

A Doubly Biomimetic Synthetic Transformation: Catalytic Decarbonylation and Halogenation at RT by Vanadium Pentoxide

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Abstract: Halogenation of C–H bond by metal-oxo-peroxo and decarbonylation of aldehyde by metal-peroxo species are routinely done in biological systems. However, metal mediated decarbonylative halogenation is unknown in Nature. In this work, we have shown that widely available vanadium pentoxide (V₂O₅) and VO(acac)₂ can carry out the decarbonylative halogenation *via* generating an intermediate vanadium-oxo-peroxo species, which was characterized by ⁵¹V NMR, UV-Vis and Resonance Raman study. Further detection of formic acid from the reaction mixture confirmed the biomimetic aspects of decarbonylative halogenation. A detailed experimental and DFT study indicated a concerted mechanism for this decarbonylative halogenation performed under simple and mild reaction conditions.

Introduction:

Vanadium haloperoxidases (V-HPO) are involved in the halogenation of more than 4500 natural products. Reaction of hydrogen peroxide with vanadium center in V-HPO results in vanadium-oxo-peroxo species formation.^[1] A subsequent halide attack forms vanadium oxyhalide intermediate, which is primarily responsible for the halogenation of several natural products as evident from literature (Scheme 1).[1c, 2] The vanadium ion is oxidatively inert during the process and maintains its V(5+) oxidation state throughout the catalytic cycle. Several synthetic complexes including an array of ligands coordinated to vanadium centers have been reported to serve as functional mimics of V-HPO.[1a] In Nature deformylation is a common phenomenon. Cytochrome-P450, 14α-demethylase and cvanobacterial aldehvde decarbonylase dependent enzymes carry out deformylation reactions via eliminating formate.[3] In these cases both mono and dinudear heme-iron(III)-peroxo species has been proposed as the plausible intermediates. Synthetic mononuclear non-heme $[Fe^{III}(TMC)(\eta^2-O_2)]^+$ (side-on peroxo) can promote deformulation of aldehydes via elimination of formate (HCO2-).[4] However, the coalescence of both the phenomenon of decarbonylation and halogenation into a single-step decarbonylative halogenation can be envisaged by the vanadium-oxo-peroxo species (Scheme 2).^[5]

Results and Discussion:

We envisioned that vanadium pentoxide, V_2O_5 (1) can produce vanadium-oxo-peroxo, upon addition of acid and hydrogen peroxide, which will carry out the decarbonylative halogenations in presence of halide and hydrogen peroxide (Scheme 3).

In addition to realizing this double-biomimetic reaction with V_2O_5 , a detailed experimental studies have been performed to elucidate the mechanism of this decarbonylative halogenation reaction. The commercial accessibility as well as the cost-effectiveness of V_2O_5 is expected to attract synthetic chemists to realize the full potential of these novel

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[**] This activity is supported by SERB-India (EMR/2015/000164).
Financial support has been received from CSIR-India/UGC-India (fellowship to S.R. and B.P.).
DM sincerely thanks Dr. Jyotishman Dasgupta (TIFR), and his group member, Ms. Ankita Das for helping to conduct Resonance Raman in hisLaboratory.

strategies.









(1) (2) We started the present investigation with decarbonylative chlorination of 2-methoxynaphthaldehyde by V_2O_5 (1) in presence of KCI and H_2O_2 . The desired 1-chloro-2methoxynaphthalene was obtained in good yield (Table 1 entry 1). In absence of V_2O_5 and keeping all other reagents (e.g. KCI, H_2O_2) constant reaction was performed with 2methoxy-1-naphthaldehyde. Expectedly no trace of 1-chloro-2-methoxynaphthalene was obtained. Further, exploration with 2-hydroxynaphthaldehyde also produced the expected 1-chloronaphthalen-2-ol (50%) (Table 1, entry 2) by successful decarbonylation and chlorination.

Table 1. Decarbonylative halogenation by using V_2O_5 as catalyst



 $V_2O_5~(0.09~\text{mmol}),~\text{substrate}~(0.5~\text{mmol}),~\text{KCl}~(0.55~\text{g},~7.5~\text{mmol}),~\text{H}_2O_2~(330~\mu\text{L},~3.25~\text{mmol}),~\text{acidic solution}~(\text{prepared by HCl}~addition~to~w~\text{ater})~2~\text{mL}$ and citrate-phosphate buffer (2 mL), acetone (1 mL).

The relatively electron deficient substrate 6-bromo-2methoxy-1-naphthaldehyde provided corresponding decarbonylative halogenated product 6-bromo-1-chloro-2-methoxynaphthalene (30%) (Table 1, entry 4). The

decrease in yield of halogenated product is due to the presence of electron withdrawing group bromo (-Br) at 6 position. α,β -unsaturated The aldehvde 3.3corresponding diphenylacrylaldehyde, provided decarbonylative halogenated product, (2-chloroethene-1,1diyl)dibenzene (10%) and benzophenone (15%) as a byproduct. Interestingly when more electron rich substrate was used corresponding aromatic ring halogenation was observed. The electron-rich 2-aminobezaldehyde provided 2,4,6-tricloroanline (20%) (Table 1, entry 5). In this case aromatic ring gets chlorinated after formation of decarbonylative halogenation product, 2-chloroaniline due to the presence of electron rich amino group (-NH₂). Scope of the V₂O₅ catalyzed bromination reaction was explored with 2-methoxy-1-naphthaldehyde and 6-bromo-2-methoxy-1naphthaldehyde in presence of potassium bromide (KBr) and H₂O₂ under standard reaction protocol. The decarbonylative bromination reaction of 2-methoxy-1-naphthaldehyde provided brominated product in 55% yield whereas 6-bromo derivatives gave 40% of desired product (Scheme 4).



