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# Reductive Electrochemical Activation of Molecular Oxygen Catalyzed by an Iron-Tungstate Oxide Capsule: Reactivity Studies Consistent with Compound I Type Oxidants

Marco Bugnola,<sup>‡,†</sup> Kaiji Shen,<sup>‡</sup> Eynat Haviv, and Ronny Neumann<sup>\*</sup>

Department of Organic Chemistry, Weizmann Institute of Science, Rehovot, Israel, 76100

ABSTRACT: The reductive activation of molecular oxygen catalyzed by iron-based enzymes towards its use as an oxygen donor is paradigmatic for oxygen transfer reactions in nature. Mechanistic studies on these enzymes and related biomimetic coordination compounds designed to form reactive intermediates, almost invariably using various "shunt" pathways, have shown that high valent Fe(V)=O and the formally isoelectronic Fe(IV)=O porphyrin cation radical intermediates are often thought to be the active species in alkane and arene hydroxylation and alkene epoxidation reactions. Although this four-decade long research effort has yielded a massive amount of spectroscopic data, reactivity studies and detailed, but still incomplete, mechanistic understanding, the actual reductive activation of molecular oxygen coupled with efficient catalytic transformations has rarely been experimentally studied. Recently, we found that a completely inorganic iron-tungsten oxide capsule with a Keplerate structure, noted as  $\{Fe_{30}W_{72}\}$ , is an effective electrocatalyst for the cathodic activation of molecular oxygen in water leading to the oxidation of light alkanes and alkenes. The present report deals with extensive reactivity studies of these {Fe30W72} electrocatalytic reactions showing (1) arene hydroxylation including kinetic isotope effects and migration of the *ipso* substituent to the adjacent carbon atom ("NIH shift"); (2) a high kinetic isotope effect for alkyl C-H bond activation; (3) dealkylation of alkylamines and alkylsulfides; (4) desaturation reactions; (5) retention of stereochemistry in *cis*-alkene epoxidation and (6) unusual regioselectivity in the oxidation of cyclic and acyclic ketones, alcohols and carboxylic acids where reactivity is not correlated to the bond disassociation energy; the regioselectivity obtained is attributable to polar effects and/or entropic contributions. Collectively these results also support the conclusion that the active intermediate specie formed in the catalytic cycle in consistent with a Compound I type oxidant. The activity of  $\{Fe_{30}W_{72}\}$  in cathodic aerobic oxidation reactions shows it to be an inorganic functional analog of iron based monoxygenases.

INTRODUCTION Collectively, iron-based monooxygenase enzymes have diverse structures and active site configurations, and also different biological roles and therefore different target substrates.<sup>1</sup> Despite this diversity in structure and biological function, they have many common mechanistic similarities. In fact, especially for hydroxylation reactions, it can be generalized that molecular oxygen activation takes place via the bonding of O2 to a Fe(II) center, followed by reductive formation of (hydro)peroxo iron intermediates. In the case of heme proteins and related biomimetic porphyrin-based models, lysis of the O-O yields a Fe(IV)=O porphyrin cation radical intermediate, also known as Compound I, responsible for the observed reactivity profiles.<sup>2</sup> For the non-heme diiron soluble methane monooxygenase enzyme, a closed bis( $\mu$ oxo)diiron(IV) active species has been the consensus,<sup>3</sup> until recently where new evidence points to a more open bisFe(IV) structure with both terminal and bridging oxo moieties.<sup>4</sup> Monoiron nonheme Fe(IV) oxo biomimetic species have also been extensively studied and in some cases quite reactive, but their activity appears to be low compared to enzyme catalysts.<sup>5</sup> The first non-heme iron(V)-oxo species based on the tetraanionic macrocyclic tetramide ligand (TAML) showed low activity relative to the isoelectronic heme compound I.<sup>6</sup> On the other hand, recent research on Fe(V) oxo species suggest that they are more reactive than their analogous Fe(IV) oxo species,7 although the published reactivity profiles for such intermediates is much more limited than for the isoelectronic Fe(IV)=O porphyrin cation radical species.

Despite the extensive research efforts described above there is a very noticeable paucity of reports on the actual reductive activation of O2 in the context of both heme and non-heme iron chemistry where a highly catalytically active intermediate is formed that results in alkane oxidation. In an early example, ascorbate was used as reductant to activate O2 over a diiron complex, but the reaction was sub-stoichiometric.8 Cathodic electrocatalytic reactions present intriguing possibilities for the activation of O2. In this context, early use of manganese(III) porphyrins showed low activity,9 and an electrocatalytic alkane oxidation with cytochrome P-450 failed allowing only the more facile sulfide oxidation.<sup>10</sup> In the past few years there have been 3 reports of cathodic activation of O<sub>2</sub> towards C-H bond hydroxylation and alkene epoxidation based on ironcatalysts. (1) A combination of Alkane Hydroxylase (AlkB) and Rubredoxin-2 (AlkG) enzymes were successfully used for hydroxylation of higher alkanes.<sup>11</sup> (2) Picket-fence iron porphyrins with an axial thiol ligand were assembled on electrodes and used for alkane hydroxylation and alkene epoxidation.<sup>12</sup> (3) An inorganic  ${Fe^{III}_{30}W^{VI}_{72}}$  molecular capsule was used by us as a homogeneous electrocatalyst in water for alkane oxygenation under ambient conditions, notably ethane to acetic acid by a cascade of oxidation reactions  $CH_3CH_3 \rightarrow CH_3CH_2OH \rightarrow CH_3CHO \rightarrow CH_3COOH$ . Oxidation of alkenes was also observed, for example,  $CH_2=CH_2 \rightarrow$  $CH_2(O)CH_2 \rightarrow HOCH_2CH_2OH \rightarrow HCHO \rightarrow HCOOH.^{13} As$ determined from the X-ray diffraction derived structure,  ${Fe^{III}_{30}W^{VI}_{72}}$  is icosahedral with 20 pores and is assembled by linking 12 pentagonal {(W)W<sub>5</sub>} oxide units with 30 Fe(III) atoms, Figure 1. The inner core of the capsule contains water and ~25 sulfate/bisulfate anions, yielding overall a water soluble polyanion.<sup>14</sup> Each Fe atom, 3 lining each pore, is hexa-coordinated to 4 bridging oxygen atoms in the equatorial plane (oxo, Fe-O<sub>e</sub> = 1.9787  $\pm$  0.002 Å); these oxygen atoms are bound to distorted octahedral neighboring W(VI) atoms. The coordination sphere around Fe(III) is completed in the axial plane by terminal oxygen atoms on the outer surface, O<sub>4,0</sub>, and inner surface, O<sub>4,i</sub>, of the capsule with bond distances of Fe-O<sub>a</sub> = 2.041 Å and 2.045 Å respectively. The coordination sphere around each Fe atom can be defined as Fe-(O<sub>c</sub> $\rightarrow$ W)<sub>4</sub>(O<sub>a</sub>)<sub>2</sub> with ~180 ° bond angles between opposite oxygen atoms, Figure 1. The Fe-Fe distances are ~6.4 Å.



