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Report on PhD Thesis of Mrs Seyma Alcicek

Thesis Title Zero- and Ultralow-Field NMR for Chemical and Biochemical Analysis

Conclusion:

The thesis is well written and in my opinion clearly meets the criteria required for the successful award of a PhD.

Detailed Report:

The thesis is submitted as 151 pages. It contains an abstract, a table of contents, a brief introduction (chapter 1), the theoretical background (chapter 2), results detailing progress on the zero-field NMR of organophosphous compounds (chapter 3), results on the zero-field NMR of biomolecules (chapter 4), results on the zero field NMR of natural abundance 15N-pyrdine derivatives with in situ SABRE hyperpolarisation (chapter 5), studies on the effect of proton exchange based hyperpolarisation of biomolecules (chapter 6), studies on zero and ultra-low field relaxometry (chapter 7) and a summary and outlook (chapter 8).

As such, the thesis contains a very impressive array of research that takes the field of zero-field NMR forward in a number of disparate directions. Taken at first glance this array of topics goes beyond what I would have expected for a PhD, especially as the thesis is 151 pages long. Nonetheless, I was very pleased however by the content, the fact the results a presented concisely and yet with rigour. I can state now that there is evidence for not only some highly novel research, but a level of rigour that is immediately to be commended.

Chapter 1:

The brief 2 page introduction sets the scene well for the thesis and needs no further discussion.

Chapter 2: Theoretical Background.

This takes the reader clearly through the area. It introduces the concepts of spin, quantisation and the Zeeman effect, before moving on to discuss the relaxation and the origin of the NMR signal. Roles for coupling between spins are discussed and this leads on to the product operator formalism. As such the basis is presented to discuss zero field NMR. The methods detection strategies are outlined

alongside the output and its link to molecular structure. The chapter then goes on to discuss hyperpolarisation by PHIP, SABRE and SABRE Relay.

In summary chapter 2 reflects a concise description of the area that both sets the thesis in context and details the processes needed to understand Zulf-NMR.

Mrs Seyma Alcicek is to be commend for this.

Chapter 3: Zero field NMR of Organophosphorus compounds.

The next 16 pages detail results on the study of five phosphates that were purchased from Sigma. These results have been published, are new, novel and add significantly to knowledge. Motivation is provided by the strong biochemical link to their use. Seyma starts by describing the sample preparation and follows this with the experimental set-up, which in itself is novel. There is clear evidence that Seyma has played a key role in making these measurements. This is evident in the section dealing with data analysis. The results are set in the context of the spin system and how it controls the observations. A number of spectra are presented. I was very impressed with this section. It took the reader clearly through the work and detailed both the challenges and limitations.

Chapter 4: Zero-field NMR of Biomolecules.

This 16-page chapter considers the effect of chemical exchange on observations in Zulf range. Again the thesis is incredibly well presented in a concise yet highly informative manner. Chemical exchange is a very important topic in NMR and I had not realised the significance of such processes in this frequency regime. Urea was used as the probe and pH used to control the exchange rate. The introduction of 2H labelling was also considered. A number of amino acids were also evaluated. This work has again been published. Zero field data was collected and analysed. Seyma found that her experiment and theoretical constructs matched. A number of figures are included and these give the reader a clear perspective on the challenge of the measurements. The results are set firmly into context and it is clear that these observation reflect the foundations of important physical constraints that will be of wide importance to Zulf-NMR.

Chapter 5

Zero-field NMR of Natural Abundance 15N pyridine derivatives.

The next 12 pages of the thesis continue with the exploration of SABRE hyperpolarisation and its use in Zulf- NMR. Seyma takes us through the methods of producing parahydrogen and then deploying it. The successful building of such equipment should not be underestimated. She then uses SABRE to enhance the signals of 7 pyridines. These results are remarkable because of the low abundance of the symmetry breaking 15N label. The results signals were shown to be diagnostic of the material. Hence Seyma demonstrated the potential of this route for chemical finger printing.

Chapter 6

Proton exchange based hyperpolarisation for biomolecules.

Let me say at this point, I felt that Seyma had already presented enough novel results to justify a PhD. Here we see though a further extension where hydrogenative PHIP is used to hyperpolarise

exchangeable protons. She used propargyl alcohol to achieve this via hydrogenation by a rhodium catalyst. Such samples were then hydrogenated in the presence of a suitable proton acceptor like urea. Seyma first explored the formation of propanol as a hyperpolarised probe. Once that was optimise she explored the sensitisation of urea through proton exchange, using 15N-INEPT to assess success. Compelling data is presented, that was correctly presented as % polarisation. Some 13C data was presented. These results were collect using a Magritek SpinSolve and are already impressive. However, Seyma then goes on to utilise the PHIP-X method in Zulf NMR. Seyma first describes the experimental approach, she then goes on to comment on how the resulting data is simulated. She starts out again with allyl alcohol and explains the observations. Spectra a presented and the results clearly match simulation. I found however the section on water to be a little short. This could be expanded. Would H_2O show a Zulf-NMR spectrum? Nonetheless, the results were clearly impressive and certainly publishable.

Chapter 7

Zero and Ultra-low field NMR Relaxometry

The next 14 pages discuss the use of relaxation in zulf-NMR. Relaxometry is another highly important method that is used widely in the assessment of oil-rocks and tablet dissolution. Here the emphasis is placed on its use in blood-oxygen content assessment. Equipment was built to enable these data to be collected. 13C labelled formic acid and methyl phospate were examined in the presence of dissolved oxygen. The effect of copper sulfate and human blood is also explored. Notably, singlet and Zeeman states were explored. Statistical relevance was ensured through averaging. The results here are consistent and compelling. They demonstrate clearly the quantitative nature of the data and its potential for future use.

Chapter 8

Summary and Outlook

A brief summary of the scope of the thesis is presented over 3 pages. This is well written and informative.

Assessment Summary

Seyma has produced a first class thesis. It fulfils all the essential criteria of being novel, critically evaluated and full of publishable results. It is concise, and if I had I criticism it would simply be that often the significance of the results is hidden in the brevity of the presentation. That does not mean the work is not well presented, but simply as a reader I was so excited by what I was reading I wanted more. Seyma must therefore be commended on her thesis. I have examined over 40 PhD students in the last 30 years. Only once before I have suggested no corrections are needed. That is my recommendation here.

Due to the unusually high quality and novelty of the presented research, coupled with the excellent presentation, I am pleased recommend the award of doctoral dissertation with distinction.

Yours sincerely

Simon Duckett