 $V_2 O_5$ (0.09 mmol), KBr (0.55 g, 4.62 mmol), substrate (0.5 mmol), H₂O₂ (30%, 330 μ L, 3.25 mmol), acidic water solution (H₂SO₄) in water (3 mL), citrate-phosphate buffer (2 mL), acetone (1 mL).

Interestingly, with bulky alkoxy groups (OR, R = allyl, propargyl, 2-chlorobenzyl) at the *ortho*- position of 1-naphthaldehyde, trace amount of halogenated products were obtained (Scheme 5). Such observations are suggestive of the importance of effective coordination of alkoxy moiety to vanadium during the decarbonylative halogenation reactions.

Scheme 5. Steric effect on decarbonylative halogenations





completion of the reaction in presence of organic substrate the yellowish-green color aqueous part which is likely to be the VO_2^+ .

UV-vis spectra recorded in absence of the exogenous substrate showed a band at 452 nm ($\epsilon = 391 \text{ M}^{-1}\text{cm}^{-1}$, Figure 1a), which indicated formation of the red-colored vanadium-oxo-peroxo species (Figure 1a).^[6] This characteristic absorption can be assigned as peroxo to vanadium (5+) charge transition band, corresponding to V⁵⁺O(O₂) species. Similar UV-vis for vanadium-oxo-peroxo species has been reported previously by J. Mayer, M. Sivak and H-J, Kruger groups. ^[6] The same red color solution of vanadium-oxo-peroxo species was further characterized by ⁵¹V NMR study. Vanadium(5+)-oxo-peroxo, VO(O₂)⁺ complex showed a sharp resonance at -534.68 ppm, that corroborated well with the literature report (Figure 2a).^[7]

Further the same red color solution of $VO(O_2)^+$ was used for Raman study. Raman spectrum of $VO(O_2)^+$, showed characteristic Raman shift of V-O_{peroxo}, at 550 cm⁻¹, O-O (*side on* peroxo) at 933 cm⁻¹ and V=O bond at 979 cm⁻¹ (Figure 3).^[8]



Figure 2. ⁵¹V NMR recorded during the course of decarbonylative halogenation reaction under standard reaction protocol (in acidic aqueous medium), (a) at the beginning of the reaction and in the absence of organic substrate (red colored species), vanadium oxo-peroxo species formed (-534.63 ppm). (b) recorded after 30 min upon addition of 2-methoxy-1-naphthaldehyde, (c) recorded after 3h (d) after completion of the reaction, yellowish-green colored species

The FT-IR analysis of V⁵⁺O(O₂) species showed one peak for V=O stretching at 987 cm⁻¹, O–O_P stretching at 910 cm⁻¹, and V–O stretching at 615 cm⁻¹.^[6a, 9]

The vanadium (5+)-oxo-peroxo species can easily form $VO(O_2)(OCI)$ (2) in presence of H_2O_2 and KCI in absence of in order to carry out the decarbonylative substrates halogenations reactions. When 2-methoxy-1-naphthaldehyde in acetone was added to the persistent red colored solution (formed under reaction standard reaction protocol) with UVvis band at 452 nm (Figure 1), the red colored solution turned green with formation of decarbonylated halogenated product 1-chloro-2-methoxynaphthalene. The green colored species displayed UV-vis bands (Figure 1) at 342 nm (sh) and 425 nm (sh).^[10] This species further showed a sharp peak at -538.15 ppm (⁵¹V NMR), which could be attributed to the formation of *cis*-dioxovanadium species (V⁵⁺O₂+).^[11] This green species turned to red colored V5+O(O2) upon addition of H₂O₂ that continued the catalytic cycle.

The ⁵¹V NMR recorded after addition of the 2-methoxy-1naphthaldehyde in acetone to the $V^{5+}O(O_2)(OH)^+$ solution. The resulting solution showed some new upfield peaks arises at ~-520,-502 ppm which might be due to the substrates coordination to the vanadium-oxo-peroxo species. After the reaction the green colored solution showed up field peak at -538.15 ppm could be due to the formation of cisdioxovanadium species (Figure 2d).^{[10d],34} The ⁵¹V NMR spectra, at the beginning of the reaction and at the end of the reaction showed chemical shifts at -537.3 and -538.1 ppm, respectively. These chemical shifts are particularly state.[11] characteristics for vanadium(+5) oxidation Therefore, vanadium(+5) oxidation state remains unaltered during the course of reaction.



Figure 3. Raman spectrum of $V^{6+}O(O_2)^+$, showing characteristic Raman shift of V-O_{peroxo}, at 550 cm⁻¹, O-O (*side on* peroxo) at 933 cm⁻¹ and V=O bond at 979 cm⁻¹.

