Review

The Haber-Weiss cycle – 70 years later

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'Those who cannot remember the past are condemned to repeat it.'
G. Santayana (1863–1952)
The Life of Reason (1905)

The chain reactions $HO^{\bullet} + H_2O_2 \rightarrow H_2O + O_2^{\bullet-} + H^+$ and $O_2^{\bullet-} + H^+ + H_2O_2 \rightarrow O_2 + HO^{\bullet} + H_2O$, commonly known as the Haber-Weiss cycle, were first mentioned by Haber and Willstätter in 1931. George showed in 1947 that the second reaction is insignificant in comparison to the fast dismutation of superoxide, and this finding appears to have been accepted by Weiss in 1949. In 1970, the Haber-Weiss reaction was revived by Beauchamp and Fridovich to explain the toxicity of superoxide. During the 1970s various groups determined that the rate constant for this reaction is of the order of $1\ M^{-1}s^{-1}$ or less, which confirmed George's conclusion. The reaction of superoxide with hydrogen peroxide was dropped from the scheme of oxygen toxicity, and superoxide became the source of hydrogen peroxide, which yields hydroxyl radicals via the Fenton reaction, $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^- + HO^{\bullet}$. In 1994, Kahn and Kasha resurrected the Haber-Weiss reaction again, but this time the oxygen was believed to be in the singlet ($^1\Delta_g$) state. As toxicity arises not from a Fenton-catalysed Haber-Weiss reaction, but from the Fenton reaction, the Haber-Weiss reaction should not be mentioned anymore.

INTRODUCTION

Oxidative damage *in vivo* is often ascribed to the Fenton reaction, the one-electron reduction of hydrogen peroxide by iron(II) (Eq. 1). As has been reviewed,[1] Fenton described the oxidation of tartaric acid by the addition of iron(II) and hydrogen peroxide or hypochlorous acid for the first time in 1876,[2] found that iron acts catalytically[3] and determined the reaction product of tartaric acid, dihydroxy-maleic acid, in 1896.[4] Fenton did not investigate the mechanism of the reaction that was later named after him; he used it as a synthetic tool to modify organic compounds.[1] That iron(II) reduces hydrogen peroxide and produces hydroxyl radicals was proposed by Haber and Weiss.[5] The history of another proposal, namely that superoxide also could reduce hydrogen peroxide, is the topic of this paper.

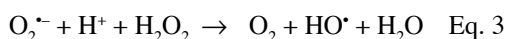## MANCHOT, HABER, WILLSTÄTTER AND WEISS

Manchot and co-workers wrote several papers between 1901 and 1928 on the stoichiometry of the reaction of hydrogen peroxide with ferrous ions, reporting that, when iron is present in excess, the simple stoichiometry of two iron(II) oxidized per hydrogen peroxide prevails. However, when hydrogen peroxide is present in excess, oxygen is evolved and more than two iron(II) are oxidized. Manchot and Lehman[6] postulated the formation of Fe_2O_5, which was reduced to Fe(III) either by excess iron(II) or by excess hydrogen peroxide, with generation of dioxygen. They were aware that, under certain conditions, even more hydrogen peroxide per iron(II) was consumed than could be accounted for by di-iron pentaoxide, as had also been observed by Wieland,[7] and proposed that iron(II) was regenerated, noting that hydrogen peroxide also could act as a reducing agent![6] Haber and Weiss[5,8] dismissed di-iron pentaoxide and showed that even more hydrogen peroxide per iron(II) is consumed when the mixing of hydrogen peroxide with iron(II) is improved by letting one solution flow into the other from a rotating burette that was modified to have a horizontal tip. They determined consumption ratios, the number of

hydrogen peroxide molecules consumed per iron(II), and determined that the reaction was first-order in iron(II) and in hydrogen peroxide. Due to experimental limitations – stopped-flow spectrophotometers had not yet been invented – Haber and Weiss could not investigate further the kinetics of these reactions. Unfortunately, in the recent literature there is confusion regarding the contributions made by these early workers. As an example, the recent statement[9] that 'the mechanism of the Fenton reaction was initially studied and essentially discovered by Wilstätter, Haber and Weiss' is incorrect because Haber and Weiss did not discover the mechanism of the iron-induced hydrogen peroxide decomposition, and because Willstätter was not involved. Furthermore, Haber and Weiss[5] did not mention Fenton.