**Figure 1.** The iron-tungsten capsule,  $\{Fe^{III}{}_{30}W^{VI}{}_{72}\}$  from single crystal XRD.<sup>14</sup> Left—ball and stick model; Fe--green, W-black, O-red, S-yellow. Not shown are the water molecules and NH<sub>4</sub> cations that are mostly on the periphery of the outer surface. Right – Coordination around the Fe atoms.

Beyond the alkane and alkene oxidations noted above, the previous research on electrocatalytic oxidation with  $\{Fe^{III}_{30}W^{VI}_{72}\}$  revealed by cyclic voltammetry that (a) the yellow  $\{Fe^{III}_{30}W^{VI}_{72}\}$  compound shows a fast, reversible, diffusion limited reduction of Fe(III) to Fe(II) at 0.47 V vs. Ag/AgCl; (b) at 0 V vs. Ag/AgCl the capsule is reduced by 10 electrons, yielding a brown  $\{Fe^{II}_{10}Fe^{III}_{30}W^{VI}_{72}\}$  species, commensurate with one reduced iron atom, Fe(II), per pore. (c) Upon exposure of  $\{Fe^{II}_{10}Fe^{III}_{30}W^{VI}_{72}\}$  to O<sub>2</sub> the initial formation of an intermediate was deduced by EPR but not directly observed; (d) no further intermediate species were identified, but the formation of hydroxy radicals as reactive species during catalysis was ruled out.



**Figure 2.** A possible catalytic cycle or hypothesis for cathodic activation of  $O_2$  and oxygenation. The electron distribution for the active species is unknown. The presentation of Fe(V)=O versus Fe(IV)-O+is a formalism. Other reactive intermediates can also be considered.

The high catalytic activity of  $\{Fe^{III}_{30}W^{VI}_{72}\}$  under cathodic aerobic conditions is an impetus to gain insight into the possible active

species responsible for reactivity. Based on a typical iron-porphyrin catalytic cycle,<sup>2</sup> a similar working hypothesis for a mono-iron catalytic cycle is presented in Figure 2.

Thus, the present report deals with extensive reactivity studies of the  $\{Fe_{30}W_{72}\}/O_2$  cathodic reactions. Reactions investigated included (1) arene hydroxylation reactions encompassing kinetic isotope effects and migration of the *ipso* substituent to the adjacent carbon atom ("NIH shift") or elimination of the ipso substituent (dehalogenation); (2) oxidation of 1,2-ethanediol towards the measurement of the kinetic isotope effect for alkyl C-H bonds (3) oxidation dealkylation of alkylamines and to some degree of alkylsulfides; (4) desaturation reactions; (5) *cis*-alkene epoxidation with retention of stereochemistry and (6) oxidation of various substrates with functional groups, where unusual regioselectivity was observed where reactivity is not correlated to the bond disassociation energy. The unusual regioselectivity observed is attributed to polar effects (water solvent and polyanionic catalyst) and/or entropic contributions. Collectively these results also support a conclusion that a Compound I type active intermediate species is formed in the catalytic cycle that explains the activity of  $\{Fe_{30}W_{72}\}$  in cathodic aerobic oxidation reactions.

# **RESULTS AND DISCUSSION**

Some information on the reactivity of the reduced capsule with O<sub>2</sub> was available by UV-vis spectroscopy. Thus, after {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} was reduced by 20 electrons, brown {Fe<sup>II</sup><sub>20</sub>Fe<sup>III</sup><sub>10</sub>W<sup>VI</sup><sub>72</sub>} was then exposed to O<sub>2</sub> in the absence of further reducing electrons. It rather slowly transformed through two isosbestic points at 242 and 390 nm in about 50 min at 4 °C, Figure 3.



**Figure 3**. Difference UV-vis spectra showing the evolution of proposed  $\{(Fe^{III}OOH)_{10}Fe^{III}_{20}W^{VI}_{72}\}$  from  $\{Fe^{II}_{20}Fe^{III}_{10}W^{VI}_{72}\}$  at 4°C in double distilled water. A 1.7  $\mu$ M solution of  $\{Fe^{III}_{30}W^{VI}_{72}\}$  capsule was reduced in situ by addition of 20 reducing equivalents of Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub> and the spectra were recorded by opening the cuvette to air.

The presence of the isosbestic points indicates that the reaction stoichiometry is constant and no secondary reactions occurred during this time period, but not necessarily is there a quantitative conversion one unique species to another.<sup>15</sup> One possible explanation is that the transformation that is being observed is as shown in equation 1:

$$\mathrm{F}\mathrm{e}^{\mathrm{II}} + \mathrm{O}_2 + 2\,\mathrm{e}^- + \mathrm{H}^+ \to \mathrm{F}\mathrm{e}^{\mathrm{III}} - \mathrm{O} - \mathrm{O}\mathrm{H} \tag{1}$$

Support for this explanation is that similar transformations were observed for other iron substituted polyoxometalates where the reduced end-on water stabilized hydroperoxo species were isolated

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and identified by x-ray crystallography.<sup>16</sup> An alternative explanation is that the reaction being observed is as shown in equation 2:

$$\operatorname{Fe}^{II} + 4\operatorname{H}^{+} + \operatorname{O}_{2} \to 4 \operatorname{Fe}^{III} + 2 \operatorname{H}_{2}\operatorname{O}$$

$$\tag{2}$$

where  $\text{Fe}^{III}$ –O–OH would only be an initial shorter lived intermediate. Support for this explanation is that the spectrum obtained after 50 min is practically identical to the spectrum of {Fe}^{III}\_{30}W^{VI}\_{72}}.

A further resonance Raman experiment was carried out where {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} was reduced by 20 electrons to yield {Fe<sup>III</sup><sub>20</sub>Fe<sup>III</sup><sub>10</sub>W<sup>VI</sup><sub>72</sub>} either electrochemically, Figure 4 ,or by addition of Na<sub>2</sub>S<sub>2</sub>O<sub>4</sub>, Figure S1 and then exposed to O<sub>2</sub>. With both reduction methods the spectra showed the appearance of a peak at 893 cm<sup>-1</sup> after addition of <sup>16</sup>O<sub>2</sub> (air) Figure 4. This peak is tentatively assigned to a high spin iron(III)-hydroperoxo species, {(Fe<sup>III</sup>OOH)<sub>10</sub>Fe<sup>III</sup><sub>20</sub>W<sup>VI</sup><sub>72</sub>}, typically observed at > 850 cm<sup>-1</sup>.<sup>17</sup> The expected isomer shift for an experiment with <sup>18</sup>O<sub>2</sub> is ~50 cm<sup>-1</sup>, which unfortunately coincides with strong M-O vibrational modes of the capsule and therefore was not observed.