Scheme 6. Generation of formic acid



In our attempt to achieve the decarbonylative halogenations, formic acid was expected to form. Indeed generation of formic acid was confirmed (yield, 50%) under standard reaction condition (Scheme 6). Such an observation, therefore, *mimics the decarbonylation reactions by metal peroxo complexes found in Nature*.

Mechanistic investigations suggested that vanadium-oxoperoxo species **2** was coordinated with aldehyde substrate. The peroxo moiety reacted with the carbonyl center in **3** to produce **4**, which in presence of chloride (CI⁻) and hydrogen peroxide provided halogenated product by generation of formic acid (Scheme 7). Active catalytic species, **2** was regenerated in presence of H_2O_2 and chloride (CI⁻) source. Throughout the catalytic cycle, vanadium (5+) oxidation state was maintained similar to that of V-HPO enzymes.^[1c, 2e] Since mononuclear vanadium-oxo-peroxo, V⁵⁺O(O₂)(OCI) (**2**) was responsible for carrying out the decarbonylative halogenation reaction, we thought to generate the similar intermediate which can be obtained from simple monomeric, V⁴⁺O(acac)₂ (**5**) under the same reaction condition of V₂O₅ catalyzed decarbonylative chlorination.^{[6a, 12],[8c]}

Scheme 7. Proposed mechanism based on experimental evidences



Interestingly, starting from V⁴⁺O(acac)₂ (5), we were successful in obtaining 1-chloro-2-methoxy naphthalene from 2-methoxy-1-naphthaldehyde under the standard reaction condition (Scheme 8). Expectedly, we observed formation of deep red solution after addition of KCI/H₂O₂ that changed to green during the course of the reaction. These observations were further supported by similar UV-vis maximum (at 450 nm) and ⁵¹V NMR (~-535 ppm).^{[8c],28} Generation of formic acid was also confirmed during the decarbonylative halogenation reaction with V⁴⁺O(acac)₂ (5).

Scheme 8. Decarbonylative chlorination by V⁴⁺O(acac)₂



Experimental Section:

General Information: Isolated compounds were characterized by ¹H and ¹³C NMR spectroscopy, GC-MS. IR spectrum was recorded on a Fourier transform infrared (FT-IR) spectrophotometer with samples prepared as KBr pellets. NMR spectra were recorded either on a Bruker 400/500 MHz or on a Varian 300/400 MHz instrument. All ⁵¹V NMR spectra were recorded in D₂O and reported in ppm relative to NH₄VO₃ (-571.5 ppm)^[13].

Procedure for decarbonylative chlorination:

Vanadium Pentoxide (V₂O₅, 18 mol%, ca. 17 mg) was taken in a 20 mL screw-capped reaction tube. A 2 mL of acidic aqueous solution (33 mL of conc. HCl in 300 mL distilled water) was added followed by 7.5 mmol (0.55 g) of KCl. Subsequently, 0.5 mmol of the substrate in 1 mL of acetone was added. Finally, 12 mmol (330 μ L) of 30 % H₂O₂ was added to the contents of the reaction tube and the screw cap was closed and sealed with paraffin. The reaction tube was kept at room temperature with constant stirring. After 12 hrs, 50 mL of dichloromethane was added to the reaction mixture and the organic component was extracted. The process was repeated and the organic parts were combined and dried over Na₂SO₄, and concentrated under reduced pressure in a rotary evaporator. The crude product thus obtained was further purified by column chromatography. Yield of isolated product was calculated with respect to starting material used in reaction.

Procedure B for decarbonylative bromination:

Vanadium Pentoxide (V₂O₅, 18 mol%, ca. 17 mg) was taken in a 20 mL screw-capped reaction tube. A 3 mL acidic water (10-15 μ L of conc. H₂SO₄ is added to 3 mL of water) solution was added followed by 2 mL of citrate-phosphate buffer. To this resulting solution 0.55 g (4.62 mmol) of KBr was added. Subsequently, 0.5 mmol of substrate in 1 mL of acetone was added. Finally, 330 μL of 30 % H_2O_2 was added to the contents of the reaction tube and the screw-cap was closed and sealed with paraffin. The reaction tube was kept at room temperature with constant stirring. After 12 hrs, 50 mL of dichloromethane was added to the reaction mixture and the organic component was extracted. The process was repeated and the organic parts were combined and dried over Na₂SO₄, and concentrated under reduced pressure in a rotary evaporator. The crude product thus obtained was further purified by column chromatography. Yield of isolated product was calculated with respect to starting material used in reaction.

Preparation of acidic water solution:

In a 500 mL beaker, 300 mL of distilled water was taken and then 33 mL conc. HCl (12 M) [from Merck Chemicals] was added in order to form dilute acid solution. Alternatively, 250 μ L of H₂SO₄ was added in 10 mL of distilled water and stirred properly to make it homogeneous. Both the acidic solution was used for the decarbonylative halogenation reactions and the characterization of reactive intermediates. We have obtained similar observations by using both the acidic solutions.

Sample preparation for ⁵¹V NMR analysis:

Vanadium Pentoxide (20 mg) was taken in vial and 2 mL of D₂O was added and subsequently 40 μ L of conc. H₂SO₄ was added. Then 330 μ L (3.25 mmol) of H₂O₂ (30%) and 0.55 g (7.5 mmol) of KCI were added and stirred for 5-10 min and then NMR was recorded. Similar solution was prepared and 2-methoxy-1-naphthaldehyde in acetone was added to the reaction solution and stirred until the green color appeared. During the course of the reaction after 30 min and 3 hour, ⁵¹V NMR was recorded. After completion of the reaction when green color appeared, ⁵¹V NMR was also recorded from that solution.