The interesting point that Haber and Weiss did raise was that hydrogen peroxide is consumed by a chain reaction. The Fenton reaction initiates the chain, Equation 1:

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^- + HO^\bullet \qquad Eq. 1$$
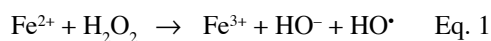
which is then followed by the chain indicated in Equations 2 and 3 (Haber, Wilstätter and Weiss wrote HO_2 or O_2H; a pKa of 4.88 was determined in 1970.[10] The accepted value is 4.7.[11]):

$$HO^\bullet + H_2O_2 \qquad \rightarrow \quad H_2O + O_2^{\bullet-} + H^+ \quad Eq. 2$$

$$O_2^{\bullet-} + H^+ + H_2O_2 \rightarrow O_2 + HO^\bullet + H_2O \quad Eq. 3$$

while chain termination is caused by Equation 4:

$$Fe^{2+} + HO^\bullet + H^+ \rightarrow Fe^{3+} + H_2O \qquad Eq. 4$$

Depending on the conditions, various ratios of hydrogen peroxide per iron(II) are consumed. Equations 2 and 3 were originally proposed by Haber and Willstätter in a paper on radical reactions in organic chemistry and biochemistry specifically to explain the action of catalase.[12] Haber and Willstätter had proposed that enzymes initiated a radical reaction, after which the chain reactions consumed the substrate. According to this view, iron acted just like an enzyme. In 1937, Weiss explained how catalase worked via this mechanism: the anion of hydrogen peroxide reduced haem iron(III) to the 2^+ state, iron(II) reduced hydrogen peroxide to hydroxyl and water, after which the chain reactions indicated in Equations 2 and 3 consumed all hydrogen peroxide.[13]

The 1934 paper by Haber and Weiss[8] was published after the death of Fritz Haber in Basel earlier that year. Due to the rise of Hitler in the early 1930s, Haber, although a Nobel laureate (1918), could no longer work in Germany because of his Jewish origins. As a chemist and a patriotic German, Haber had headed the German poison gas programme during the first World War. Although he and his co-workers did not work on nerve gases, he remained involved in the development of poisonous gases until the late 1920s,[14] during which time he and his co-workers developed Zyklon

A–C to combat pests. The Zyklons, which released hydrocyanic acid, ironically were used in Germany during the second World War to exterminate Jews. After leaving Germany in 1933 with his assistant J. Weiss, he worked for a few months in Cambridge and, while travelling in Switzerland, he died of heart disease at the age of 65.[14] The use of chain reactions in chemistry and biochemistry was indeed his last, but certainly not his most important, contribution to chemistry. Haber was a multidisciplinary chemist, and as mentioned in Haber's obituary by Schlenk:[15] 'every one of us, may he be a physical, inorganic, organic or analytical chemist or also a biochemist, is certainly familiar with one or more topics that Haber worked on' ('*ist gewiss jedem von uns, mag er physikalischer, anorganischer, organischer oder analytischer Chemiker oder auch Biochemiker sein, das eine oder andere der von Haber bearbeiteten Probleme vertraut*'). Prior to the postulation of Equations 2 and 3, chain reactions played a role in Haber's research on radical reactions in flames.[14]

During the 1930s, two other important discoveries were published. In 1934 Neuman,[16] a post-doctoral fellow working with Pauling, reported that alkali oxides that had been assigned formulae like K_2O_4 were, in fact, superoxides by measuring their magnetic susceptibilities, confirming Pauling's suspicion that an ion $O_2^{\bullet-}$ would contain a two-electron and a three-electron bond.[17] No references were made to the earlier works of Marshall,[18] Haber and Willstätter,[12] and Haber and Weiss,[5] where hydrogen dioxide had been invoked as a chain carrier. As described by Neuman[16] and Pauling,[17] the name superoxide was coined in 1933 (The venerable name superoxide is still allowed, the systematic names dioxide(•1–), or, derived from oxidane, dioxidanidyl, are recommended by IUPAC. Similarly, $HO_2^\bullet$ is named hydridodioxygen(•) or dioxidanyl, but hydrogen dioxide is also a systematic and acceptable name.[19]). In 1938, Mann and Keilin reported their discovery of a copper-containing protein, haemocuprein, in blood.[20,21] Approximately 30 years later, McCord and Fridovich showed that haemocuprein dismutated superoxide radicals.[22]

It is clear that what has become known as the Haber-Weiss cycle should be called the Haber-Willstätter cycle. Although the oft-quoted English-language paper by Haber and Weiss[8] appropriately credits the paper by Haber and Willstätter,[12] that earlier paper is in German and is apparently widely overlooked because of language.

