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Review

Research Progress on the Molecular Mechanism of Polymorph Nucleation in Solution: A Perspective from Research Mentality and Technique

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Abstract: Based on the importance of polymorphic regulation, the molecular mechanism of nucleation has been widely concerned. This review begins by introducing the development and limitations of nucleation theory for organic small molecule crystals, followed by a summary of the general research mentality adopted by current researchers. Moreover, the progress of the molecular mechanism of polymorphic nucleation and its application to the regulation of crystal forms are discussed. In addition, the development of scientific tools for the study of the molecular mechanism of polymorphic nucleation is also summarized, including experimental characterization and computational simulation, providing reference for relevant researchers. Finally, according to the main defects of current research and research ideas, research models and development directions of prospects and recommendations are put forward.

Keywords: crystallization; phase change; polymorph; nucleation; molecular route; mechanism; research mentality

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Citation: Shi, P.; Han, Y.; Zhu, Z.; Gong, J. Research Progress on the Molecular Mechanism of Polymorph Nucleation in Solution: A Perspective from Research Mentality and Technique. *Crystals* **2023**, *13*, 1206. https://doi.org/10.3390/cryst13081206

Academic Editor: Borislav Angelov

Received: 9 July 2023
Revised: 31 July 2023
Accepted: 1 August 2023
Published: 3 August 2023

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1. Introduction

Polymorphism is a phenomenon in which the same basic unit (atom, ion, molecule, etc.) exists in two or more different crystal structures. For examples, diamond, graphite, fullerenes, and carbon nanotubes are all polymorphs of carbon (allotropes of carbon) that differ in their properties. As early as 1822, Mitscherlich et al. discovered that different crystal forms of phosphate and arstate showed different physical and chemical properties, and formally recognized the existence of polymorpism [1]. In 1832, the polymorphs of benzamide, an organic compound, were noticed by Liebig and Wohler [2]. However, because one of the crystal forms was extremely unstable and quickly transformed into a stable crystal form, its crystal structure was not resolved until 170 years later [3]. The polymorphism phenomenon of organic molecular crystals was defined by McCrone as the presence of two or more different molecular arrangements of the same compound in a solid crystal [4]. In the more than 100 years after benzamide, the polymorphs of organic molecules gradually received extensive attention from physical chemists and crystallographers [5–7]. The crystal forms of many substances were confirmed one by one, which is exactly what McCrone said in 1965, "the number of crystal forms found in each compound is positively related to the time and efforts [4]". Due to their different microscopic crystal structures, polymorphs of small organic molecules often exhibit significant differences [8] in macroscopic physical and chemical properties, involving all aspects of performance, as shown in Figure 1. For example, for drugs, the solubility and dissolution rate of different crystal forms affect the bioavailability and efficacy of drugs [9]. In 1998, Ritonavir was withdrawn from the market due to crystal transformation, resulting in a loss of hundreds of millions of dollars for Abbott [10]. Two crystal forms of ranitidine hydrochloride have different properties and form II exhibits better manufacturability characteristics as it showed improved

filtration and drying properties than form I [9]. In terms of food, five crystal forms of cocoa butter show different flavors [11]. For photoelectric materials and mechanical materials, the photoelectric and mechanical properties shown by different crystal microstructures also have significant differences [12–15]. Crystals exist widely in human life, and more and more crystal form problems are also reflected in all aspects. This greatly determines the necessity and importance of regulating polymorphs, and therefore has been widely concerned and invested in scientific research by scientists for more than 100 years. The regulation of polymorphs has become the key to realizing the value of crystal forms [16]. In essence, the behavior of the molecules during nucleation determines what crystal form the molecules assemble into. Therefore, in order to achieve the precise regulation of polymorphs, it is necessary to deeply understand and recognize the mechanism of molecular assembly in the process of polymorph nucleation from a microscopic point of view.