Sample Preparation for UV-vis study:

Vanadium Pentoxide (20 mg) was taken in 20 mL glass vial followed by 2 mL water and 50 μ L of H₂SO₄ was added to it. Subsequently 330 μ L (3.25 mmol) of H₂O₂ (30%) and 0.55 g (7.5 mmol) of KCI were added to the previous solution. Then 2 mL of citrate-phosphate buffer was added and UV-vis was recorded from the resulting solution, which showed UV-vis band at 452 nm. Alternatively, Vanadium Pentoxide (20 mg) was taken in a vial; 2 mL of H₂O and 40 μ L of conc. H₂SO₄ were added and stirred for 5 minutes. After that 330 μ L (3.25 mmol) of H₂O₂ and KCI (0.55 g, 7.5 mmol) were added and stirred 5 minutes. The resulting solution was used for the UV-vis study. By using the acid solution prepared from conc. HCl in distilled water also provides same spectra of vanadium-oxoperoxo complex.

Raman Spectroscopy:

We recorded resonance Raman spectra of the vanadiumoxo-peroxo species using confocal Raman microscope (alpha 300R, WITec, Germany). Frequency doubled DPSS Nd:YAG laser 532 nm was used at a power of 5 mW to excite vanadium-oxo-peroxo sample in mili-Q water under constant flow through 1 mm flow-cell. The scattered light in the focal plane was collected through 100 μ m core multimode fiber as pinhole. Spectrum was collected at an integration time of 60s using lens based ultrahigh throughput spectrometer (UHTS300, 1800 grooves/mm grating) coupled to a back illuminated CCD-camera (1024 x 128 pixels, ~2 cm⁻¹ per CCD pixel).

Sample preparation for Raman study:

Vanadium Pentoxide (20 mg) was taken in 20 mL glass vial followed by addition of 2 mL water and 40 μ L of H₂SO₄. Subsequently 330 μ L (3.25 mmol) of H₂O₂ (30%) and 0.55 g (7.5 mmol) of KCI were added to the previous solution. The solution was stirred for 5-10 minutes. The resulting solution showed UV-vis band at 452 nm. The prepared solution was used for Raman study.

DFT Study:

In order to understand the intricate steps in this reaction, we carried out DFT study to probe the mechanism of this reaction. Based on the experimental observations, the following mechanistic scheme was adapted for DFT calculations (Scheme 9). We have explored the energy landscape for the interaction of aldehyde with vanadium-oxoperoxo hydroxo, $[V^{5+}O(O_2)(OH)]$ species as well as with the vanadium-oxo-peroxo hypochlorite species, [V5+O(O2)(OCI)] (2). Our calculations reveal that the interaction of aldehyde with hypochlorite species is exothermic by 8 kJ/mol than the vanadium-oxo-peroxo hydroxo species. Thus we have decided to begin our reaction with the vanadium-oxo-peroxo hypochlorite species (2). Although vanadium hypobromites are commly known,^[1c, 14] recent reports suggest involvement of hypochlorite as the catalytically active species particularly for heme-iron systems.^[15] This along with the computed energetics suggest vanadium hypochlorite as the starting species in our catalytic reaction. Besides this species bears also high relevance to the active site of vanadium haloperoxidase.[16] The geometry around vanadium was trigonal planar and the V=O bond was calculated to be 1.580 Å, while the other two peroxo oxygen atoms were symmetrically bonded with a distance of 1.787 Å. The V-O(CI) bond distance was estimated to be 1.797 A. Owing to the significant relevance of the species in the mechanistic course of the reaction.

In the next step, the ligand L (L=2-methoxy napthaldehyde, Scheme 9) was assumed to coordinate to the vanadiumoxo-peroxo hypochlorite species. The optimized structure of this pre-reacting species is shown in Scheme 9. Energetically this step was estimated to be exothermic in nature by -34.9 kJ/mol. This species, besides having wide literature precedents^{[16a],[14b]}, had significant relevance to the active site of the vanadium haloperoxidase, with the only difference being coordination of the aldehyde oxygen atoms instead of a nitrogen atom of an imidizole ring. Selected bond parameters of the optimized structures are given in Table S1.^[8c]

The optimized structure revealed that the oxygen atom of the –CHO group formed a strong coordinate bond to the vanadium (2.012Å) while the oxygen atom of the –OMe group coordinated weakly (3.111Å) to the center. The V=O distance was estimated to be 1.590 Å, while the peroxo oxygen atoms were found to be asymmetrically coordinating to the Vanadium atom (1.799 Å and 1.836 Å). The V-O(CI) and O-CI distances were found to be 1.825 Å and 1.706 Å, respectively. A significant difference in the structure here compared to the reactant species was the asymmetric nature of the peroxo group with one long and one short V-O bonds. Significant σ/π -donation from the carbonyl oxygen influenced the peroxo bonding since a clear π donation from only one of the oxygen (possessing shorter V-O distance) was now visible (Figure 4). Another

significant distinction noticed here was on the ligand moiety, where the aldehyde carbon atom (noted as C(1)) developed significant positive charge (Mulliken charge analysis reveal an increase from 0.89 from free ligand to 1.22 in *int*2) upon coordination.

