

Molecular Mechanism of Crystal Nucleation of Small Organic Molecules from Solution

Xin Li¹, Shuyi Zong¹, Di Wu¹, Na Wang¹, Xin Huang¹, Ting Wang¹ and Hongxun Hao^{1,2*}

¹National Engineering Research Center of Industrial Crystallization Technology, School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, People's Republic of China

²State Key Laboratory of Chemical Engineering, Tianjin University, Tianjin 300072, People's Republic of China

*E-mail: hongxunhao@tju.edu.cn

Abstract: As a key step and initial stage of crystallization, crystal nucleation determines the structure and morphology of crystal product, and thus affects the product quality and material performance. However, because of the complexity of flexible small molecules, the molecular mechanism of small flexible molecules nucleation is still not well understood, which affects the design and preparation of corresponding crystal products. Therefore, it is necessary to explore the crystal nucleation mechanism of flexible small molecules to achieve precise preparation of polymorphs. Tolbutamide and 5-nitrofurazone were used as model compounds to explore the molecular mechanism of nucleation from solution by using spectroscopic analysis and molecular simulation techniques. Firstly, the molecular conformation and inter/intra-molecular interactions in the different solutions were studied. It was found that multi conformations and different aggregates could exist in the solution, although the distribution of them might change with different operating conditions. Then, the molecular mechanism of nucleation of flexible small molecules was studied. By nucleation induction period experiments, spectral analysis, and molecular simulation, it was found that the same molecule could undergo different nucleation pathway under different conditions. Solvent-solute effect could affect the conformation and assembly of molecules, thus affecting the resulting polymorphs of crystals. The structural similarity between the molecular aggregates in solution and the final product, the solvent-solvent interaction, and the free energy of solvation all affect the nucleation process.

Keywords: Nucleation, conformation, organic molecules, aggregates