are close to reported values,[8] although our reaction conditions are different. Definitive assignments cannot be made as ^{51}V NMR values are known to vary owing to the nature of the substituents, geometry (tetrahedron, pyramidal, octahedral, *etc.*), coordination environment and solvent effects. Oxyperoxides and hydroxyperoxides are known to be the oxidizing species in titanium- and vanadium- containing silicate molecular sieves (TS-1, VS-1, V-NCL-1, *etc.*) in the presence of H_2O_2.[2,9–12] The peroxovanadium **6** has also been implicated in oxidation studies.[13] The halogenating species can be X^+ as XOH or X_3^-,[14] but extreme *ortho* selectivity associated with electron-rich aromatics is intriguing.[15] The absence of iodination can be understood in terms of easy reduction of oxovanadium **5** with iodide,[16] thereby destroying the catalyst, whereas the absence of fluorination can be explained in terms of the instability of F-OH species.[17,18]

This study may contribute to understanding the evolution of halogenated organic substrates in the marine world, and to developing environmentally safer catalytic halogenation methodologies in aqueous media.

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Footnote

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