Report on Thesis submitted by Fatemeh Safari for the Degree of Doctor of Philosophy

Thesis title – *The story of resorcinol crystals and a new perspective for stabilizing high-pressure polymorphs at ambient conditions*

This thesis describes a series of high-pressure structural studies of the archetypal compound resorcinol and its solvates. Resorcinol is of particular significance not only on account of its ubiquity – a natural product, its widespread cosmetic and pharmaceutical applications, and in the production of resins – but also because of its significance as the first organic compound for which the crystal structures of two polymorphs were obtained in the 1930s. The thesis also presents and demonstrates a novel method for nucleating and stabilising high-pressure polymorphs at ambient pressure. This approach is particularly significant and demonstrates great insight from the candidate – see later for more comment about this achievement.

The thesis is very well written and presented, with clear diagrams and explanations. The candidate has successfully provided the wider context of the research, including clear explanations of the importance of polymorphism in the pharmaceutical industry. The introduction to high-pressure research of molecular compounds is explained cogently, together with a wide selection of relevant references. The experimental work is thoroughly described and the results have been carefully analysed. It should be noted that even with modern advances in instrumentation, high-pressure crystallography remains technically very demanding and this is compounded by the challenges associated with both data collection and analysis caused by the geometric constraints of the diamond-anvil cell. The candidate is to be commended on both the quality and quantity of the results obtained during the research programme. The candidate demonstrates clear evidence of originality and critical judgement in the subject, together with demonstration of the wider implications of the research for crystallisation science. The work described undoubtedly makes an original and significant contribution to knowledge, and contains material worthy of peer-reviewed publication. Indeed, three published papers have already emerged from this work in high quality, international journals.

The first publication investigated the relative stabilities of the α- and β-forms of resorcinol as a function of pressure and mapped the P-T phase diagram. The structural origins of the $\alpha \rightarrow \beta$ transition were also elucidated – pressure changes the conformation of one of the hydroxyl groups with associated effects on the hydrogen-bonding network.

The second publication explored the effects of pressure on the solvation of resorcinol and the associated formation of solvates. Despite extensive studies of resorcinol over many decades, no hydrates or methanol solvates have ever been identified at ambient pressure. The candidate demonstrated that crystallisation of resorcinol from water or methanol at elevated pressures produces two new hydrates and a methanol solvate that were characterised by single crystal X-ray diffraction. The formation of these solvates under pressure was then rationalised in terms of volume changes associated with different conformations of resorcinol molecules.

The third publication demonstrates the crystallisation of two polymorphs of resorcinol (ε-form and ξ-form) can be crystallised at elevated pressures. Neither are thermodynamically stable at ambient pressure and so cannot be recovered to ambient conditions. However, the candidate succeeded in stabilising the ε-form at ambient pressure by crystallising resorcinol in the presence of selected dopant molecules that occupy higher molecular volumes. This remarkable effect was then rationalised by the development of a structural model based on the concept of internal pressure. Incorporation of dopant molecules into the lattice shifts the thermodynamic equilibrium for nucleation towards the crystallisation of high-pressure polymorphs. This revolutionary approach offers a convenient route for access to high-pressure polymorphs at ambient pressure – with great significance for the control of polymorphism in the pharmaceutical industry.

Based on the comments above, it is my view that the thesis submitted by Fatemeh Safari fulfils all of the requirements of a PhD dissertation in chemical sciences and that the candidate should therefore be admitted to the next stages of the examination process. Furthermore, given the obvious exceptional quality of the thesis (described above) combined with ***three publications as first author in top-quality and internationally leading journals***, I have no hesitation in recommending that the dissertation is worthy of distinction.

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