CRITICISMS

During the 1930s, the suggestion was made that the reaction of ferrous ion with hydrogen peroxide could yield oxoiron(IV):[23]

$$Fe^{2+} + H_2O_2 \rightarrow FeO^{2+} + H_2O \qquad Eq. 5$$
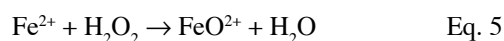
and, by the late 1940s, the mechanism for the decomposition of hydrogen peroxide by Haber and Weiss had been criticised by George[24] and Abel.[25] Medalia and Kolthoff[26] reviewed the *status quo* at that time and dismissed the proposed mechanism of Gorin and Bray,[23] because when hydrogen peroxide is mixed with excess iron in the presence of ethanol, the reaction between oxoiron(IV) and iron(II) would be subject to a salt effect, and this was not observed. Abel[25] proposed that, during the decomposition, iron(III) ions could be reduced by hydrogen dioxide – a reaction already considered by Haber and Weiss[8] (see below) – or superoxide, and, to initiate the chain in the presence of iron(III), by the anion of hydrogen peroxide (HOO⁻, dioxidanide). To be noted here is that the reduction of ferric ions by superoxide is now part of the accepted mechanism of iron-induced hydrogen peroxide decomposition.

GEORGE VERSUS WEISS

George mixed solid potassium superoxide with water (acidic and alkaline), hydrogen peroxide, acidic iron(II) solutions and a 'strong' catalase solution and measured the amount of dioxygen formed.[24] He showed that the potassium superoxide in water yields dioxygen and hydrogen peroxide, and that the amount of dioxygen is the same whether or not hydrogen peroxide is present. This amount of dioxygen corresponds to the amount of potassium superoxide added to the solution. Had superoxide reacted with hydrogen peroxide, as in Equation 3, and started the chain consisting of Equations 2 and 3, then the amount of dioxygen would have corresponded to the amount of hydrogen peroxide present. Thus, George concluded: 'that under these experimental conditions the chain-propagation reaction, proposed by Haber and Weiss for the evolution of oxygen in the catalytic decomposition of hydrogen peroxide, does not occur'.[24]

The response of Weiss can be found in the discussion of the same paper:[27] 'I do not think that the experiments of Dr George have any bearing on the mechanism of the hydrogen peroxide reaction. It is quite clear from his paper that the experiments were carried out in a *heterogeneous* system – *solid* KO_2 in H_2O_2 *solutions*'.
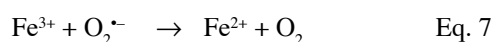
It was argued by Agar and Dainton[28] that the high concentration of dissolved superoxide around the solid potassium superoxide favours the dismutation over Equation 3, because superoxide would not have time to diffuse away from the potassium superoxide particles. George addressed the issue of diffusion and presented results from experiments in which potassium superoxide was dissolved in concentrated hydrogen peroxide (85 and 96.5%) and showed:[29] '...that with this very concentrated hydrogen peroxide no more oxygen is evolved than is observed with water alone'.

Weiss's reluctance to accept George's finding may have had to do with Haber and Willstätter's definition of superoxide; namely, that it is a radical and that it decomposes hydrogen peroxide with formation of dioxygen, water and the hydroxyl radical ('...*wird der Verbindung O_2H der Charakter eines Radikals und die Eigenschaft beigelegt, Hydroperoxyd unter Entstehung von molekularem Sauerstoff, Wasser und ungeladenem Hydroxyl zu zersetzen.*').[12]

