"NMR Crystallization": New *In-Situ* NMR Techniques for Time-Resolved Monitoring of Crystallization Processes

Kenneth D.M. Harris

School of Chemistry, Cardiff University, Wales

E-mail: HarrisKDM@cardiff.ac.uk

The development of *in-situ* techniques for exploring details of crystallization processes from solution promises to yield significant new insights on fundamental aspects of such processes. With this motivation, we have developed new *in-situ* solid-state NMR techniques [1-6] that exploit the ability of NMR to *selectively* detect the solid phase in heterogeneous solid/liquid systems (of the type that exist during crystallization from solution), with the liquid phase "invisible" to the measurement. The technique allows the first solid particles produced during crystallization to be observed and identified, and allows the evolution of different solid phases (e.g. polymorphs) to be monitored as a function of time. This *in-situ* NMR strategy has been shown to be a powerful approach for establishing the sequence of solid phases produced during crystallization and for the discovery of new polymorphs.

A recent development of this *in-situ* NMR technique [4] exploits the fact that NMR can study *both* the liquid phase *and* the solid phase in heterogeneous solid/liquid systems using the same instrument, simply by changing the pulse sequence. By alternating between two different pulse sequences during an *in-situ* NMR study of crystallization, alternate solid-state NMR and liquid-state NMR spectra are recorded, yielding essentially simultaneous information on the time-evolution of *both* the solid phase *and* the liquid phase. This new strategy is called CLASSIC NMR (**C**ombined **L**iquid- **A**nd **S**olid-**S**tate **I**n-situ **C**rystallization NMR). We have shown that the CLASSIC NMR strategy significantly extends the scope and capability of *in-situ* NMR monitoring of crystallization processes, particularly by providing complementary information on the changes occurring in both the solid and liquid phases as a function of time.

The lecture will give an overview of *in-situ* solid-state NMR techniques for the study of crystallization processes, and the current state-of-the-art in the application of these techniques will be demonstrated by wide-ranging examples from our recent research in this field. In addition to highlighting the successes achieved in the application of the "NMR Crystallization" approach, challenges in extending the future scope of the methodology [5] will also be discussed.

References

1. C. E. Hughes, K. D. M. Harris, *J. Phys. Chem. A*, **2008**, *112*, 6808.
2. C. E. Hughes, K. D. M. Harris, *Chem. Commun.*, **2010**, *46*, 4982.
3. C. E. Hughes, P. A. Williams, T. R. Peskett, K. D. M. Harris, *J. Phys. Chem. Lett.*, **2012**, *3*, 3176.
4. C. E. Hughes, P. A. Williams, K. D. M. Harris, *Angew. Chemie Int. Ed.*, **2014**, *53*, 8939.
5. C. E. Hughes, P. A. Williams, V. L. Keast, V. G. Charalampopoulos, G. R. Edwards-Gau, K. D. M. Harris, *Faraday Discuss.*, **2015**, *179*, 115.
6. K. D. M. Harris, C. E. Hughes, P. A. Williams, G. R. Edwards-Gau, *Acta Crystallogr.*, **2017**, *C73*, 137.