From Molecules to Crystals: A "Quick-and-Dirty" Overview

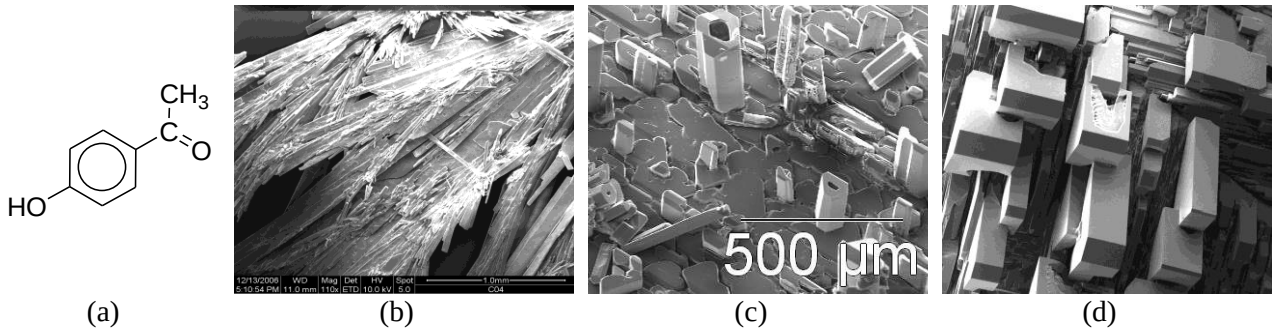
C. E. S. Bernardes

Centro de Química e Bioquímica e Centro de Química Estrutural, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, 1749-016 Lisboa, Portugal
cebernardes@fc.ul.pt

Crystallization is one of the oldest methods used in industry to obtain highly pure solid materials. Despite this, our current understanding of what happens during the earlier stages of crystallization is still incipient. As a result, the development of new crystallization processes is mostly performed on a trial and error basis. Any contribution to depart from this essentially empirical methodology can have a strong industrial impact, given that, for example, the pharmaceutical industry invests over 50 billion euros each year in crystallization related work, in Europe alone [1].

An important topic within this scope is the ability to control and forecast the molecular architectures of crystallized materials. It is well known that organic compounds can often exist in more than one crystal form (polymorph). Different polymorphs can be considered different materials, since they often exhibit significantly distinct physical properties (e.g. color, fusion temperature, and solubility). Consequently, the lack of control over a specific crystallization process can often lead to undesired crystalline forms and to difficulties in manufacturing products with highly reproducible properties. Nevertheless, from a fundamental point of view, the study of polymorphism provides also an opportunity to elucidate the mechanisms of crystallization and the interactions that determine the arrangements and stability of molecules in the solid state. A clear understanding of these aspects is a basic step towards polymorphism control. Particularly important are the aggregation processes occurring at early stages of crystallization, since there is evidence that they play a critical role in the formation of a specific polymorphic form.

In this presentation, an overview of how state-of-the-art studies of early crystallization stages (crystal nucleation) can be carried out using theoretical and experimental methods will be given. Particular focus will be placed on 4'-hydroxyacetophenone system (Figure 1), which has proved to be an excellent model to illustrate the tricks of the trade [2-4].



(a) (b) (c) (d)

Figure 1. (a) Molecular structure of 4'-hydroxyacetophenone (HAP); (b) to (c) with HAP crystals obtained by recrystallization from water, under different conditions. The crystals in panel (b) corresponds to a hydrate phase while (c) and (d) belong to the same polymorph, Form I, but with distinct morphologies.

Acknowledgements.
This work was supported by Fundação para a Ciência e a Tecnologia (FCT), Portugal through Projects PTDC/QUI-OUT/28401/2017 (LISBOA-01-0145-FEDER-028401) and UID/MULTI/00612/2013. A Post-Doctoral grant from FCT (SFRH/BPD/101505/2014) is acknowledged.

References.

[1] *Memorandum of Understanding; CMST COST Action CM1402*, 2014.
[2] C. E. S. Bernardes, M. F. M. Piedade, M. E. Minas da Piedade *Cryst. Growth Des.* **2008**, *8*, 2419.
[3] C. E. S. Bernardes, M. L. S. Matos Lopes, J. R. Ascenso, M. E. Minas da Piedade *Cryst. Growth Des.* **2014**, *14*, 5436.
[4] C. E. S. Bernardes *J. Comput. Chem.* **2017**, *38*, 753.