Coordination of the ligand, which induced asymmetry in the peroxo moiety, held the key to the next step where the longer V-O bond was expected to cleave. This was assumed to take place *via ts1* (Figure 4) leading to the formation of V-O-O⁻ species as an intermediate (*int2*; Figure 4).^[8c]

Scheme 9. Proposed mechanism for the decarbonylative halogenations based on DFT studies



The V-O bond cleavage occurred in a heterolytic fashion. This was consistent with the mechanism proposed for the vanadium haloperoxidases mimics.^[14b, 14c, 16a]

oxygen atom. The calculated barrier height for this step was estimated to be 74.2 kJ/mol (Figure 4). Formation of the *int2* species was slightly endothermic with respect to *int1*, however from the reactant energy; it was still exothermic in nature.

Thus the next logical step expected was the attack of the end-on peroxo species on the aldehyde carbon atom *via* ts2 (Figure 4).^[8c]

The nucleophilic characters of the end-on/side-on peroxo species with various metal ions were probed in detail. Particularly, the deformylation by the iron(III)-peroxo species clearly indicated that these species were nucleophilic in character (nature).[17] Thus all these literature precedents support our mechanistic hypothesis. The attacks of the distal oxygen at the carbon atom lead to elongation of the O-O bond to 1.415 Å (from 1.343 Å). The newly forming O(2)-C(1) distances were estimated to be 1.900 Å showing significant bonding interaction even at the transition state level. The transition state showed stronger interaction between the methoxy oxygen atom with the vanadium center (from 2.567 Å at int2 to 2.210 Å here, Figure 4).^[8c] The barrier height for this step was estimated to be 91.7 kJ/mol from int2, while from the reactant scale it was 63.3 kJ/mol (Figure 4 below).[8c]

In the next step, the newly forming O(2)-C(1) bond completes (1.434Å) leading to *int3* (Figure 4).^[8c] This intermediate formation was exothermic in nature by 82.6 kJ/mol from the reactant suggesting feasible formation of this species.



Figure 4. B3LYP computed energy (in solvent; ΔG in kJ/mol) profile diagram for the decarbonylative halogenations

In *ts1*, the V-O bond elongated from 1.836 Å to 2.300 Å while the other V-O bond of the peroxo moiety shortened. The O-O bond distance also shortens significantly as greater electron density was now available at the distal

Incidentally, a five coordinated hypochlorite attacking the carbon atom was ruled out based on the following arguments (i) the OCI group was far away from the C(2) carbon atom (4.986Å) (ii) as per the experimental conditions, the solution contained significant amount of

chloride ions thus making the external attack by a Cl⁻ ion feasible (iii) a dissociative pathway where O-Cl bond breaking first leading tothe generation of Cl⁻ species was unlikely as the bond-dissociation energy for the O-Cl bond was found to be very large (+443.5 kJ/mol).

At the transition state, the newly forming Cl-(C2) bond distance was estimated to be 2.45 Å (Figure 4). Interestingly, attack of the chloride ion at the C(2) position *via* this transition state was found to be a concerted process where the approach of chloride ion triggered two structural changes;

(i) At the transition state, the O—O bond breaks away (2.422 Å at *ts*3) and (ii) a new O(2)-C(3) bond was formed (1.443 Å at *ts*3). Besides, there was also slight elongation of C(1)-C(2) bond distance (1.530 Å at *ts*3). At the transition state, steps (i) and (ii) were already completed, while step (iii) showed sign of progress towards cleavage of the C(1)-C(2) bond. The Intrinsic reaction coordinate (IRC) calculations affirmed this point, at 2.5 Å CI-(C2) distance, the peroxo bonds were not broken, however at 2.45 Å CI-(C2) distance, the O-O bond was broken and the O(2)-C(3) bond was partially formed. Despite all these structural changes, the barrier height computed for this transition state was 1.2 kJ/mol from the *int*3, revealing nearly a barrier less process leading to the formation of *int4* (Figure 4).^[8c]

In the next step the C(I)-(C2) bond was formed completely (1.829Å) and the O(2)-C(3) bond strengthened further (1.425Å). The formation of this intermediate was found to be excessively exothermic in nature (-150.3 kJ/mol from the reactant). It is worthwhile to mention here that at this intermediate (*int4*), a constrained four membered ring (C-C-C-O, Figure 4) existed and in the next step, this ring was expected to cleave via *ts4* (Figure 4). Here C(1)-C(2) and O(2)-C(3) bonds were cleaving resulting in the formation of formic acid and decarbonylated halogenated product.