Prior to this exchange, Weiss had added another reaction to the original set of four reactions (Equations 1–4), namely Equation 6:

$$Fe^{3+} + HO_2^- \rightleftharpoons Fe^{2+} + HO_2^{\bullet} \qquad \text{Eq. 6,–6}$$
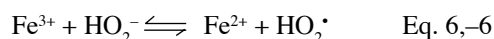
and, in 1949, added Equation 7:[30]

$$Fe^{3+} + O_2^{\bullet-} \rightarrow Fe^{2+} + O_2 \qquad \text{Eq. 7}$$

Equations 6 and 7 also were given in the 1934 paper,[8] but were not considered important. In the paper of 1949,[30] it was stated that Equation 7: '...in the presence of ferric ions, largely replaces Equation 3', *i.e.* the reduction of hydrogen peroxide by superoxide.[30] The next three pages in that issue of *Nature* contains an article by Barb, Baxendale, George and Hargrave entitled *Reactions of ferrous and ferric ions with hydrogen peroxide.*[31] In this paper, the authors observed that under conditions of high H_2O_2/Fe^{2+} ratios and pH 1–3: (i) Equation 1 is initially first-order in iron(II) and in hydrogen peroxide, but deviates from these kinetics as the reaction proceeds; (ii) above a certain H_2O_2/Fe^{2+} ratio the amount of dioxygen evolved is independent of the hydrogen peroxide concentration; (iii) when iron(III) is added, total oxygen evolved is increased and the reaction proceeds more slowly; and (iv) in the presence of fluoride, total dioxygen evolution is decreased. They concluded that: '(a) the oxygen is **not** evolved as the result of a reaction between HO_2 and hydrogen peroxide ...; (b) the oxygen is evolved in a reaction involving ferric ... ions; (c) ferrous ions are regenerated by the oxygen evolution reaction; and (d) another reaction which removes ferrous ions occurs in addition to Equation 4. ... The kinetics can be accounted for if the additional reaction is between ferrous ions and HO_2.'

The necessary reactions are given in Equations 1, 2, 4, –6 and 7. A more extensive description followed in 1951,[32,33] and in the first of these two papers, one finds a reference to Fenton's first full description of the oxidation of tartaric acid.[34] In a 1952 paper on the action of X-rays on iron(III)- and iron(II)-containing solutions, Weiss and co-workers no longer took Equation 3 into account.[35]

The work involved in establishing a reaction mechanism was far more complicated than it is now. Mixing of iron(II) and iron(III) with hydrogen peroxide was carried out at low pH, so as to avoid inactive iron-hydroxo complexes, or at a pH where iron(II) would remain in solution, but

iron(III) would not. Reactions were initiated, quenched at a particular time and the products were determined. As a result, it was not always possible to determine a rate constant. It also should be noted that, at the time of these investigations, the pKa of hydrogen dioxide was not known precisely. A re-examination by pulse radiolysis of the rate constants of iron(II) and (III) with hydrogen dioxide and superoxide in 1985[36] corroborates the mechanism proposed by Barb *et al.*[32,33]
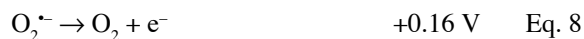
Thus, already in 1949, George and co-workers had shown that the reduction of hydrogen peroxide by superoxide, Equation 3, is too slow in comparison to the dismutation reaction of superoxide to be important,[31] and Weiss appeared to have accepted that conclusion.[30]

Weiss continued with his investigations into the events that take place when ionising radiation interacts with water, and is rightfully regarded as one of the pioneers of radiation chemistry. He proposed that, upon irradiation of water, two radicals are formed, namely the hydrogen atom and the hydroxyl radical. Proof of the latter was obtained in 1950, when the irradiation of benzene led to diphenyl and phenol.[37] He also was interested in radiobiology, specifically the interaction of radiation with DNA.[38,39]
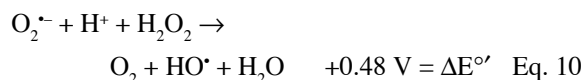
George studied the intermediates that are formed when hydrogen peroxide reacts with haem proteins such as myoglobin,[40] cytochrome *c* peroxidase and horse radish peroxidase.[41,42] The resultant higher oxidation states of iron had been reported by Keilin and Theorell around 1940.[43] George was interested in their structures and the kinetics of their formation,[44,45] and appeared to have introduced the term 'Compound' for these intermediates.[41] In 1964, his well-known review *The fitness of oxygen* appeared, in which he discusses why respiration is based on dioxygen, and not on other small molecular weight compounds such as dinitrogen or difluorine.[46]