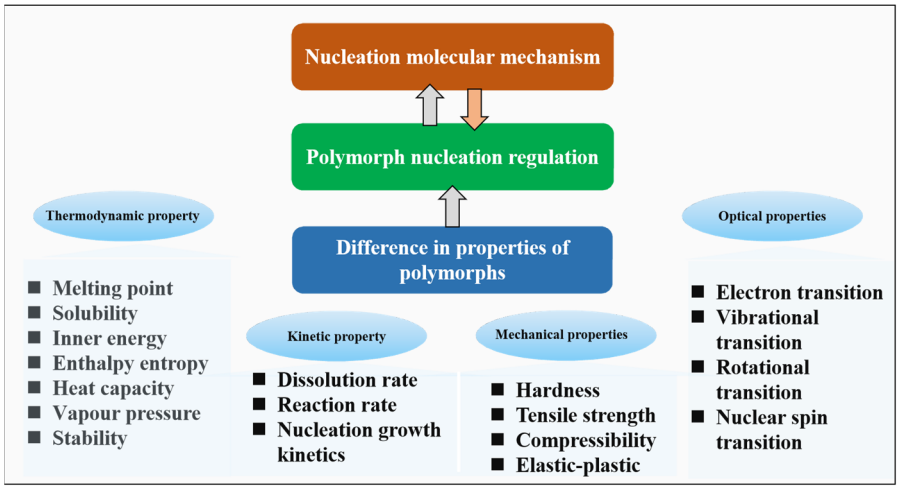


Figure 1. Necessity and significance of studying the mechanism of polymorph nucleation and transformation.

2. Development of Crystal Nucleation Theory and Its Defects

Crystal nucleation theory has been developed for nearly 300 years, dating back to the 18th century when Fahrenheit studied the freezing of supercooled water and established the "old" dynamical model of nucleation [17]. With the further development of nucleation research, two schools have gradually arisen, as summarized in Figure 2, respectively, providing corresponding "structural models" to describe the nucleation process [17]. Classic Nucleation Theory (CNT) is the earliest widely accepted nucleation theory [17,18] and has a relatively comprehensive thermodynamic and kinetic basis [18,19]. It holds that fluctuations in density and order occur together in supersaturated solutions, forming solution molecular clusters, and the assembly structure of such clusters can reflect all possible polymorphic structures of solute molecules. That is to say, the nucleus formed has the same microscopic packing structure as the mature crystals. In recent years, with the rapid development of computer technology, spectroscopy, and other advanced methods and equipment, the study of crystal nucleation has deepened. More and more experimental and molecular simulation evidence reveals that there are stable pre-nucleation precursors in some solutions, meaning the nucleation path may be two-step or even multi-step. And then, the corresponding non-classical nucleation path is gradually derived [20,21], such as the two-step nucleation mechanism [18] (Figure 2). In this theory [22], the formation of crystal-ordered structures is preceded by dense but disordered liquid phase separation, and density fluctuation and order fluctuation are unrelated, that is, the solution will first form dense disordered clusters similar to liquids, and then produce crystalline order. At present, both theories have formed the corresponding thermodynamic and kinetic basis [17–19], which will not be detailed here.

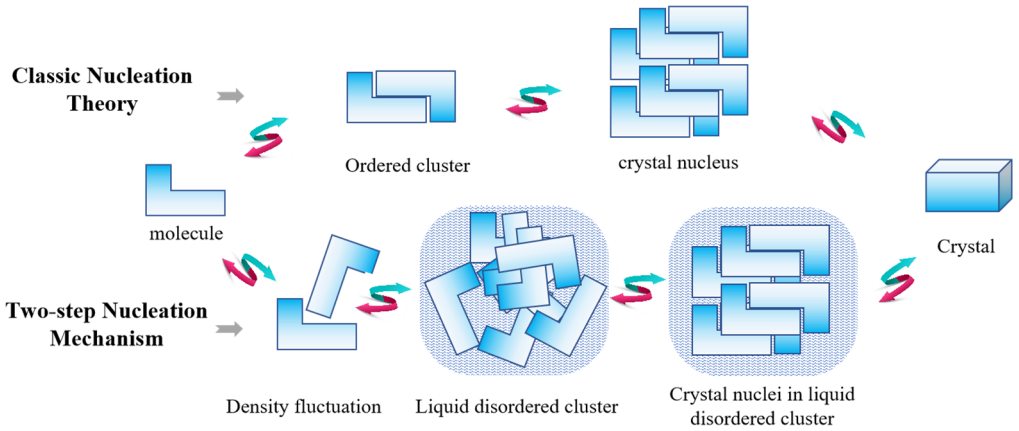


Figure 2. The two alternative structural models currently used for the dynamics of cluster formation during crystal nucleation.