The C(1)-C(2) and O(2)-C(3) distances were found to be 2.292 Å and 1.567 Å respectively. Although there was a significant kinetic barrier for this species from int4, from the reactant surface, it lied at 26.5 kJ/mol, suggesting the feasible formation of the product. The final product formation was found to be a thermodynamic sink, with a stabilization of -196.9 kJ/mol and this energy gain was likely to ease the barrier heights required for the next catalytic cycle.[18] The potential energy surface developed for the catalytic cycle studied is shown in Figure 4. The catalytic cycle was assumed to start from vanadium-oxoperoxo hypochlorite species. This species was characterized by spectroscopic methods. In the next step the ligand was assumed to coordinate to this species leading to the formation of $[V(O)(O_2)(OCI)(L)]$ species. This step was computed to be exothermic and formation of this species was also witnessed in the experiments by variation in the ⁵¹V chemical shift. The ⁵¹V chemical shifts were qualitatively associated with the HOMO-LUMO gap and such analysis is well supported by literature reports for several vanadyl complexes.^[19] For species 2, the HOMO-LUMO gap was computed to be 3.1 eV while that drastically dropped to 1.2 eV for int1 suggesting significant shift in the ⁵¹V shift as observed in the experiments.^[20]

The first transition state had a barrier height of 74.2 kJ/mol while the second transition state had a much higher energy barrier (91.7 kJ/mol). These two transition states formed the key to the product formation with the second step being the rate limiting. Although the absolute barrier height of 91.7 kJ/mol seemed high, on a relative scale to the reactant, the peak energy was placed at 63.3 kJ/mol *i.e.* the energy gained upon ligand coordination, eased the kinetic

requirement. The large energy barrier computed also correlates with the experimental fact that the reactions were very slow and required long hours for completion (nearly 6-24 hrs for completion).

The first transition state required significant energy as strong V-O bond of the peroxo group was needed to be broken. Apart from strong σ -interaction, there were also significant π -donation from the peroxo group that enhanced the barrier height. Stronger π -interaction was correlated to the formal oxidation state of the V(5+) ions. For other transition metal ions possessing half-filled and more than half-filled orbitals, breaking up of the peroxo species was a facile step leading to the formation of highly reactive end-on peroxo/superoxo species.^[17a, 17c, 21] Although the second transition state was electrostatically favorable as discussed earlier, significant penalty in energy arose due to structural distortion required to attain this transition state and unfavorable orientation of the $\pi^*(C=O)$ orbital (Figure 4).^[8c] Large exothermic gain upon reaching intermediate 3, made other steps feasible and facilitated faster reaction. The ts3 was a concerted process where several key structural alterations were taking place as affirmed in our IRC calculations. The approach of chloride ion was essential to trigger a series of structural alterations.

Such concerted step also correlated to the experimental observation that decarbonylative products are not detected in the reaction mixture. Without addition of KCI, no product formation (decarbonylation, oxidation of aldehyde etc.) was detected thereby suggesting a necessity of external stimuli to drive the reaction as revealed by ts3. Thus the proposed mechanism rationalizes all the experimental observations, suggesting that this is the likely pathway through which the chlorination of aromatic compounds takes place. Among the species computed, only marginal changes in the vanadium charge was noted (1.09 to 1.27, Table S2^[8c]. This suggests that the 5+ oxidation state of vanadium was maintained throughout the reaction. A recent ⁵¹V NMR studies on Haloperoxidases Vanadium enzyme suggests spectroscopically silent V(5+) during the catalytic cycle as revealed in our biomimic models.[16b] The mechanism proposed has high relevance to the biology particularly when the vanadium haloperoxidase is found to halogenate thousands of natural products. Some of the key steps are likely to be common to both the enzymes and the bio-mimic chemistryproposed in this work.

Conclusion:

We have developed decarbonylative halogenation starting with simple available vanadium pentoxide. We have shown that *insitu* formed vanadium-oxo-peroxo species is responsible for decarbonylative halogenation reaction in presence of chloride ion *via* elimination of formate. The experimentally proposed mechanism of decarbonylative halogenation by vanadium-oxo-peroxo species is well supported by detailed DFT studies.

Computational Details:

Using the Gaussian 09 suite of program carried out all the calculations.^[22] The geometry optimizations were performed with B3LYP functional.^[23] The B3LYP had a proven track record of predicting the structures and the energetics accurately for such metal mediated catalytic reactions. LACVP basis set comprising LanL2DZ - Los Alamos effective core potential for V^[24] and a 6–31G*^[25] basis set for the other atoms (B-I) had been employed for geometry optimization and the optimized geometries were then used to perform single point energy calculations using a TZVPP basis set (B-II) on all atoms.^[26] The solvation energies had

been computed using PCM solvation model employing acetonitrile as the solvent.^[27] Frequency calculations were performed on the optimized structures at B-I level to verify that they were minima on the potential-energy surface (PES) and also to obtain free energy corrections. The quoted DFT energies were B3LYP solvation energies incorporating zero point energies correction at the B-I level computed at the temperature of 298.15 K, unless otherwise mentioned. The transition states were characterized by single negative frequency corresponding to the reaction coordinate and were verified by animating the frequency using visualization software such as Molden.^[28]

References:

[1] (a) F. H. Vaillancourt, E. Yeh, D. A. Vosburg, S. Garneau-Tsodikova, C. T. Walsh, *Chem. Rev.* 2006, *106*, 3364-3378;
(b) D. G. Fujimori, C. T. Walsh, *Curr. Opp. Chem. Biol.* 2007, *11*, 553-560; cA. Butler, M. Sandy, *Nature* 2009, *460*, 848-854; (d) L. C. Blasiak, C. L. Drennan, *Acc. Chem. Res.* 2008, *42*, 147-155.