THERMODYNAMICS OF THE REDUCTION OF HYDROGEN PEROXIDE BY SUPEROXIDE

It should be pointed out that Equation 3 is possible from a thermodynamic point of view: the Gibbs energy of reaction is calculated from $E^{\circ\prime}(O_2/O_2^{\bullet-}) = -0.16$ V ($1m$ O_2), and $E^{\circ\prime}(HO^\bullet/H_2O) = 0.32$ V (pH 7)[47] as follows:

$$O_2^{\bullet-} \rightarrow O_2 + e^- \qquad\qquad +0.16 \text{ V} \qquad \text{Eq. 8}$$

$$H_2O_2 + e^- + H^+ \rightarrow HO^\bullet + H_2O \qquad +0.32 \text{ V} \qquad \text{Eq. 9}$$

summing Equations 8 and 9:

$$O_2^{\bullet-} + H^+ + H_2O_2 \rightarrow$$
$$O_2 + HO^\bullet + H_2O \qquad +0.48 \text{ V} = \Delta E^{\circ\prime} \quad \text{Eq. 10}$$

Via $\Delta G^{\circ\prime} = -nF\Delta E^{\circ\prime}$ one calculates -11.1 kcal/mol or -46.3 kJ/mol at pH 7. It is important to bring this up as it

Table 1. Measured bimolecular rate constants for the reaction of $O_2^{\bullet-}$ and $HO_2^\bullet$ with H_2O_2

Authors	k (M^{-1}s^{-1})	
	$O_2^{\bullet-} + H_2O_2$	$HO_2^\bullet + H_2O_2$
Ferradini and Seide[50]		0.20 ± 0.01
Rigo *et al.*[51]	$\leq 5 \times 10^{-3}$	
Ferradini *et al.*[52]	2.25 ± 0.20	
Koppenol *et al.*[53]		3.0 ± 0.6
Melhuish and Sutton[54]	< 0.3	
Weinstein and Bielski[55]	0.13 ± 0.07	0.05 ± 0.09

has been asserted recently that the reaction is unfavourable and therefore needs a catalyst![48]

REVIVALS

After the discovery of an enzymatic function for haemocuprein by McCord and Fridovich,[22] it was renamed superoxide dismutase. This enzyme also presented a dilemma in that superoxide is not a very reactive radical, yet the enzyme removes it at a nearly diffusion-limited rate. Therefore, it was thought, superoxide must be the precursor to a more reactive species. But, what species? The formation of the hydroxyl radical from the reaction of superoxide with hydrogen peroxide seemed to answer that question and, in 1970, the Haber-Weiss reaction was revived.[49] Several groups determined rate constants and showed without regard to the literature, that, indeed, superoxide reacts slowly, if at all, with hydrogen peroxide (Table 1), and also with organic peroxides.[56]

Surprisingly, in 1994 the reaction of superoxide with hydrogen peroxide surfaced again,[57] but this time with the twist that the dioxygen is in the singlet ($^1\Delta_g$) state, which implies a positive Gibbs energy change. Not only is this reaction unlikely from a kinetic point of view, as discussed here, but also the energetics argue against its occurrence!

DÉNOUEMENT

During the late 1970s, the reduction of an iron(III) complex by superoxide, and the subsequent oxidation of this iron(II) complex by hydrogen peroxide, became known as the 'Fenton-catalysed Haber-Weiss reaction'. Later it was realized and accepted that other compounds (ascorbate, for instance) could reduce the iron(III) complex. While this is true, one should not forget Fenton's observation, namely that iron acts catalytically.[3] This is understandable if the organic radical formed from the reaction of the hydroxyl radical with the organic parent compound re-reduces the

iron to the 2^+ state. Thus, a reducing agent is only necessary to initiate the reaction. In summary, toxicity arises not from a Fenton-catalysed Haber-Weiss reaction, but from the Fenton reaction.

The non-reaction of superoxide with hydrogen peroxide has been named the Haber-Weiss reaction, and is the second reaction in the Haber-Weiss cycle (Eqs 2 and 3). If one wanted to name this reaction it should have been the Haber-Willstätter reaction. But why name a reaction that does not take place? The reader is, therefore, urged never to mention Equation 3 again.

Given the periodicity of the Haber-Weiss reaction, we expect the next report on its occurrence in the year 2018, 44 years before the next appearance of Halley's comet.

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