**Figure 4.** Normalized Raman spectra showing the formation of the proposed { $(Fe^{III}OOH)_{10}Fe^{III}_{20}W^{VI}_{72}$ } from { $Fe^{II}_{20}Fe^{III}_{10}W^{VI}_{72}$ }. A 14  $\mu$ M solution of Na<sub>x</sub>{ $Fe^{III}_{30}W^{VI}_{72}$ } was reduced at 4°C in double distilled water in situ by addition of 20 reducing equivalents electrochemically (blue). The spectrum of { $(Fe^{III}OOH)_{10}Fe^{III}_{20}W^{VI}_{72}$ } was recorded by opening the cuvette to air (red) or <sup>18</sup>O<sub>2</sub> (green).

The Raman spectrum of  ${Fe^{III}}_{30}W^{VI}_{72}$  reduced by 10 electrons upon exposure to O2 showed no evidence for the formation of an iron(III)-superoxo species, { $(Fe^{III}OO \bullet)_{10}Fe^{III}_{20}W^{VI}_{72}$ }. That is no peak expected at ~1100 cm<sup>-1</sup> was observed. Further along the reaction pathway, the suggested high iron(III)-hydroperoxo species, {(Fe<sup>III</sup>OOH)<sub>10</sub>Fe<sup>III</sup><sub>20</sub>W<sup>VI</sup><sub>72</sub>} could undergo heterolytic bond cleavage to yield an Fe(V)-oxo species as hypothesized in Figure 2. Alternatively, homolytic bond cleavage would yield a hydroxyl radical. The formation of "free" hydroxyl radical can in principle be identified by trapping it with a nitrone spin trap such as BMPO (5tert-butoxycarbonyl 5-methyl-1-pyrroline N-oxide) that would yield a BMPO/OH• spin adduct with its associated EPR spectrum. Indeed, such a spectrum was initially observed, Figure S2. However, this experiment has an important caveat in that BMPO/OH. spin adducts are typically also observed as a result of the decay of originally formed BMPO/OOH. spin adduct that may also be metal catalyzed. In order to differentiate between this decay process and "free" OH• radicals directly reacting with BMPO, DMSO should be added to the solution as a scavenger (reacts faster than BMPO) of free OH• radicals. The formation of BMPO/CH<sub>3</sub>• spin adducts is expected when free OH• radicals are present.<sup>18-20</sup> This was not observed. Instead, under these experimental conditions an

EPR spectrum associable to a combination of the two conformers of the BMPO/OOH• adduct, was obtained Figure 5.<sup>20</sup> The manner in which the BMPO/OOH• adduct is formed and then observed under these conditions is typically indicative of the trapping of a superoxide anion. In addition, the experiments exclude the formation of "free" hydroxyl radicals and homolytic cleavage in the proposed iron(III)-hydroperoxo intermediate species.



**Figure 5.** Formation of the BMPO/OOH• spin adduct. A 14  $\mu$ M solution of Na<sub>x</sub>{Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} was reduced in situ at 4°C in double distilled water with 10 % DMSO by addition of 10 reducing equivalents electrochemically; 10 mg BMPO were added and then the solution was opened to air.

The further spectroscopic investigation of this catalytic cycle after the proposed formation of the hydroperoxo species was stymied by (a) the aqueous reaction medium that made low temperature capture of reactive intermediates difficult, (b) the strong absorption by tungsten of <sup>57</sup>Co gamma rays that led to a very noisy and uninformative <sup>57</sup>Fe Mössbauer spectrum even of the pristine starting compound {Fe<sup>III</sup><sub>30</sub>W<sup>II</sup><sub>72</sub>}, (c) the strong and broad Raman peaks of W-O and Fe-O in {Fe<sup>III</sup><sub>30</sub>W<sup>II</sup><sub>72</sub>}, Figure 4, that prevented observation of new peaks that may be associable to additional Febased intermediates and (d) the magnetic exchange interactions between Fe atoms that prevented useful EPR measurements.

In lieu of the lack of spectroscopic data on isolatable reactive intermediates, reactivity studies with different types of substrates could be excellent indicators of a possible active intermediate that would explain the overall reactivity observed. The cathodic oxidation of ethane to acetic acid was efficient (1.9  $\mu$ mol {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>}, 2.5 mL H<sub>2</sub>O, 1 bar air, 2 bar ethane, 20 °C, 24 h, platinum mesh cathode, platinum wire anode, cell potential 1.8 V) the reaction of methane was two-orders of magnitude slower or less efficient. We, therefore, initially focused on the challenging oxygenation of benzene since the hydroxylation of arenes is also paradigmatic for compound 1. Benzene reacted to initially form phenol, which further reacted to yield hydroquinone and catechol, Scheme 1.

Scheme 1. Cathodic Aerobic Hydroxylation of Benzene



Reaction conditions: 1.9  $\mu$ mol {Fe<sup>III</sup><sub>30</sub>W<sup>V1</sup><sub>72</sub>}, 2.5 mL D<sub>2</sub>O, air 1 bar, 100  $\mu$ mol benzene, 20 °C, 24 h, platinum mesh cathode, platinum wire anode, potential 1.8 V. Faradaic efficiency 24%. Products are reported in  $\mu$ mol and were characterized and quantified by <sup>1</sup>H NMR (see Figure S3). There was no reaction without {Fe<sup>III</sup><sub>30</sub>W<sup>V1</sup><sub>72</sub>} excluding the possibility of anodic activation of H<sub>2</sub>O at the Pt anode.

Since a strong oxidant was surmised, Figure 2, the absence of quinones in the reaction mixture was initially puzzling. It was, however observed that benzoquinone is easily reduced to hydroquinone under the reaction conditions used. This along with the prevalence of the uncoupled oxidation reaction (reduction of the reactive Fe=O species before its reaction with the substrate) can explain the Faradaic efficiency observed.<sup>21</sup>

## Scheme 2. Cathodic Aerobic Oxidation of 1,4-Difluorobenzene



Reaction conditions: 1.9  $\mu$ mol {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>}, 2.5 mL D<sub>2</sub>O, air 1 bar, 100  $\mu$ mol 1,4 difluorobenzene, 20 °C, 24 h, platinum mesh cathode, platinum wire anode, potential 1.8 V. Faradaic efficiency 5.3%. A total of 2.94  $\mu$ mol products were formed, which were characterized and quantified versus dimethylsulfone as standard by <sup>1</sup>H NMR and <sup>19</sup>F-NMR(see Figures S4-S7).

The hydroxylation of benzene also presented the opportunity to study the mechanism of this arene hydroxylation via investigation of the "NIH shift" reaction. A typical mechanism proposes the formation of a  $\sigma$ -complex followed hydride migration and formation of a ketone. Keto to enol tautomerization, thermodynamically driven by the formation of the arene, leads to products with partial retention of the migrated hydrogen atom.<sup>22</sup> Loss of the ipso hydrogen has also been observed and an analogous dehalogenation is a major pathway for haloarene oxidation that is catalyzed by bifacial iron phthalocyanine complexes,<sup>23-24</sup> presumably because halides are better leaving groups compared to hydride. We used 1,4difluorbenzene as a substrate, where product formation through the shift reaction and dehalogenation can be easily followed by <sup>1</sup>H and <sup>19</sup>F NMR, Scheme 2. The results clearly show the predominance of the dehalogenation reaction, but also the NIH shift reaction was observed, both hallmarks of an iron-oxo reactive intermediate. The prevalence of attack at the ipso position is very noticeable even in the presence of an activating hydroxyl moiety as evidenced by the final product distribution via the initial formation of 4-fluorophenol as intermediate.

