A new paradigm for high sensitivity ^{19}F MRI of Perfluorooctylbromide

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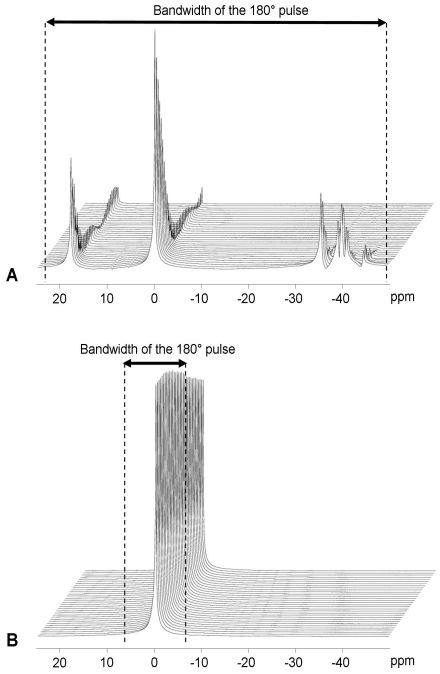

Fig.1. Stacked plot of a series of PFOB spectra obtained with a Hahn spin-echo sequence and a refocusing pulse bandwidth equal to (A) 26 kHz and (B) 3 kHz. Values of TE are ranging from 4 ms to 128 ms with a 4 ms increment.

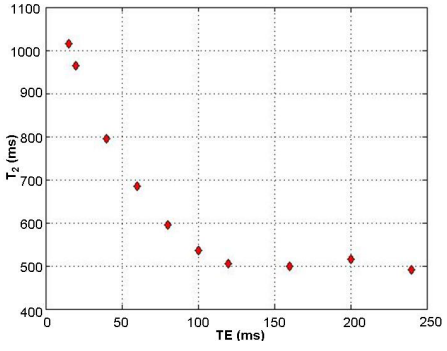

Fig.2. The T_2 of PFOB at 37°C as a function of the interpulse delay TE in the MSE sequence with J-coupling cancellation.

Introduction:

Perfluorooctylbromide (PFOB) is a perfluorocarbon which is well tolerated by the human body and used in many biomedical applications. Hence, PFOB is a promising contrast agent for ^{19}F MRI, particularly in the context of pharmaceutical targeting or cell labeling. However, the complex multipeak spectrum yielded by PFOB and the scalar J-coupling between the CF_2 and the CF_3 group [1] complicate the choice of an imaging method. Moreover, due to the low concentration of the contrast agents, it is critical to achieve the best possible sensitivity. In this context, the goal of the present work was *i)* to investigate the NMR properties of PFOB, and *ii)* to derive an optimized acquisition strategy.

Materials and Methods:

A 7 T MRI scanner (Bruker PharmaScan, Ettlingen, Germany) was used with an in-house double tuned ^{1}H/^{19}F linear birdcage. Experiments were carried out on pure PFOB (Fluorochem, Derbyshire, UK) and PFOB nanocapsules [2]. Among the three main ^{19}F resonances of the PFOB spectrum (fig. 1), we chose to form images from the CF_3 signal only (at 0 ppm). Other resonances were eliminated by adjusting the acquisition bandwidth.
The effects of J-coupling between the CF_3 and CF_2 resonances (at -40 ppm) were investigated using Hahn spin-echo sequences with increasing TE and different bandwidths for the refocusing pulse, in order to demonstrate that selective refocusing of the CF_3 resonance leads to J-coupling suppression [3]. Imaging was performed using a slice selective, multi spin echo (MSE) sequence, with selective refocusing of the CF_3. T_2 was measured for different interpulse delays TE. An optimized MSE sequence with adequate pulse bandwidth and TE was finally implemented in order to yield the highest sensitivity.

Results and Discussion:

Effects of J-coupling could be cancelled out by selectively refocusing the CF_3 while excluding the CF_2 from the refocusing pulse bandwidth (fig. 1). In the MSE sequence, once the J-coupling had been cancelled out, the CF_3 group exhibited a T_2 dramatically dependant on TE, unveiling an extremely long T_2 (up to ~1 s) for short TE (fig. 2). This proved to be true for pure PFOB as well as for nanocapsules. Additional experiments suggested a quantum origin for this T_2 increase at short TE: under the effect of J-coupling, spins oscillate between two coherence modes (phase and antiphase), one of them (the antiphase coherence mode) having a much shorter T_2. At short TE, spins get locked around the long T_2 coherence mode, leading to T_2 enhancement. This feature allowed us to increase the number of echoes (up to 60 echoes for TE=15.5 ms, fig. 3) which yielded an excellent sensitivity unchallenged by 'naive' sequences ignoring this 'hidden' property of PFOB. Indeed, the sensitivity of the MSE sequence with J-coupling suppression and T_2 enhancement was compared to short TE/TR spectroscopic imaging and gradient echo imaging, demonstrating a 6 and 4 times higher sensitivity, respectively. As a result, we achieved *in vivo* detection of nanocapsules in a mouse brain (fig. 3C), which would have been impossible with spectroscopic and gradient echo imaging, due to a too low SNR.

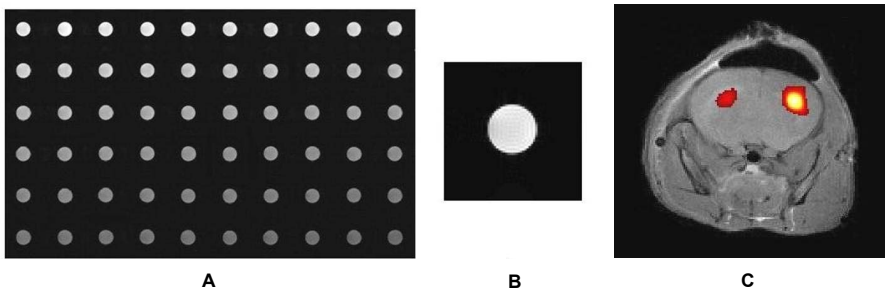

Fig.3. (A) The 60 echoes obtained with our MSE sequence. (B) The resulting ^{19}F image of PFOB after averaging all echoes. (C) Superposition of ^{19}F signal from the nanocapsules (in orange) obtained with our MSE sequence and registered with the anatomical ^{1}H image of the mouse brain after intracerebral injection of nanocapsules; two easily distinguishable doses of 15 nM (left) and 30 nM (right) were injected. SNR was ~10 on the left and ~20 on the right, acquisition time was 30 minutes.

Conclusion:

The unparalleled sensitivity yielded by our MSE sequence with J-coupling cancellation and T_2 enhancement is promising for future applications of PFOB imaging, notably for targeted nanoparticles where PFOB concentration will be very low.

References:

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