Effect of the synthetic malaria pigment β-hematin on water NMR relaxation times: implications for malaria diagnosis by NMR

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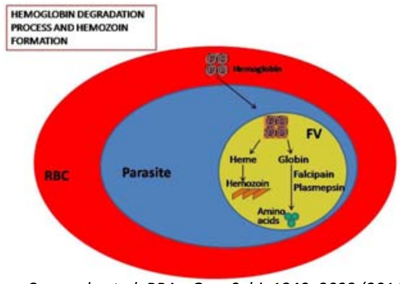
Reliable, fast and low-cost diagnosis of malaria is crucial for an efficient treatment. A method using the paramagnetism of hemozoin - a by-product of haemoglobin detoxification by the parasite causing the disease - has recently been proposed with a detection based on the Nuclear Magnetic Resonance (NMR) relaxation induced by hemozoin. In this work the magnetic and NMR relaxometric properties of β-hematin, the synthetic analog of hemozoin, are studied.

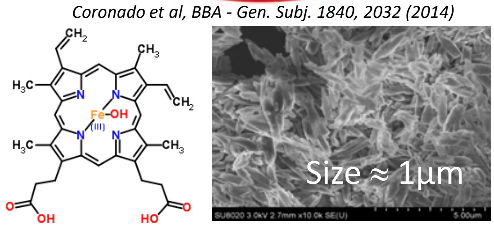
1. Malaria, hemozoin and β-hematin

- About 200 million patients suffer from malaria, a parasitic disease.
- Caused by protozoans of the genus Plasmodium transferred to humans by mosquito bites.
- Production of hemozoin because of the detoxification of haemoglobin released by red blood cells.
- β-hematin = synthetic analog of hemozoin, both contain Fe^{3+} ions and form microscopic crystals.

Figure 1: *(a) Production of hemozoin in infected red blood cells, (b) structure of hematin and (c) crystals of β-hematin*



Coronado et al, BBA - Gen. Subj. 1840, 2032 (2014)



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2. Magnetic properties of β-hematin: para- or superpara-magnet?

- β-hematin supposed to be paramagnetic because of Fe^{3+} ions, as shown by Brémard[1].
- A recent study[2] hypothesized a superparamagnetic behavior for β-hematin crystals
- Easy to check : is there any remanence at very low temperature? If no => Paramagnetic

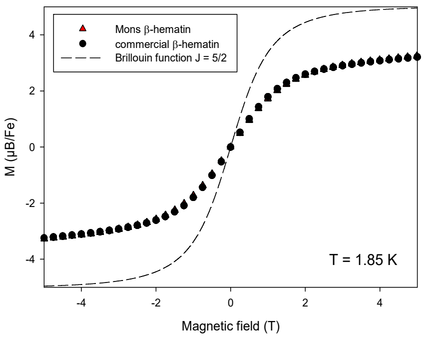


Figure 2: *M-B curve of β-hematin samples (powders)*

For our samples: no remanence at 1.85 K,

⇒ Hematin is paramagnetic.

⇒ (very) Small magnetic moments compared to those of superparamagnetic particles.

Anisotropy of the iron magnetic moments in the hematin crystals[3].

⇒ Significantly different from the the Brillouin function.

3. NMR relaxometry to detect β-hematin and malaria

- During the infection, production of hemozoin by the parasites
- ⇒ Creation of magnetic field inhomogeneities by the large magnetic crystals.
- ⇒ Shortening of T_2, the transverse relaxation time of water protons[4].
- ⇒ Could be detected by a measurement of T_2[4,5].
- But is the effect strong enough for a sensitive detection ?
- Which are the best conditions (T_1 or T_2, magnetic field, echo time?)

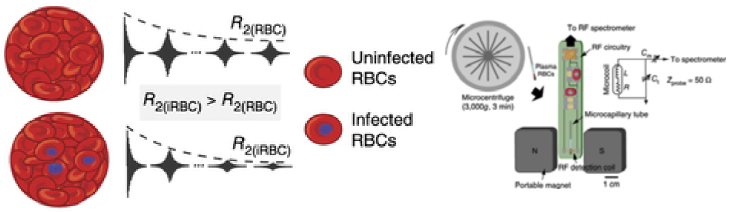
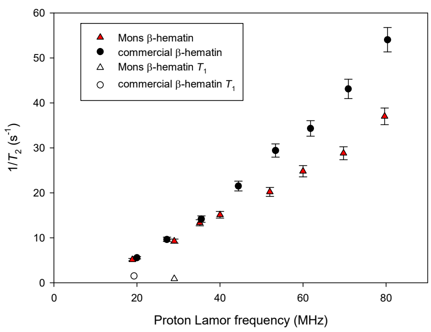


Figure 2: *(a) Effect of the presence of hemozoin on water transverse relaxation in blood and (b) micromagnetic resonance relaxometry system(reproduced from [5])*

Figure 3: *Evolution of $1/T_2$ with magnetic field (expressed as Larmor frequency) of β-hematin samples (3.88 mg/ml) at 25°C. A value of T_1 is also shown for comparison.*



Sample	Normalised $1/T_2$ at 60 MHz (s^{-1}ml mg^{-1})
Commercial β-hematin	8.84±0.27 (at 62 MHz)
Mons β-hematin	6.39±0.19
β-hematin, Karl et al[4]	8.33

Table: Normalised $1/T_2$ of the β-hematin samples and comparison with previous data

What do we learn from these graphs

- ✓ T_1 effect far smaller => use T_2!
- ✓ $1/T_2$ increases with the field
- ⇒ High fields are better
- ✓ $1/T_2$ increases with the intercho time of the CPMG sequence
- ⇒ Use large echo times

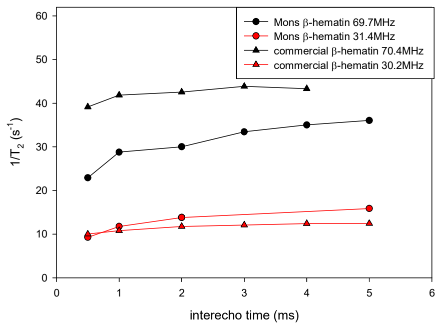


Figure 4: *Effect of the interecho time on the transverse relaxation time*

Is it possible?

- High fields for micro NMR?? Not easy
- Long echo times ↔ excellent B_0 homogeneity
- Sensitivity of the method: not so good without the centrifugation step!
- The centrifugation used in [5] allows to increase [hemozoin] by a factor of 170?

4. References

1. Brémard, C. et al. J Mol Struct 267, 117–122 (1992).
2. Inyushin, M. et al. Sci. Rep. 6, 26212 (2016).
3. Butykai, A. et al. Sci. Rep. 3, 1431 (2013).
4. Karl, S. et al. Am. J. Trop. Med. Hyg. 85, 815–817 (2011).
5. Peng, W. K. et al. Nat. Med. 20, 1069–1073 (2014)