## Table 1. Cathodic Aerobic of Halobenzenes

Substrate	Total yield, μmol	Products, mol %
fluorobenzene	4.7	2-fluorohydroquinone 13 hydroquinone/catechol 64 formic acid 23
chlorobenzene	5.9	2-chlorohydroquinone 46 4-chlorophenol 5 hydroquinone/catechol 20 formic acid 23
bromobenzene	7.5	2-bromohydroquinone 36 4- bromohydrocatechol 8 hydroquinone/catechol 40 formic acid 16

Reaction conditions:  $1.9 \,\mu\text{mol} \{\text{Fe}^{III}_{30}\text{W}^{VI}_{72}\}$ , 2.5 mL D<sub>2</sub>O, air 1 bar, 100  $\mu$ mol substrate, 20 °C, 24 h, platinum mesh cathode, platinum wire anode, potential 1.8 V. Products were characterized and quantified by <sup>1</sup>H NMR and <sup>19</sup>F-NMR (see Figures S8-S10).

The results for the oxidation of other halobenzenes summarized in Table 1. The most notable observations are that (1) the overall reactivity was BrPh > ClPh > FPh which is proportional to Hammett  $\sigma^+$  values and commensurate with a positively charged transition state in the rate determining step and an electrophilic oxidant. This is what would be expected from the mechanism presented in Scheme 2 and the results of the kinetic isotope effect experiment shown below. In addition, as may be also expected, nitrobenzene was less reactive (2.6 µmol products) and yielded mostly 3nitrophenol (96%) and some hydroquinone (4%). (2) The reaction at the ipso position was predominant for fluorobenzene but less so for bromobenzene and chlorobenzene leading to the perhaps counterintuitive observation that defluorination is more facile despite the stronger C-F bond ( $C_6H_5$ –F = 125.6 Kcal/mol,  $C_6H_5$ – Cl = 95.5 Kcal/mol; C<sub>6</sub>H<sub>5</sub>-Br = 80.4 Kcal/mol);<sup>25</sup> C-halogen bond cleavage is not rate determining. It should be noted that the preference for defluorination over dichlorination has been observed in the past, for example in the cytochrome P-450 catalyzed oxidation of 1,3,5-trichloro-2,4,6-trifluorobenzene.<sup>23a</sup> Subsequent DFT calculations point towards the probability that the initial  $\pi$  attack of the arene ring before formation of the sigma-bond intermediate is rate determining and has a lower barrier for C-F versus C-Cl.<sup>26</sup>

The mechanism presented in Scheme 2, implies that the rate determining step of the reaction does not involve C-H bond cleavage, therefore, there should be no primary kinetic isotope effect, KIE, for the hydroxylation of arenes. Since the benzene has limited solubility in water and is also quite volatile, the KIE was measured for phenol, using ~1:1 C<sub>6</sub>H<sub>5</sub>OH/C<sub>6</sub>D<sub>5</sub>OH in a competition experiment. KIE ~1.0 was measured (see Figures S11-S13 for the data) supporting a mechanism that does not involve C-H bond cleavage in the rate determining step. Another experiment that was carried out was to test for the possible exchange of the oxo moiety of the proposed Fe(V)=O active species with water.<sup>27</sup> This was done by carrying out a cathodic aerobic oxidation of reaction using <sup>18</sup>O<sub>2</sub> and  $H_2^{16}O$ . Thus, 1.9 µmol {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} in 2.5 mL DDW (natural abundance H<sub>2</sub><sup>16</sup>O), was deaerated by 5 pump/thaw cycles using 99.999%  $N_2$  and then 30 mL 96.2%  $^{18}\mathrm{O}_2$  was added to the sealed electrochemical cell. Electrolysis was carried out at 20 °C for 2 h using a platinum mesh cathode and a platinum wire anode at a potential of 1.8 V. Phenol was analyzed by GC-MS and showed 79% Ph<sup>18</sup>OH and 21% Ph<sup>16</sup>OH. Considering that <sup>16</sup>O<sub>2</sub> is continuously formed at the anode, the experiment shows that the reactive oxidant remained mostly <sup>18</sup>O labeled. This allows one to conclude that the proposed  $Fe(V)=^{18}O$  active species reacts faster with the benzene or is reduced in an uncoupled transformation (not shown) compared to an exchange reaction with  $H_2^{16}O$  to yield  $Fe(V)={}^{16}O$ , Scheme 3. Note that the absence of a phenyl radical, even if it could exist, would require a C-H bond activation in the rate determining step which was not observed. Thus, in this type of arene hydroxylation reaction one can rule the reaction of such a radical with <sup>18</sup>O<sub>2</sub> to vield Ph<sup>18</sup>OH.

### Scheme 3. Cathodic Hydroxylation of Benzene with <sup>18</sup>O<sub>2</sub>



Reaction conditions: 1.9  $\mu$ mol {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>}, 2.5 mL H<sub>2</sub>O, 1.3 mmol 96.2%  $^{18}\text{O}_2$ , 100  $\mu$ mol benzene, 20 °C, 2 h, platinum mesh cathode, platinum wire anode, potential 1.8 V.

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Alkene epoxidation is a common reaction catalyzed also by various biomimetic models of heme and non-heme iron compounds.  ${Fe^{III}_{30}W^{VI}_{72}}$  also catalyzes the oxidation of alkenes, but the initial epoxide formed, for example ethene oxide from ethene quickly reacts via C-C bond cleavage to form the corresponding formaldehyde and then formic acid. It was shown that cytochrome P-450 epoxidized alkenes by stereoselective *cis*-addition,<sup>28</sup> and as expected the more reactive the oxidant, e.g. Mn(V)-oxo versus Mn(IV)-oxo porphyrins, the higher retention of *cis*-geometry.<sup>29</sup> A water soluble *cis*-stilbene was chosen as a suitable substrate. Thus, the oxidation of 75 µmol cis-4,4'-(ethene-1,2-diyl)dibenzoic acid basified with 1.8 eq of LiOH was carried out in the presence of 1.9  $\mu$ mol {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} in 3 mL D<sub>2</sub>O. Electrolysis was at 20 °C for 15 min using a platinum mesh cathode and a platinum wire anode at a potential of 1.8 V. <sup>1</sup>H NMR spectra from 0.5 mL aliquots, after precipitation of  $\{Fe^{III}_{30}W^{VI}_{72}\}$  with CsCl, after 1, 5 and 15 min, the <sup>1</sup>H NMR showed a peak associable to the *cis*-epoxide at 4.24 ppm, Figure S14, but no peak at <4.0 ppm that could be attributed to the trans-epoxide.<sup>30,31</sup> After 15 min the further C-C cleavage reaction yielded 4-carboxybenzaldehyde as the predominant product.