[2] (a) R. Wever, H. Plat, E. de Boer, *biochimica et biophysica acta* **1985**, *830*, 181-186; (b) J. Littlechild, E. Garcia Rodriguez, M. Isupov, *J. Inorg. Biochem.* **2009**, *103*, 617-621; (c) A. Butler, J. N. Carter-Franklin, *Nat. Prod. Rep.* **2004**, *21*, 180-188; (d) W. Hemrika, R. Renirie, S. Macedo-Ribeiro, A. Messerschmidt, R. Wever, *J. Biol. Chem.* **1999**, *274*, 23820-23827; (e) V. Conte, A. Coletti, B. Floris, G. Licini, C. Zonta, *Coord. Chem. Rev.* **2011**, *255*, 2165-2177; (f) A. Messerschmidt, R. Wever, *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 392-396; (g) J. Littlechild, E. Garcia-Rodriguez, *Coord. Chem. Rev.* **2003**, *237*, 65-76; (h) M. Weyand, H. J. Hecht, M. Kieß, M. F. Liaud, H. Vilter, D. Schomburg, *J. Mol. Biol.* **1999**, *293*, 595-611.

[3] (a) K. Sen, J. C. Hackett, J. Phys. Chem. B 2009, 113, 8170-8182; (b) K. Sen, J. C. Hackett, J. Am. Chem. Soc. 2010, 132, 10293-10305; cC. Krebs, J. M. Bollinger Jr, S. J. Booker, Curr. Opp. Chem. Biol. 2011, 15, 291-303; (d) K. M. Henry, C. A. Townsend, J. Am. Chem. Soc. 2005, 127, 3724-3733; (e) A. Schimer, M. A. Rude, X. Li, E. Popova, S. B. del Cardayre, Science 2010, 329, 559-562; (f) L. J. Rajakovich, H. Nørgaard, D. M. Warui, W.-c. Chang, N. Li, S. J. Booker, C. Krebs, J. M. Bollinger, M.-E. Pandelia, J. Am. Chem. Soc. 2015, 137, 11695-11709.

[4] (a) J. Annaraj, Y. Suh, M. S. Seo, S. O. Kim, W. Nam, *Chem. Comm.* **2005**, 4529-4531; (b) A. Shokri, L. J. Que, *J. Am. Chem. Soc.* **2015**, *137*, 7686-7691.

[5] S. Rana, R. Haque, S. Ganji, D. Maiti, *Inorg. Chem.* **2013**, *52*, 2927-2932.

[6] (a) C. R. Waidmann, A. G. DiPasquale, J. M. Mayer, *Inorg. Chem.* 2010, *49*, 2383-2391; (b) M. Sivak, *Chem. Pap. Chem. Zvesti* 1987, *41*, 311-319; (c) M. Sivak, P. Schwendt, *Transition Met. Chem.* 1989, *14*, 273-276; (d) H. Kelm, H. J. Kruger, *Angew. Chem. Int. Ed.* 2001, *40*, 2344-2348; (e) R. M. Totaro, P. A. M. Williams, M. C. Apella, M. A. Blesa, E. J. Baran, *J. Chem. Soc., Dalton Trans.* 2000, 4403-4406; (f) A. Shaver, J. B. Ng, D. A. Hall, B. I. Posner, *Mol. Cell. Bio.* 1995, *153*, 5-15; (g) A. B. P. Lever, H. B. Gray, *Acc. Chem. Res.* 1978, *11*, 348-355.

[7] L. L. G. Justino, M. L. Ramos, F. Nogueira, A. Sobral, C. Geraldes, M. Kaupp, H. D. Burrows, C. Fiolhais, V. M. S. Gil, *Inorg. Chem.* **2008**, *47*, 7317-7326.

[8] (a) J. E. Molinari, I. E. Wachs, *J. Am. Chem. Soc.* 2010, *132*, 12559-12561; (b) L. L. Sun, K. E. Hermann, J. Noack, O. Timpe, D. Teschner, M. Hävecker, A. Trunschke, R. Schlögl, *J. Phys. Chem. C* 2014, *118*, 24611-24622; (c) Supporting Information; (d) P. Schwendt, M. Sivak, A. E. Lapshin, Y. I. Smolin, Y. F. Shepelev, D. Gyepesova, *Transition Met. Chem.* 1994, *19*, 34-36.

[9] (a) G. J. Colpas, B. J. Hamstra, J. W. Kampf, V. L. Pecoraro, *J. Am. Chem. Soc.* **1994**, *116*, 3627-3628; (b) G. J. Colpas, B. J. Hamstra, J. W. Kampf, V. L. Pecoraro, *J. Am. Chem. Soc.* **1996**, *118*, 3469-3478.

[10] (a) G. Asgedom, A. Sreedhara, C. P. Rao, E. Kolehmainen, *Polyhedron* **1996**, *15*, 3731-3739; (b) M. R. Maurya, S. Khurana, W. Zhang, D. Rehder, *J. Chem. Soc., Dalton Trans.* **2002**, 3015-3023; (c) M. R. Maurya, S. Khurana, W. J. Zhang, D. Rehder, *Eur. J. Inorg. Chem.* **2002**, 1749-1760; (d) M. R. Maurya, *J. Chem. Sc.* **2011**, *123*, 215-228; (e) M. R. Maurya, N. Chaudhary, F. Avecilla, *Polyhedron* **2014**, *67*, 436-448.