In recent years, in the nucleation study of inorganic substances such as calcium phosphate [23,24] and calcium carbonate [25], it has gradually been discovered that there may be stable aggregates in solution, namely pre-nucleation clusters (PNCs) [21,26], which are simultaneously involved in the phase separation process [27]. Different from CNT and the two-step nucleation theory, the theory holds that the nucleation process occurs through collision among the PNCs into a large solid amorphous state, and then recombination to form crystals. It is, rather than the monomer, a gradual accumulation to form crystal nuclei assumed by CNT, and is also different from the unstable dense disordered intermediate liquid phase as the nucleation precursor in the two-step nucleation theory [26,28]. Besides inorganic systems, solute aggregates have also been reported to exist in some organic amino acid solution systems [29]. CNT, as the first proposed nucleation theory, explains the randomness of nucleation and a comprehensive theoretical model of nucleation dynamics was formed after many years of development. However, the nucleation rate measured by experiments is far less than its predicted results [30]. Indeed, some experimental and computational results show that there are transient dense disordered droplets or clusters in the solution before nucleation [25,31,32], which poses a challenge to the CNT model. On this basis, the two-step nucleation mechanism explains the crystallization kinetics of some protein systems. However, it is only limited to the formation of disordered clusters in solution, and not all systems have found such disordered clusters [30]. The definition of these transition-phase dense disordered clusters is also vague. In addition, the liquid–liquid phase separation as evidence for the formation of dense disordered clusters via two-step nucleation has also been questioned [18]. Both CNT and two-step nucleation theory simplify molecules into hard spheres, which means that the most important intermolecular and intramolecular interactions and molecular conformational changes in molecular assembly are ignored. Therefore, the corresponding molecular conformation and assembly laws are impossible. In contrast, the mechanism of PNCs pays more detailed attention to the evolution process of the clusters' assembly structure and crystal nucleus structure. However, since PNCs originates from inorganic systems, its embodiment and application in organic systems are still rare and there are obvious deficiencies. In most organic systems currently under study, the nucleation process does not involve a solid amorphous intermediate; rather, it directly transitions into a crystalline state [18,33]. Despite the existence of solution aggregates in some organic systems, their structure and degree of association, as well as their role in the nucleation process, remain unknown. In summary, the molecular mechanism and path of organic crystal nucleation remain unclear, both in terms of classical nucleation theory and non-classical nucleation paths. Even though PNCs are not applicable to organic systems, the discovery and proposal of solution pre-clusters provides an important approach and idea for revealing the molecular path of nucleation processes, making it a popular research topic.

3. Categorization of Organic Small Molecule Polymorphs

The polymorphs of small organic molecules can be classified into conformational and configurational (stacked) polymorphs based on their structural characteristics [34], as illustrated in Figure 3. Conformational polymorphs are formed due to different molecular conformations, while configurational polymorphs arise from distinct ways of packing molecules despite similar or identical molecular conformations in various crystal forms [34]. Conformation refers to the different arrangement of atoms in space in a molecule that rotates around a carbon–carbon single bond (σ bond) [35].

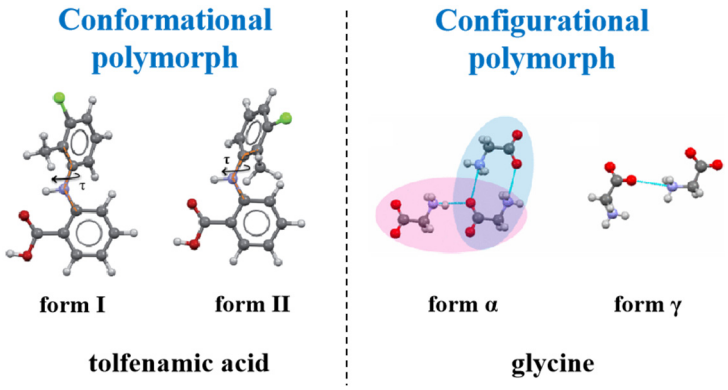


Figure 3. The classification of polymorphs of molecular crystals.