*N*-dealkylation and to a much lesser extent, *S*-dealkylation reactions are also well established for high valent Compound I.<sup>2</sup> The competing transformation is oxygen transfer to the heteroatom, which is much more common for sulfides. The oxidation of triethylamine catalyzed by  $\{Fe^{III}_{30}W^{VI}_{72}\}$  reacted only via a *N*dealkylation pathway, Scheme 4.

### Scheme 4. Cathodic Aerobic Oxidation of Triethylamine

(a) $(Et)_3 N \longrightarrow [(Et)_2 NCH(OH)CH_3] \longrightarrow (H)_2 NCH(OH)CH_3$	CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> NH +	CH₃CHO →	CH <sub>3</sub> COOH
(b) $(Et)_3 N \longrightarrow [(Et)_2 NCH_2 CH_2 OH] \longrightarrow$	(CH <sub>3</sub> CH <sub>2</sub> ) <sub>2</sub> NH	+ 2 HCHO	- HCOOH
L J	20.6 µmol	26.2 µmol	1.6 µmol

Reaction conditions: 1.9  $\mu$ mol {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>}, 2.5 mL D<sub>2</sub>O, air 1 bar, 50  $\mu$ mol triethylamine, 20 °C, 24 h, platinum mesh cathode, platinum wire anode, potential 1.8 V. Faradaic efficiency 5.3%. A total of 2.94  $\mu$ mol products were formed, which were characterized and quantified versus dimethylsulfone as standard by <sup>1</sup>H NMR, Figure S15.

Such N-dealkylation reactions are thought to take place via formation of a  $\alpha$ -hydroxylation intermediate that decomposes to yield diethylamine and acetaldehyde, Scheme 4a.<sup>32</sup> The mechanism by which the  $\alpha$ -hydroxylation intermediate is formed is under debate, with evidence for pathways involving either hydrogen atom transfer (HAT) or formation of a nitrogen centered radical cation by electron transfer. Either way in the reaction presented in Scheme 4a, one indeed could expect the formation of acetaldehyde as the initial product that then would be oxidized quickly to acetic acid. However, in the past acetaldehyde was always an observable by-product in the oxidation of ethane. Now we also observed separately that the oxidation of trifluoroethanol under the conditions described in Scheme 4 yielded trifluoroacetaldehyde/trifluoroacetic acid in a >5:1 ratio after 24 h, bringing up the question - Why is acetaldehyde absent in the analysis of the triethylamine oxidation reaction? In addition, what is not explicable for such a reaction sequence and not observed in the oxidation of acetaldehyde, is the formation of significant amounts of formaldehyde. Note also in this context the good mass balance between the amount of diethylamine and other products formed. This raises the possibility of a competing or dominant HAT initiated reaction at the  $\beta$ -position, to form a  $\beta$ hydroxylation intermediate, Scheme 4b. Such an intermediate could yield formaldehyde, acetic acid and diethylamine by any number of conceivable pathways. Support for such unusual hydroxylation regioselectivity will be presented below for reactions involving C-H bond activation by HAT of functionalized alkanes including those substituted with electron donating hydroxyl groups, that is alcohols.

# Scheme 5. Cathodic Aerobic Oxidation of Thioanisole

PhSMe {Fe <sub>30</sub> W <sub>72</sub> }	PhS(O)Me	+ PhS(O) <sub>2</sub> Me	+ Ph-Ph	+ PhSSPh
	94.1%	2.2%	2.3%	1.3%

Reaction conditions: 1.3 µmol {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>}, 2.0 mL H<sub>2</sub>O, 1.3 mmol, air 1 bar, 100 µmol thioanisloe, 20 °C, 24 h, platinum mesh cathode, platinum wire anode, potential 1.8 V, total conversion of thioanisole - 9.2 mol %.

The oxidation of thioanisole was also examined in order to compare *S*-dealkylation versus *S*-oxidation, Scheme 5. Here very clearly the *S*-oxidation is the preferred reaction with only formation of a small amount of *S*-dealkylation products.

As shown previously the aerobic reductive electrocatalytic oxygen of light alkanes in water was rather extraordinary with the oxidation of ethane to acetic acid being the preferred reaction upon consideration of both activity and selectivity.<sup>13</sup> In order to gain additional data, the KIE of the oxidation of ethylene glycol was studied. The observable products of this reaction were glycolaldehyde and formic acid, Figure S16. The reaction was first order in ethylene glycol and the KIE = 12.2, Figures S17-S19. Thus, the KIE supports a hydrogen abstraction-oxygen rebound mechanism for hydroxylation of aliphatic C-H bonds and is different than the KIE for phenol. As proposed the arene and alkane hydroxylation occur through different pathways.

Carbon-hydrogen bond activation and oxygenation was studied for various additional functionalized compounds. In the case of cyclic ketones, Scheme 6, one can observe that for cyclopentanone the major product (>98%) is cyclopent-2-en-1-one. On the other hand, for cyclohexanone and cycloheptanone, no significant oxygenation at the carbon atom adjacent to the ketone was observed, even though the bond dissociation energy of the  $\alpha$ -C-H bond to the ketone is significantly weaker.<sup>33</sup> The very high selectivity observed for the formation of 1,4-cyclohexanedione from cyclohexanone is especially compelling.

# Scheme 6. Cathodic Aerobic Oxidation of Cyclic Ketones



Reaction conditions: 1.3 µmol {Fe<sup>III</sup><sub>30</sub>W<sup>V1</sup><sub>72</sub>}, 2.0 mL H<sub>2</sub>O, air 1 bar, 250 µmol substrate, 20 °C, 48 h, platinum mesh cathode, platinum wire anode, potential 1.8 V. Conversions were determined by <sup>1</sup>H NMR. Turnover number (TON) is mol products/mol {Fe<sup>III</sup><sub>30</sub>W<sup>V1</sup><sub>72</sub>}. Turnover frequency (TOF) was determined as an estimate of the coverage of {Fe<sup>III</sup><sub>30</sub>W<sup>V1</sup><sub>72</sub>} on the anode.<sup>34</sup> Quantification of the products and their identification was by <sup>1</sup>H NMR and <sup>13</sup>C NMR; see Figures S20-S25.

The oxidation of the analogous cyclic alcohols might have been expected to yield the corresponding ketones, considering the BDE of the  $\alpha$ -C-H bond in a linear primary alcohol is about 5 kcal/mol weaker than the corresponding  $\beta$ -C-H bond,<sup>35</sup> and the observation

that the reactivity of cyclohexanol with a *tert*-butylperoxy radical favors the reaction at the  $\alpha$ -C-H bond versus  $\beta$ -C-H bond by three orders of magnitude.<sup>36</sup> Despite this expectation, very surprisingly, cyclic alcohols were oxidized at the  $\alpha$ -C-H bond only with a 50-60 % selectivity. In addition, oxidation occurred in significant amounts (40-50%) also at  $\beta$ -C-H bond to yield very selectively the  $\alpha$ ,  $\omega$ -dialdehyde as shown in Scheme 7.

