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► **To cite this version:**

B. Meunier, Anne Robert. Comment on “Free-Radical Formation by the Peroxidase-Like Catalytic Activity of MFe_2O_4 (M = Fe, Ni, and Mn) Nanoparticles”. *Journal of Physical Chemistry C*, 2019, 123 (46), pp.28513-28514. 10.1021/acs.jpcc.9b09075 . hal-02399318

HAL Id: hal-02399318

<https://hal.science/hal-02399318>

Submitted on 10 Nov 2020

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Comment on "Free-radical formation by the peroxidase-like catalytic activity of MFe_2O_4 (M = Fe, Ni and Mn) nanoparticles"

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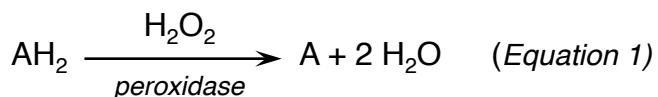
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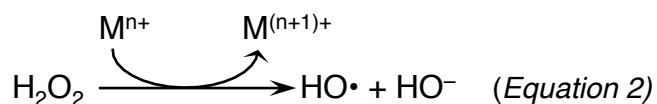
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The peroxidase-like activity of magnetite and its connection with a neurodegenerative disease such as Alzheimer's disease has been recently questioned by our group,¹ despite claims by Gao *et al.*² Since reproducibility is the essential factor in experimental sciences, the article of Moreno Maldonado *et al.* on the peroxidase-like activity of magnetite attracted our attention.³ As a matter of fact this new report is providing additional evidences on the absence of peroxidase activity of magnetite derivatives. The following comments are not a question of semantics, but are driven by the necessity to correctly describe the different possible origins of the oxidative stress involved in many neurodegenerative pathologies.

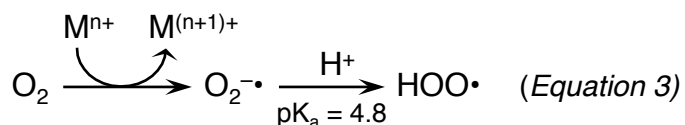
First question: are the authors really observing a "peroxidase-like catalytic activity" as claimed in the title? Peroxidases are enzymes able to perform the 2-electron oxidation of a substrate AH₂ using hydrogen peroxide as oxidant (see equation 1).



Mechanistic details concerning peroxidases and biomimetic models are available in textbooks.^{4,5} The authors did not report the catalytic oxidation of a peroxidase substrate, but they detected by spin-trap methods the presence of two radicals, HO• or HOO•, derived from the reaction of hydrogen peroxide or molecular oxygen, respectively, with low-valent metal ions. The hydroxyl radical HO• is the one-electron reduction product of hydrogen peroxide, generated by a low-valent metal ion in a Fenton-type reaction (see equation 2).



The hydroperoxyl radical HOO• is the protonated form of the superoxide anion O₂•⁻, which is the result of the one-electron reduction of molecular oxygen by a low-valent metal ion (equation 3). The protonation of superoxide anion with a pK_a value of 4.9 generates the neutral radical HOO• (named hydroperoxyl or perhydroxyl).⁶



These two oxygen-centered radicals are clearly not the products of a peroxidase-type reaction.

Second question: are both oxygen-centered radicals generated by a catalytic reaction? Peroxidases are highly efficient catalysts. For instance, a 2×10^{-11} M concentration of the paradigm horseradish peroxidase (HRP) achieves oxidation of 4×10^{-5} M of tetramethylbenzidine within 5 min, in acetate buffer pH 3.5, thus giving rise to a turnover number of 2 millions of catalytic cycles within this short period of time, which corresponds to a turnover rate of 7000 cycles per second.¹ In the article by Moreno Maldonado *et al.*, the total production of $\text{HO}^{\cdot} + \text{HOO}^{\cdot}$ with magnetite was slightly below 2000 nM (lanes “Fe-MNP”, Figure 4 of the ref. 3) for an initial concentration of Fe(II) of 1600 μM (120 μg of $\text{Fe}_{0.81}^{\text{II}}\text{Fe}_{2.19}^{\text{III}}\text{O}_4$ in 260 μL of solution, Experimental Methods). So the yield of these two oxyl radicals was only 0.13% with respect to Fe(II), a substoichiometric number, far from a catalytic activity. The reported initial concentration of H_2O_2 was 0.49 M (Experimental Methods). The production of 2 μM of $\text{HO}^{\cdot} + \text{HOO}^{\cdot}$ therefore corresponds to the conversion of 0.0004%, a very small fraction of the starting amount of H_2O_2 . So, the very low and non-catalytic yield of $\text{HO}^{\cdot} + \text{HOO}^{\cdot}$ with respect to Fe(II)] is probably the result of a Fenton-type chemistry induced by adventitious redox-active iron impurities contained in the isolated nanoparticles or generated by traces of reductants.

In conclusion, the experimental results reported by Moreno Maldonado *et al.*, provide an additional proof that magnetite nanoparticles has no peroxidase activity. In addition, the authors mentioned that "no radical formation was evidenced for any sample at pH = 7.4", a value

corresponding to physiological pH. So, the biomedical claims are not consistent with the reported results. Consequently, the title of the article and all comments concerning a "peroxidase-like catalytic activity" (and putative biomedical claims) of magnetite and other ferrite nanoparticles, did not resist to a careful examination of experimental results. All the reported results can be summarized by the following sentence: "*No peroxidase activity is observed with MFe_2O_4 ($M = Fe, Ni$ and Mn) nanoparticules and only traces of hydroxyl and hydroperoxyl radicals are observed at $pH = 4.8$. At physiological pH , these radicals are not detected*".

References

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