The variations in molecular conformation and packing serve as the structural foundation for the formation of polymorphs of molecular crystals, while also providing inherent structural clues for investigating the mechanism of polymorphic nucleation, which is emphatically proposed in this paper.

4. Research Mentality and Technique of Molecular Pathways of Polymorphic Nucleation in Solution

With the advancement of computational chemistry and spectral technology, scholars have increasingly focused on the correlation between solution and crystal structure in organic small molecule nucleation research. This aims to gain a better understanding of the nucleation path and mechanism by examining structures before and after nucleation. In recent years, there has been significant international progress in understanding the molecular pathways involved in organic compound solution nucleation and regulating crystal nucleation [18,36]. On the one hand, the correlation between solute structures in solution and in solid state is utilized as a tool to investigate the process of molecule-to-crystal nucleation. Therefore, multi-structure systems, such as polymorphs [37,38], eutectic [39], and solvates [40–42], are selected as study models that can provide a richer structure probe. For example, Desiraju et al. monitored the process from solution through supramolecular synthons to co-crystals between aniline-phenol with NMR [43]. On the other hand, different methods are used to control the nucleation of crystals (e.g., polymorphs), such as changing the solvent [44,45], supersaturation [46–48], adding soluble additives [49–51] or insoluble templating agents [52], and introducing laser [53], etc. The two aspects mutually support, promote, and complement each other. Therefore, studying the nucleation pathway of ubiquitous polymorphs is a crucial component in understanding crystal nucleation pathways and has been extensively researched [18] (Figure 4). According to the classification of crystal form structures, two corresponding research routes are conclusively identified here. Few research reports have summarized the progress of crystal research according to this classification.

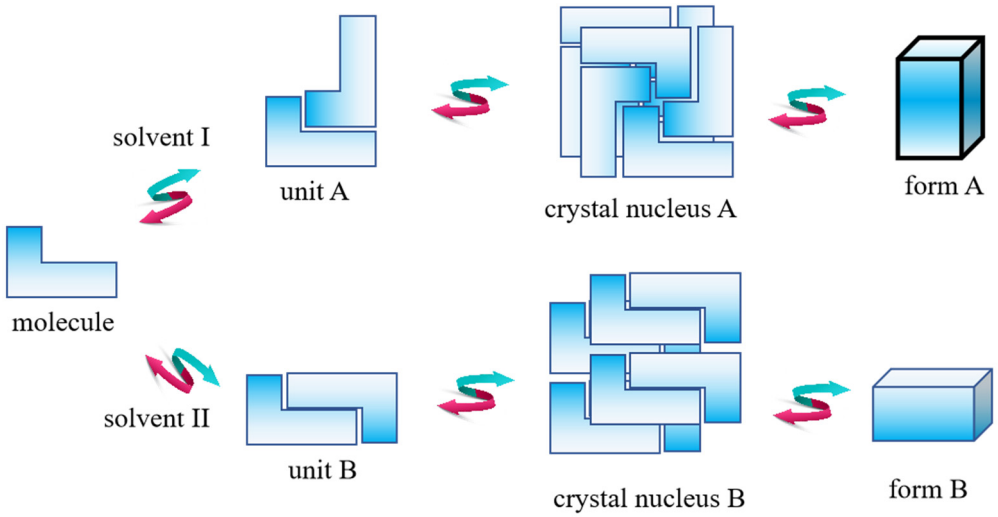


Figure 4. Self-association in different solvents might lead to the formation of different packed nuclei corresponding to crystal forms.

