Subcritical clusters of liquid benzoic acid: insights from molecular dynamics simulations

L. Sironi[1], G. Macetti[1], L. Lo Presti[1]

[1]Department of Chemistry, Università degli Studi di Milano, Milan, Italy,
luca.sironi1@unimi.it

Nucleation is a crucial process in material science and pharmaceutical chemistry, yet it remains poorly understood and presents numerous unanswered questions. How does a crystal nucleus form? Does it emerge from a completely disordered liquid phase through the continuous addition of building units, as suggested by Classical Nucleation Theory? And is the structure of the nucleus identical to that of the resulting crystal? Recent studies [1,2], suggest that for benzoic acid, nucleation may occur via a non-classical pathway. This is due to the formation of stable aggregates in the liquid phase, which persist for several picoseconds but do not share the same structure as the final crystal. However, a precise and unique definition of these so-called *subcritical clusters* is elusive, due to their dynamic nature.

In this work, we perform molecular dynamics simulations on liquid benzoic acid employing the free MiCMoS platform [3-6], and propose a definition of subcritical clusters based on three criteria: molecular connectivity, time persistence, and energetic stability. Finally, we describe the structural and dynamic characteristics of subcritical clusters comparing them with the crystallographic structure.

Subcritical clusters must be aggregates of bonded molecules: two molecules are considered bonded if their interaction energy is more negative than a specified energy threshold. Additionally, these aggregates must be persistent, meaning that their lifetime must exceed that of thermal fluctuations. Furthermore, they must be energetically "stable": we introduce the concept of excess energy as a stability condition, defined as the difference between the cohesive energy of the aggregate and the interaction energy between the aggregate and the surrounding molecules. Only aggregates meeting all these criteria are considered subcritical clusters: they must exhibit interaction energies more negative than an arbitrary “binding” threshold, lifetimes longer than thermal fluctuations, and a negative average excess energy. Interestingly, while the $P2_1/c$ crystal structure of benzoic acid consists of cyclic dimers, the subcritical clusters are composed of folded H-bonded catemers with a globular shape (Fig. 1). Longer simulations and a systematic study of their temporal evolution could potentially reveal the growth of these subcritical clusters and their eventual rearrangement into a crystal nucleus.

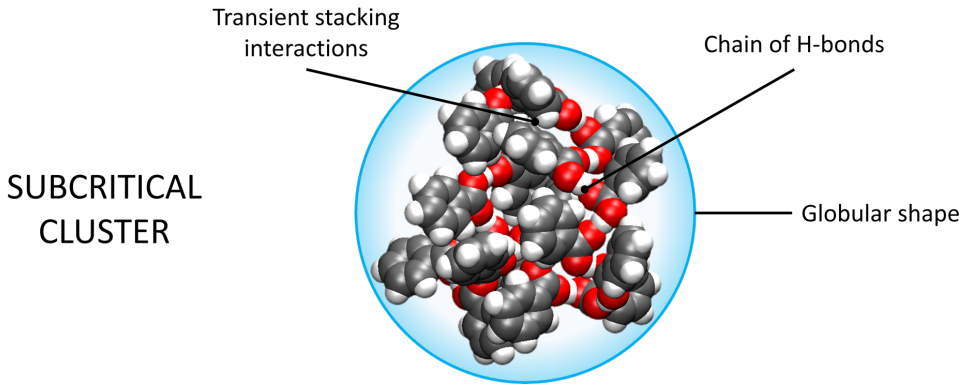

Figure 1. Subcritical cluster of benzoic acid consisting of 17 molecules, with a maximum lifetime exceeding 130 ps.

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