## Scheme 7. Cathodic Aerobic Oxidation of Cyclic Alcohols



Reaction conditions: 1.3  $\mu$ mol {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>}, 2.0 mL H<sub>2</sub>O, air 1 bar, 250  $\mu$ mol substrate, 20 °C, 48 h, platinum mesh cathode, platinum wire anode, potential 1.8 V. Conversions were determined by <sup>1</sup>H NMR. Turnover number (TON) is mol products/mol {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>}. Turnover frequency (TOF) was determined as an estimate of the coverage of {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} on the anode.<sup>32</sup> Quantification of the products and their identification was by <sup>1</sup>H NMR and <sup>13</sup>C NMR; see Figures S26-S31

# Scheme 8. Oxidation of Primary Linear Alcohols



Reaction conditions: 1.3 µmol {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>}, 2.0 mL H<sub>2</sub>O, air 1 bar, 300 µmol substrate, 20 °C, 48 h, platinum mesh cathode, platinum wire anode, potential 1.8 V. Conversions were determined by <sup>1</sup>H NMR. Turnover number (TON) is mol products/mol {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>}. Turnover frequency (TOF) was determined as an estimate of the coverage of {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>}on the anode.<sup>32</sup> Quantification of the products and their identification was by <sup>1</sup>H NMR and <sup>13</sup>C NMR; see Figures S32-S35. Some products ( $\leq$ 15%) were not identified.

The observation that the  $\alpha$ ,  $\omega$ -dialdehydes did not react within a relatively long reaction time to yield observable quantities of carboxylic acids was also quite unexpected and in line with the large amounts of formaldehyde remaining in the oxidation triethylamine, Scheme 4 and the slow formation of trifluoroacetic acid from trifluoroacetaldehyde. In this context, the oxidation of 1,4-butanediol yielded only 4-hydroxybutanal that in D2O appeared as a mixture of the acyclic product and the intramolecular hemiacetal, lactol. Therefore, it is conceivable that the formation of hydrates and hemiacetals stabilizes aldehydes towards further oxidation in these  ${Fe^{III}}_{30}W^{VI}_{72}$  catalyzed reactions. On the other hand, the reaction of 1,4-butanediol only at the  $\alpha$ -C-H bond was in contrast to what was observed with the cyclic alcohols. Thus, the reactivity of linear primary alcohols was also surveyed, Scheme 8. As may be observed reactions occur at the CH<sub>2</sub>OH moiety and at all the secondary methylene groups, but not at the primary methyl groups yielding a non-selective mixture of products. Based on the reactivity profiles that have been observed it can be noted that certain substrates could be very selectively oxidized. For example, adipic acid, solubilized in water by the addition of one equivalent of LiOH was oxidized exclusively at the  $\beta$ -C-H bond yielding the 3-oxoadipate Figure S36.

It is typically observed that aliphatic hydrocarbons react at the C-H bonds with the lowest BDE and therefore according to a Brønsted-Evans-Polanyi correlation.<sup>37,38</sup> Although the examples shown above in Schemes 4, 6-8 show unusual regioselectivity, there are some examples where it was observed that oxidation of (functionalized) aliphatic hydrocarbons are in contrast to reactivity correlated to BDE's and the Brønsted-Evans-Polanyi formalism. In general for aliphatic C-H bond activation polar effects, stereoelectronic effects, solvents and strain can influence regioselectivity.<sup>39</sup> This is the case also for metalloporphyrin catalyzed oxyhalogenation reactions where weak  $\alpha$ -C-H bonds adjacent to electron withdrawing moieties such as ketones and esters were shown to be deactivated.<sup>40</sup> Furthermore, using a non-heme iron catalyst, oxidation reactions at distal methylene positions was observed where both electronic, that is electron withdrawing groups, and steric effects related to the structure of the substrate and those emanating from the catalyst structure have been utilized to attain nonconventional chemo/regioselectivity.41

Since  ${Fe^{III}}_{30}W^{VI}_{72}$  has a spherical capsular structure the site at which catalysis occurs is important in terms of steric and confinement effects. Thus, one can consider three different environments for the active oxidizing intermediate. (1) on the inner surface of the  ${Fe^{III}_{30}W^{VI}_{72}}$  capsule where the active oxo unit is in the axial position,  $O_{a,ij}(2)$  on the outer surface where the active oxo unit is in the axial position,  $O_{a,o}$ ; or (3) in the pore where the active oxo unit is in the equatorial position, Oe. In the past there have been measurements on analogous capsules with slightly larger pores, {Mo132}, that demonstrated by NMR measurements the encapsulation of alkanes and arenes when the inner surface was lined with acetate or propionate ligands as opposed to sulfate in the presently used  ${Fe^{III}_{30}W^{VI}_{72}}$  capsule.<sup>42,43</sup> The likelihood of an active oxo unit being at the O<sub>a,i</sub> position is low considering the fast reaction of bulky substrates such as cis-4,4'-(ethene-1,2-diyl)dibenzoate. To verify this point, {Mo<sub>132</sub>} with sulfate ligands was prepared as an analog of {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} since the presence of paramagnetic Fe(III) prevented direct NMR measurments.<sup>44</sup> Encapsulation studies even with small substrates such as ethane, using also low concentration sensitive chemical exchange saturation transfer <sup>1</sup>H NMR,<sup>45</sup> showed no indication that ethane was encapsulated. This finding suggests that the O<sub>a,i</sub> position is not the active site.

Another aspect to consider is that the initial catalyst,  $\{Fe^{III}_{30}W^{V1}_{72}\}$ , is coordinatively saturated around the iron(III) center. In the past we have computationally shown for the Keggin type  $H_3PV_2Mo_{10}O_{40}$  polyoxometalate that water and the surrounding high valent metal centers can stabilize coordinatively unsaturated species through the breaking of bridging (equatorial)  $V^{IV}$ -O bonds.<sup>46</sup> In that case the terminal V=O is significantly shorter than the bridging V-O bond. In this case, however, the axial Fe-O<sub>a</sub> bond is slightly longer (2.041 Å) than the bridging Fe-O<sub>e</sub> bond (1.979 Å) although the former is too short to be considered a labile aqua ligand. At this point the binding site for O<sub>2</sub> activation is still undetermined but our tentative proposal is activation at the equatorial position, also from statistical considerations (4 positions versus 1 position), Figure 2.