4.1. Research on Nucleation Pathways Based on Configurational Polymorphs

Due to its higher structural differentiation, the study of nucleation paths based on configurational polymorphism is the earliest and most common. As early as 2001, Davey et al. reported the polymorphic nucleation law of 2,6-dihydroxybenzoic acid [54]. Based on the study of the ultraviolet spectrum and crystal structure, it was discovered that the carboxylic acid dimer is the primary structural unit in toluene, leading to nucleation crystal form I. In chloroform, the presence of a hydrogen-bonded chain as the main solute species led to the nucleation of crystal form II based on this chain as the structural unit. Similarly, in 2005, Davey's team utilized infrared spectroscopy to establish a direct correlation between molecular self-association in butyneic acid solutions and hydrogen bonds in the subsequently crystal form for the first time [40]. Furthermore, the application of infrared spectroscopy in detecting the structure of solutions, particularly carboxylic acid molecules, has been further validated and expanded [55]. Samir et al. reported on the correlation between solute assembly and the nucleation results of isonicotinamide in different solutions, using IR and Raman spectra as well as computational chemistry results [56]. In addition, researchers have also discovered many similar compounds, such as 5-fluorouracil [57], sulfonamides [58], carbamazepine [59], α-inosine [60], and so on. Ouyang et al. reported that the carbonyl group of carbamazepine in acetone obstructed the NH···O interaction between the dimer in form II by emulating the same interaction with CBZ, thereby promoting the nucleation of form III. The aromatic–aromatic interaction between CBZ and the solvent molecules such as toluene reduced solute–solute interactions and facilitated the formation of form II, covering molecular recognition between solute–solute molecules or solute–solvent molecules [61]. Hao et al. employed a rigid molecule of 3,5-dinitrobenzoic acid as the model compound to investigate the correlation between nucleation kinetics and the molecular existing form/intermolecular interactions in different solvents; thus, the nucleation mechanism was revealed [62]. They also found that not only solvent–solute interactions but also solute–solute interactions and structural similarities between molecular self-assemblies in the solution and synthons in the crystal structure can significantly influence the nucleation induction time [63]. The correlation between molecule assembly in solution and synthons in crystal structures accords with the fundamental hypothesis of CNT. However, further improvement is still necessary. Some cases have been also found in which solution structure is not associated with synthons in crystal structures, such as mandelic acid in acetonitrile, methanol and nitromethane, inosine hydrate in water [18], and so on. Due to the limitation of microscopic observation tools, researchers have sparked discussion and controversy in some cases. For example, for the topic of whether there is a

correlation between the self-assembly of tofenic acid in solution and polymorphic nucleation results, different scholars have come to different conclusions [64–66]. Additionally, some scholars elucidate the mechanism of polymorphic nucleation through an examination of crystal growth, which can be viewed as a form of configurational assembly. For instance, the asymmetric growth of γ-GABA exemplifies this concept [67]. Therefore, investigating growth mechanisms is also crucial in this regard.