[11] D. Rehder, M. Casny, R. Grosse, *Mag. Res. Chem.* **2004**, *42*, 745-749.

[12] C. D. Nunes, P. D. Vaz, V. Felix, L. F. Veiros, T. Moniz, M. Rangel, S. Realista, A. C. Mourato, M. J. Calhorda, *Dalton Trans.* **2015**.

[13] (a) S. Hayashi, K. Hayamizu, *Bull. Chem. Soc. Jpn.* **1990**, *63*, 961-963; (b) H. Eckert, I. E. Wachs, *J. Phys. Chem* **1989**, *93*, 6796-6805.

[14] (a) A. Butler, *Coordination Chemistry Reviews* **1999**, *187*, 17-35; (b) G. J. Colpas, B. J. Hamstra, J. W. Kampf, V. L. Pecoraro, *J. Am. Chem. Soc.* **1996**, *118*, 3469-3478; (c) G Zampella, P. Fantucci, V. L. Pecoraro, L. De Gioia, *Inorg. Chem.* **2006**, *45*, 7133-7143.

[15] Z. Cong, S. Yanagisawa, T. Kurahashi, T. Ogura, S. Nakashima, H. Fujii, *J. Am. Chem. Soc.* **2012**, *134*, 20617-20620.

[16] (a) J. M. Winter, B. S. Moore, *J. Biol. Chem.* 2009, *284*, 18577-18581; (b) R. Gupta, G. Hou, R. Renirie, R. Wever, T. Polenova, *J. Am. Chem. Soc.* 2015, *137*, 5618-5628.

[17] (a) A. Ansari, P. Jayapal, G. Rajaraman, *Angew. Chem. Int. Ed.* **2015**, *54*, 564-568; (b) A. Yokoyama, J. E. Han, J. Cho, M. Kubo, T. Ogura, M. A. Siegler, K. D. Karlin, W. Nam, *J. Am. Chem. Soc.* **2012**, *134*, 15269-15272; (c) J. Cho, S. Jeon, S. A. Wilson, L. V. Liu, E. A. Kang, J. J. Braymer, M. H. Lim, B. Hedman, K. O. Hodgson, J. S. Valentine, E. I. Solomon, W. Nam, *Nature* **2011**, *478*, 502-505.

[18] (a) S. Kozuch, S. Shaik, *Acc. Chem. Res.* **2011**, *44*, 101-110; (b) D. Usharani, D. Janardanan, C. Li, S. Shaik, *Acc. Chem. Res.* **2013**, *46*, 471-482.

[19] (a) M. Debnath, A. Dutta, S. Biswas, K. K. Das, H. M. Lee, J. VÃcha, R. Marek, J. Marek, M. Ali, *Polyhedron* **2013**, *63*, 189-198; (b) P. B. Chatterjee, O. Goncharov-Zapata, L. L Quinn, G. Hou, H. Hamaed, R. W. Schurko, T. Polenova, D. C. Crans, *Inorg. Chem.* **2011**, *50*, 9794-9803; (c) O. Goncharova-Zapata, P. B. Chatterjee, G. Hou, L. L. Quinn, M Li, J. Yehl, D. C. Crans, T. Polenova, *CrystEngComm* **2013**, *15*, 8776-8783.

[20] M. P. Waller, M. Bühl, K. R. Geethalakshmi, D. Wang, W. Thiel, *Chem. Eur. J.* **2007**, *13*, 4723-4732.

[21] (a) M. H. Dickman, M. T. Pope, *Chem. Rev.* **1994**, *94*, 569-584; (b) D. Maiti, J. S. Woertink, A. A. Narducci Sarjeant E. I. Solomon, K. D. Karlin, *Inorg. Chem.* **2008**, *47*, 3787-3800; (c) M. S. Seo, J. Y. Kim, J. Annaraj, Y. Kim, Y.-M. Lee, S.-J. Kim, J. Kim, W. Nam, *Angew. Chem. Int. Ed.* **2007**, *46*, 377-380.

[22] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. J. Bearpark, J. Heyd, E. N. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. P. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R.

Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford, CT, USA, **2009**.

 [23] (a) C. T. Lee, W. T. Yang, R. G. Parr, *Phys. Rev. B*, **1988**, 37, 785-789; (b) A. D. Becke, *J. Chem. Phys.* **1993**, *98*, 5648-5652.

[24] (a) P. J. Hay, W. R. Wadt, *J. Chem. Phys* **1985**, *8*2, 270-283; (b) W. R. Wadt, P. J. Hay, *J. Chem. Phys* **1985**, *8*2, 284-298.

[25] (a) P. J. Hay, W. R. Wadt, *J. Chem. Phys* **1985**, *82*, 299-310; (b) Ditchfie.R, W. J. Hehre, J. A. Pople, *J. Chem. Phys.* **1971**, *54*, 724.

[26] (a) A. Schafer, H. Horn, R. Ahlrichs, J. Chem. Phys
1992, 97, 2571-2577; (b) A. Schafer, C. Huber, R. Ahlrichs, J. Chem. Phys
1994, 100, 5829-5835.

[27] B. Mennucci, WIREs Comput Mol Sci 2012, 2, 386-404.
[28] G. Schaftenaar, J. H. Noordik, J. Comput. Aided Mol. Des. 2000, 14, 123-134.

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