Understanding the process of prenucleation clustering (PNC) during crystal growth is of significant importance in envisaging the polymorphism. Structural investigation of stable and metastable polymorphs reveals that supramolecular synthons share a close relationship with PNCs which subsequently helps in understanding of nucleation phenomena.[1] Preferential crystallization of a thermodynamically stable crystal during nucleation suggests self-assembly of molecules through energetically favoured supramolecular synthons. However, slight change in the crystallization conditions like, solvent, temperature, impurity, etc. can lead to metastable polymorphs. To gain more insight into the nucleation dynamics, the polymorphic behaviour of conformationally flexible sulfonamide/sulfoester derivatives during crystallization was investigated with and without additive.[2] Absence of additive during crystallization at various conditions exclusively produced thermodynamically stable crystals wherein molecule acquired syn conformation facilitated by energetically favoured intra and intermolecular p-stacking interactions. Surprisingly, exploitation of pyrazinamide as an additive in different stoichiometric ratios during crystallization produced elusive metastable polymorphs. The melt crystallization and lattice matching studies revealed that pyrazinamide played a pivotal role in providing an alternate nucleation pathway (epitaxial growth) thereby defying natural process of crystal growth. This suggests that it is possible to envisage the selective polymorphic form using tailor-made auxiliaries, although it is critical to design such additives in more general way to control its inhibition or promotion.


Keywords: additive induced polymorphism, intermolecular interactions, phase transition