4.2. Research on Nucleation Pathways Based on Conformational Polymorphs

The above studies on the nucleation paths of polymorphs are introduced based on the differences of crystal packing units (synthons), that is, on the basis of configurational polymorphs. In fact, besides the stacking mode, molecular conformation is another crucial structural basis that can serve as a unique and essential tool for investigating polymorphic nucleation paths. And, with the advancement of research methods and technology, there has been a growing interest in investigating solution conformation and conformational polymorphic nucleation mechanisms. For instance, the formation of two different conformational polymorphs of N-phenoxyamic acid has been linked directly to the dominant conformation in two distinct solvents, indicating a straightforward nucleation pathway: namely, the distribution of molecular conformations in solution determines polymorphic nucleation [68]. The crystal phase of 1,1,3,3,5,5-hexachloro-1,3,5-trigermanecyclohexane which is composed of molecules in the metastable boat conformation, can form only in n-hexane. Combined with the results of crystal structure analysis and computer simulation, it is suggested that there is an intermediate solvated path in the nucleation process [69]. The conformations of mefenamic acid molecules in its saturated solution in supercritical CO_2 were investigated under isochoric heating conditions in the temperature range of 80–220 °C, while being exposed to different polymorphs of mefenamic acid in the bottom phase. A correlation has been observed between the polymorphic modifications of mefenamic acid and its conformers in a CO_2 fluid phase. The findings from this study demonstrate the feasibility of monitoring the polymorphic transformation of mefenamic acid's crystalline phase by screening its molecular conformations in a fluid solution [70]. The conformational preferences of tolfenamic acid and flufenamic acid were also studied in supercritical CO_2 systems with 2D NOESY [71,72]. Hao's group investigated the molecular mechanism of conformational polymorphism in solution nucleation using 5-nitrofurazon as a model compound. Various analytical techniques were employed to analyze and compare conformations in solutions obtained by dissolving different polymorphs. Additionally, 1H NMR spectra of solutions with varying concentrations were utilized to illustrate the conformational evolution and potential desolvation pathways. The findings from this study offer novel insights into the pathway of molecular conformational evolution during 5-nitrofurazone nucleation, thereby advancing current research in this field. Furthermore, these results confirm that pre-nucleation conformation was significantly impacted by the ratios of conformers [73]. In addition, Davey et al. utilized both computational and spectroscopic techniques to propose a potential nucleation mechanism for ethenzamide, which involves the rearrangement of a low-energy conformation into a high-energy conformation [74]. Shi et al. investigated the solvent dependence of conformational polymorphic nucleation in undecanedioic acid and expanded their study to include the entire homologous series of straight-chain dibasic acids. Through this broadened scope, they discovered that solvation plays a crucial role in the formation of conformational polymorphs; specifically, systems with easily removable solvents exhibit sufficient conformational rearrangement and are more likely to form a stable crystal [75] (Figure 5). In conclusion, the relationship between molecular conformational stability in solution and nucleation remains unclear, with different conclusions drawn regarding the association of conformation before and after nucleation.

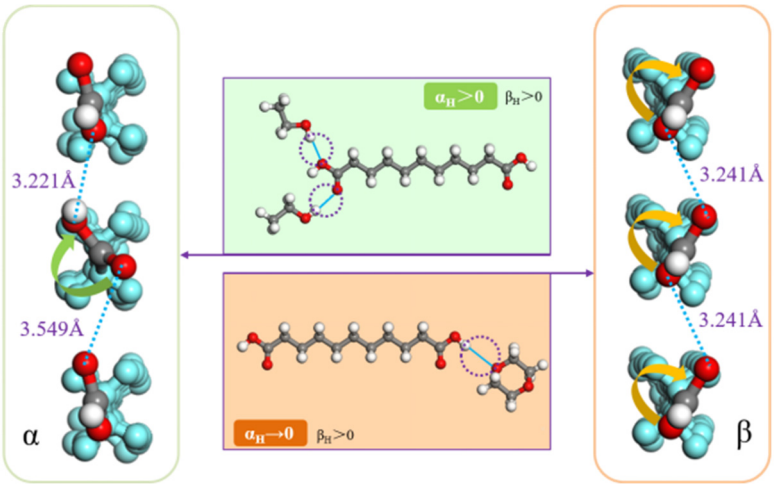


Figure 5. The solvent-dependent nucleation of the conformational polymorph of undecane dibasic acid [75].

4.3. The Regulation of Polymorphic Nucleation Based on Molecular Mechanisms

From the perspective of crystal engineering, the molecular route of polymorphic nucleation can provide theoretical guidance for crystal form regulation. Currently, scientists are attempting to apply their understanding of molecular pathways to regulate crystal form formation. However, reported cases of controlling crystal nucleation outcomes have primarily relied on differences in synthons. Zeng et al. employed ionic liquid molecular recognition to manipulate the stability difference between the carboxylic (or amide) dimer and catenate structure of the solutes in solution, thereby regulating the polymorphic products corresponding to the corresponding structures of tetrolic acid and isonicotinamide [76]. Similarly, the polymorphic nucleation of pyrazinamide [51], isonicotinamide [77,78], 2,6-dihydroxybenzoic acid [78], and sulfathiazole [79] was controlled by designing solid templates with special molecular sites based on synthonic differences among crystal forms. The Gong group developed the strategy of an additive-induced polymorph to realize the selective crystallization of the elusive form II of γ-aminobutyric acid based on crystal assembly structure differences [67]. In contrast, reports on the structural pathways of conformational polymorph formation are comparatively few, and are rarely used to guide crystallization control. Abramova has reported a correlation between the predicted (and in some cases observed) changes in conformational distribution in different solvents and the crystallization results for conformational polymorphs, as demonstrated by four examined examples [80]. Based on the conformational polymorphic nucleation molecular path of diacids described above, Shi designed additives to achieve the precise regulation of crystal form nucleation, and further verified the mechanism through nuclear magnetic resonance spectrum (NMR), solution infrared, and quantum mechanics methods, forming a closed loop of research [81] (Figure 6). This system is one of the most comprehensive cases studied to date, forming closed-loop research as shown in Figure 1. Moreover, based on the preliminary nucleation mechanism, researchers have devised a specific approach for screening novel crystal structures [82–84].