## CONCLUSIONS

Oxidation of alkanes, alkenes, arenes and functionalized aliphatic and aromatic compounds catalyzed by iron-heme and iron nonheme biomimetic compounds have been extensively investigated

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for about 40 years.<sup>2,3</sup> Very significant mechanistic insight has been gained during this period. Synthetic applications are less developed, 2 especially as regards the reductive activation of O2 and probably 3 also because of the inherent instability of the organic ligands used. At the basis of this research project were the following questions: (1) Could an inherently stable inorganic metal oxide containing 5 iron function to activate O2 under electrochemical reducing condi-6 tions? (2) If this is the case, is the reaction mechanism related to 7 heme and non-heme-iron oxidation chemistry? Phenomenological-8 ly, we had already previously observed that an iron-tungsten cap-9 sule, {Fe<sup>III</sup><sub>30</sub> $W^{VI}_{72}$ }, was indeed able to cathodically activate O<sub>2</sub> lead-10 ing to interesting transformations such as the oxidation of ethane to 11 acetic acid at ambient conditions, low potentials and in water.<sup>13</sup> 12 This paper reports on some mechanistic details concerning the 13 catalytic cycle of this reaction. A generic catalytic cycle for O2 acti-14 vation, Figure 2, involves reduction of Fe(III) to Fe(II) which was 15 shown to occur at 0.67 V versus NHE, for one Fe atom in each of 16 the 20 identical pores of  $\{Fe^{III}_{30}W^{VI}_{72}\}$ .<sup>13</sup> Addition of O<sub>2</sub> to such a 17 Fe(II) center would yield by the Weiss model the superoxide, 18 Fe(III)-OO--,<sup>47</sup> as the first plausible intermediate in the catalytic 19 cycle. We were unable to observe such an intermediate by Raman 20 spectroscopy (expected v -1100-1200 cm<sup>-1</sup>), but the formation of 21 such an intermediate was deduced using a BMPO spin trap. Since 22 electrons are often delocalized in polyoxometalates (rates of intra-23 molecular electron transfer are  $\sim 10^{11}$  to  $10^{12}$  s<sup>-1</sup> for polyoxotung-24 states at room temperature),48 the further intramolecular reduction 25 of a superoxo species to a hydroperoxo intermediate is reasonably fast. In fact, reduction of  $\{Fe^{III}_{30}W^{VI}_{72}\}$  to form a twenty electron 26 reduced species, that is two Fe(II) atoms per pore of  $\{Fe^{III}_{30}W^{VI}_{72}\}$ 27 yielded an observable species by Raman spectroscopy that was 28 assigned as a hydroperoxo species, Fe(III)-OOH upon addition of 29 O2. Such hydroperoxo species have been shown to be stabilized by 30 hydrogen bonding to water as determined by X-ray diffraction for a 31 different iron containing polyoxometalates.<sup>15</sup> Here a Raman spec-32 trum supported such a scenario - the formation of a hydroperoxo 33 intermediate, nominally {(Fe<sup>III</sup>OOH)<sub>10</sub>Fe<sup>III</sup><sub>20</sub>W<sup>VI</sup><sub>72</sub>}, although the 34 isotope labeling experiments with <sup>18</sup>O<sub>2</sub> were foiled by interfering 35 peaks of the  ${Fe^{III}}_{30}W^{VI}_{72}$  capsule, rendering the experiment less 36 conclusive. 37

As noted above, further Mössbauer, Raman and EPR spectroscopic measurements to identify the active oxidizing moiety were not feasible because of the strong absorption of  $\gamma$ -rays by W, overlapping vibrational modes of the capsule and magnetic exchange interactions. In lieu of spectroscopic studies, extensive reactivity studies were carried out on various substrate types whose activity, especially towards Fe(IV)=O-porphyrin+ (compound I) and isoelectronic Fe(V)=O species has been thoroughly investigated. (1) Oxidation of 1,4-difluorobenzene showed both a NIH shift reaction and dehalogenation reactions quite unique for compound I. (2) A further KIE experiment on phenol (KIE =  $\sim$  1) also supported an arene oxidation mechanism where an addition reaction of a Fe(V)=O species at the arene ring is rate determining. (3) Oxidation of benzene using <sup>18</sup>O<sub>2</sub> showed high incorporation of <sup>18</sup>O and (4) epoxidation of *cis*-4,4'-(ethene-1,2-diyl)dibenzoate showed conservation of stereochemistry. Both experiments suggest that the active species formed is a very potent oxidant so that exchange with 55 M water is slower than oxygen transfer to benzene and a planar intermediate in the epoxidation reaction is not formed before epoxide ring formation. (5) A KIE experiment carried out on ethylene glycol (KIE = 12.2) is supportive of an oxygen rebound mechanism associated with a compound I type species that was

previously postulated<sup>13</sup> to explain the ethane to acetic acid oxidation via formation of ethanol and acetaldehyde. (6) Dealkylation of triethyl amine and to some extent of thioanisole also supports compound I type species as active species.

A further survey of the oxidation of *water-soluble* substrates with aliphatic C-H bonds revealed reactivity that was not commensurate with the Brønsted-Evans-Polanyi formalism where reactivity is a function of the bond disassociation energy (BDE). Such regioselectivity has been observed in the past with electron-withdrawing substituents such as ketones and carboxylic acids. The regioselectivity attained has been attributed in the past to polar effects. Considering the anionic outer surface of the  ${Fe^{III}_{30}W^{VI}_{72}}$  capsule, where the reaction likely occurs according to the NMR measurements, and the water solvent the explanation of polar effects on the reactivity seems reasonable. More uniquely here, primary and cyclic alcohols, and likely amines also showed unusual regioselectivity and did not react according to the Brønsted-Evans-Polanyi formalism. Especially notable here are the C-C bond cleavage reaction for cyclic alcohols and triethylamine and the unexpected low reactivity of aldehydes with weak aldehydic C-H bonds. On may speculate that this may be due to substrate protonation or binding to a metal. Finally, it should be noted that entropic effects may also play an important role in the selectivity that has been observed. In the absence of an isolatable intermediate, the activation energies,  $\Delta H^{*}$  and  $\Delta S^{*}$ , cannot be directly evaluated. It is however worth noting that the reaction of an isolated Mn(V)=O polyoxometalate-based species with 1-octene to yield 1-octene oxide was under entropic control with a  $\Delta H^{*}$  < 4 kcal mol^{-1} and  $\Delta S^{*}$  < –50 cal mol^{-1} K^{-1}.49 It is reasonable in this context that the higher charge of the transition state due to charge transfer from the substrate to the anionic polyoxometalate during the rebound reaction versus the initial polyoxometalate leads to increased solvation of transition state by the water solvent molecules. This may lead to the electrostriction of the solvent, a loss of degrees of freedom, thereby leading to a high negative entropy of activation. Such electrostriction of the solvent may be especially significant in or at the pores of  $\{Fe^{III}_{30}W^{VI}_{72}\}$ .

In summary, we presented data and explanations for the unique reactivity of  $\{Fe^{III}_{30}W^{VI}_{72}\}$  for the cathodic activation of O<sub>2</sub> and subsequent oxygenation. The formation of a Fe(III)-OOH species is followed by the formation of a compound I type species active species that shows reactivity commensurate with many reactivity studies carried out in the past. Unique regioselectivity obtained in the oxidation of several substrate types is atypical and explained by polar and/or entropic effects. Finally, although reactivity is clearly commensurate with compound I type active intermediate, the spectral identification of this species remains elusive. The simplest explanation as presented in Figure 2 is that the active species is an Fe(V)=O intermediate. Another reasonable possibility is the formation of a bis Fe(IV)=O species by fast intramolecular electron transfer within a pore of the capsule with a bridging O-W-O unit as shown in Scheme 9.

Scheme 9. Representation of the Formation of a bis Fe(IV)=O Species from an Initial Fe(V)=O Species.





