Effects of Solution Complexation on Crystallization Processes

by

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Technical Summary

Crystallization is a separation technique widely used in chemical processes to produce high-purity solid products. The exact impact of solution chemistry on the kinetics and thermodynamics of crystallization processes is neither well understood nor properly characterized. Therefore, there exists a need for research to develop chemistry that can exploit and productively manipulate the effect of impurities, additives and foreign molecules on the chemistry within crystallizing solutions. The use of rational chemical interactions has the potential of enhancing the controllability of crystallization unit operations, providing a new process handle for chemical engineers with which they can create new crystal forms, enhance product purity, improve yields, or inhibit the formation of undesirable crystals.

This thesis focuses on the use of small-molecule chemical additives that exhibit selective intermolecular interactions with crystallizing solutes or their impurities. Within the work reported, there were two major areas of study: purification and nucleation control. Additive-driven solution complexation with impurities was demonstrated to be a powerful tool for enhancing the purity of crystal product, without penalizing process yields. The technique was implemented for the separation of structural isomers, and tested for the purification of a large pharmaceutical compound with challenging chemical features. The results discussed helped elucidate the capabilities of complex-assisted crystallization, and also outline the thermodynamic and chemical limitations of the technique. The second half of the work explored the impact on nucleation rates of dilute impurities that interact with the supersaturated crystallizing solute. For the first time, impurity-driven nucleation inhibition was systematically and quantitatively proven, using high-throughput induction measurements. The experimental results were used to discern the thermodynamic and kinetic impact of the inhibitor on nucleation, and to elucidate a potential underlying mechanism for the observed behavior. Data demonstrated that even a weakly-interacting dilute additive can lead to massive nucleation rate depression through a kinetic pathway, most likely due to the disruption of the ordering of the solute molecules within high-concentration clusters during nucleation.

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