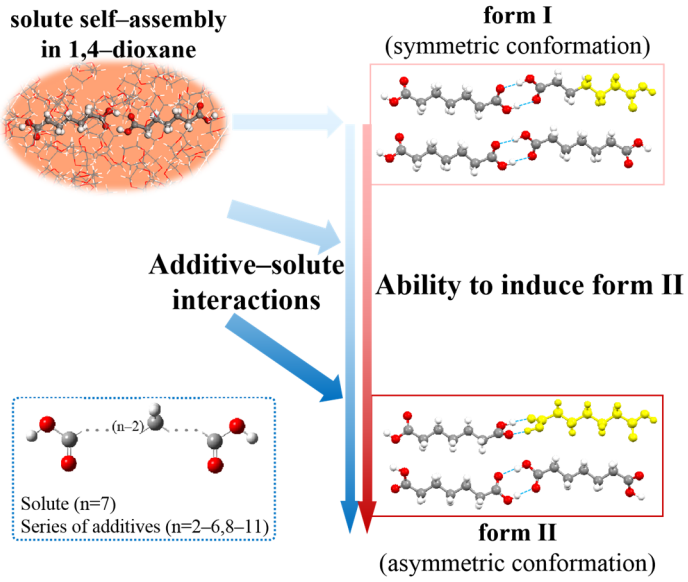


Figure 6. The design of additives for polymorph regulation based on the conformational polymorph nucleation mechanism of straight–chain dibasic acids [81].

4.4. The Progress and Application of Relevant Research Tools

Decades of research on organic polymorphic nucleation pathways have been accompanied by the development of research methods and tools, mainly including experimental analysis methods and computational simulation methods.

4.4.1. Experimental Analysis Methods

According to the above overall research idea, it is divided into two aspects of solution structure and solid state structure to introduce the content. Firstly, to determine and analyze the solid state structure, single crystal X-ray diffraction (SCXRD) technology is utilized as the core method, which can directly identify atomic positions [85,86]. Combining the corresponding software (Mercury, Diamond, etc.), the molecular assembly law and characteristics can be clarified. As well as the current powder X-ray diffraction (PXRD) technology for resolving crystal structure, other techniques such as Fourier transform infrared spectroscopy (FTIR), Raman spectroscopy, and NMR are utilized to reflect the structural characteristics of the solid state [37,75,87,88]. SCXRD is considered the gold standard for non-destructive structure characterization, but its time-consuming nature stems from the requirement of single crystal samples to be dozens of microns in size, which can sometimes be unattainable. On the other hand, PXRD is commonly employed as a rapid and cost-effective method for polymorph identification; however, it falls short in solving crystal structures due to the lack of three-dimensional (3D) information. The microcrystal electron diffraction (MicroED) technique complements these two methods by providing not only 3D information but also requiring crystalline powder samples alone. This technique has been successfully utilized in determining the crystal structures of remdesivir [89]. As all three methods are based on crystal structure diffraction; their results can be mutually validated. A variety of microscopes, such as the Scanning Electron Microscope (SEM) [77], Transmission Electron Microscope (TEM) [90,91], and Atomic Force Microscope (AFM) [92], etc., are utilized to provide crucial information on particle morphology and surface characteristics at different scales.