For most of the experiments including the reactivity studies  $(NH_4)_x\{Fe^{III}_{30}W^{VI}_{72}\}$  was used. For Raman and CEST NMR experiments that required higher solubility 1.5 g of  $(NH_4)_x\{Fe^{III}_{30}W^{VI}_{72}\}$  was dissolved in 20 mL of 18.2 M $\Omega$  water and the solution was transferred to a cellulose dialysis membrane tube with a molecular weight cut-off of 12000. The cellulose dialysis membrane tube water for 15 h. The cellulose dialysis membrane tube then immersed in 50 mL of 8.2 M $\Omega$  water for 1 h to remove excess sulfate (6 times). This entire procedure was repeated twice and after that the solution inside the dialysis tube was evaporated to dryness to give  $(Na)_x\{Fe^{III}_{30}W^{VI}_{72}\}$ .

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Electrochemical Oxidation Reactions. Typically, the required amounts of  $(NH_4)_x$ {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} were dissolved in of D<sub>2</sub>O or H<sub>2</sub>O was placed in an undivided electrolysis cell. The required amount of substrate (100-300 µmol) of substrate was added while stirring. The electrocatalysis was performed for the given time period by applying a  $\Delta E$ = -1.8 V between cathode and anode. The working electrode (cathode) was an 80 mesh platinum gauze and the counter electrode (anode) a platinum wire. Reactions carried out in D<sub>2</sub>O were solution were typically analyzed by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and <sup>19</sup>F-NMR (11.7 T Bruker Advance III HD Spectrometer) as required after precipitating  $(NH_4)_x$ {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} by addition of CsCl. In these reactions, products were quantified by <sup>1</sup>H NMR after addition of dimethylsulfone as standard. Product quantification was performed by recording 100 scans at the appropriate time intervals. For reactions carried out in H<sub>2</sub>O, similar procedures were used, but analysis was carried out after extraction of substrates and products into CDCl<sub>3</sub>. Product yields were directly assessed from the <sup>1</sup>H NMR spectra. Typical Faradaic efficiences were 20-35%.

**Kinetic Isotope Effect - Phenol**. A solution of  $(NH_4)_x \{Fe^{III}_{30}W^{VI}_{72}\}$ (120 mg in 6 mL of D<sub>2</sub>O) was placed in an undivided electrolysis cell. 13.8 µmol of a mixture phenol/ deuterated phenol (0.99: 1) was added. The electrocatalytic oxidation was performed for 3 hours applying  $\Delta E$ = -1.8 V between cathode and anode. The working electrode (cathode) was a 80 mesh platinum gauze and the counter electrode (anode) a platinum wire. A sample was taken every 30 min. The solution was analyzed by <sup>1</sup>H-NMR after precipitating the capsule with CsCl and adding dimethylsulfone as standard. The quantification was performed recording 100 scans with the appropriate time intervals. The solutions were then analyzed by GC-MS, after extracting the products with ethyl acetate.

**Kinetic Isotope Effect - Ethylene Glycol.** A solution of  $(NH_4)_{x}$ {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} (120 mg in 6 mL of  $10\%D_2O + 90\%H2O$ ) was placed in an undivided electrolysis cell. 22.2 µmol of a mixture ethylene glycol/ deuterated ethylene glycol (1: 1) was added. The electrocatalytic oxidation was performed for 5 hours applying  $\Delta E = -1.8V$  between cathode and anode. The working electrode (cathode) was a 80 mesh platinum gauze and the counter electrode (anode) a platinum wire. A sample was taken and analyzed every hour, for 5 h. The solutions were analyzed by <sup>1</sup>H-NMR and <sup>2</sup>H-NMR, after precipitating the capsule with CsCl. A standardized solution containing dimethylsulfone or methanol-d<sub>4</sub> was added to quantify the substrates. The quantification was performed recording 100 scans for <sup>1</sup>H-NMR and 250 scans for <sup>2</sup>H-NMR at the appropriate time intervals.

**UV-vis spectroscopy.** UV/Vis spectra at 4°C were recorded using a diode array spectrometer Agilent 8453 and a Unisoku Cryostat for temperature control. Thus, 3 mL of 1.7  $\mu$ M solution of  $(NH_4)_x$ {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} in a 1 cm quartz cuvette was purged 10 times with Ar and placed in the UV-vis spectrometer at 4 °C for 10 min. Sodium dithionite (2.4 mg, 20 electron equivalents) was added yielding the reduced dark brown capsule, nominally {Fe<sup>III</sup><sub>20</sub>Fe<sup>III</sup><sub>10</sub>W<sup>VI</sup><sub>72</sub>}. The cuvette was opened to air and spectra were recorded every 30 s.

**Raman spectroscopy.** Raman spectra were measured on a Thermo Scientific DRX2 spectrometer using a 455 nm solid state laser.

Temperature was controlled by a Ventecon low temperature cell. Thus, 200 mg (Na)<sub>x</sub>{Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} was dissolved in 2.5 mL DDW and placed in an undivided electrolysis cell. The solution was purged 10 times with Ar and placed in a glove box. (Na)<sub>x</sub>{Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} was reduced by 20 electrons per capsule at -0.6 V versus Ag/AgCl (4 mA\*h). The solution was sampled into a 1 cm quartz cuvette, cooled in the Raman spectrometer to 4 °C and opened to air or <sup>18</sup>O<sub>2</sub> for measurement of the Raman spectrum.

**EPR spectroscopy.** EPR spectra were measured at RT by a X-band CW EPR using a Bruker ELEXSYS 500 spectrometer equipped with a Bruker ER4102ST resonator at 20 K with microwave power of 20 mW, 0.1 mT modulation amplitude and 100 kHz modulation frequency. Thus, 50 mg  $(NH_4)_x$ {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} was dissolved in 2.5 mL DDW and placed in an undivided electrolysis cell. The solution was purged 10 times with Ar and placed in a glove box.  $(NH_4)_x$ {Fe<sup>III</sup><sub>30</sub>W<sup>VI</sup><sub>72</sub>} was reduced by 20 electrons per capsule at -0.6 V versus Ag/AgCl (4 mA\*h). BMPO (10 mg) was added and the solution was sampled into a flat cell while opened to air.

Gas chromatography. GC-MS measurements were carried out on an Agilent 6890 gas chromatograph equipped with a 5973 mass selective detector. A HP-5MS column ( $30 \text{ m} \times 0.32 \text{ mm}$  i.d.; 0.25 µm film thickness) was used with He as carrier gas. GC-FID measurements were also carried out on Agilent 6890 gas chromatograph. A HP-5MS column ( $30 \text{ m} \times 0.32 \text{ mm}$  i.d.; 0.25 µm film thickness) was used with He as carrier gas.

## ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Raman and NMR spectra, and kientic profiles (PDF)

## AUTHOR INFORMATION

#### Corresponding Author

\* Email: <u>ronny.neumann@weizmann.ac.il</u>

# ORCID

Ronny Neumann: 0000-0002-5530-1287

### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript. ‡ These authors contributed equally.

## Notes

The authors note no competing financial interest

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