For obtaining solution chemistry information such as intermolecular interactions, solute aggregates, and molecular conformation in solution, spectroscopy methods are widely used, including ultraviolet (UV/vis) [54], solution FTIR [37,55], solution Raman [93], solution NMR [94,95], and so on. The determination of dimers and tetramers of 3,5-dinitrobenzoic acid through mass spectra (MS) in toluene has significant implications for future studies [62]. In addition to Small/wide angle X-ray diffraction (SAXS/WAXS) [96],

photoelectron spectroscopy (PES) [97], and neutron scattering, other techniques are also utilized [98]. Liquid cell transmission electron microscopy (LC-TEM) is a recently developed in situ observation technique that has gained widespread use for the examination of nanoscale objects in liquid environments [99,100], facilitating the observation of potential nucleation precursors.

4.4.2. Computational Simulation Methods

Furthermore, as computational chemistry has advanced, software programs such as Crystalexplorer and XPac have been developed by computational chemists, physical chemists, and crystallographers to analyze solid state structures based on theoretical principles [101]. These programs can calculate intermolecular interactions, action proportion, electrostatic potential energy surface, hole size, and other parameters [47,102]. Scientists have also created computational models of molecules with varying precision or suitable for different physicochemical environments to analyze the conformation or molecule assembly in vacuum or solution. For example, density functional theory (DFT) is used to calculate the interaction energy between molecular pairs at different sites of action [93,103]. The recessive or dominant solvent model, which is based on quantum mechanics and molecular mechanics, has been established to calculate the stability of single molecules or molecular pairs, multi-molecule aggregates, and other solution aggregates in a given environment. Additionally, it can determine the conformational stability of molecules and their transition energy barriers under specific environments [65]. The calculation of solvation free energy using molecular dynamics [104] and the Radial Distribution Function (RDF) is employed to characterize the interaction between solutes and solvents [47,105]. In recent years, a Connolly solvent shell model based on quantum mechanics has been developed to improve the simulation accuracy of solute solution environment, and then complete the analysis of solution structure [93,106]. Moreover, based on the correlation between crystal nucleation and growth, predicting crystal habit can also provide some insight into intermolecular interactions during the process of crystal nucleation [107].

In addition, computational methods have facilitated the development of Crystal Structure Prediction (CSP) [108], prediction of solid-form transition temperatures [109], kinetic hindrance affecting crystallization of forms [110], co-crystal prediction [111,112] and other predictive techniques that aid in understanding crystal assembly mechanisms. With the advancement of machine learning (ML), it has gradually been applied to the investigation of crystal structure prediction or nucleation [99,112]. ML has been used to detect numerous nanometer-sized nuclei of sodium chlorate [99].

5. Conclusions and Prospects

Based on the importance and necessity of polymorph regulation, the molecular nucleation pathway that urgently needs to be found has been paid more and more attention by scientists. Although spectroscopy and other experimental analysis and calculation methods have rapidly developed, the information they provide is fragmented and indirect when it comes to microscopic changes in the nucleation process. The nucleation pathway of organic molecular crystals is mainly speculated and explained through the relationship between structures before and after nucleation, making it challenging to draw consistent, robust, and universal conclusions.

To advance the study of nucleation mechanisms, it is imperative to enhance observation methods. Therefore, there should be an accelerated focus on research and development in related fields such as electron microscopy. Moreover, we should increase our focus on conducting research that combines different fields and takes into account insights from other areas in a thoughtful way. Furthermore, we should enhance the utilization and promotion of recently introduced research methodologies in nucleation studies, while expanding the application scope and establishing a reliable database, particularly for monitoring molecular conformation in solution.

Computational simulation methods have developed rapidly, and similarly, the development of solution conformational simulation should also be focused on. With the rise of ML, we can try to apply it further. For example, solution chemical information, crystal structure data, and even molecular simulation data and crystal structure prediction data from many nucleation mechanism research cases are mined and studied to provide corresponding molecular mechanisms and regulatory means. This is complemented by the quantity and quality of data samples collected from nucleation researchers worldwide.

Due to the lack of research means for visualization, structural clues that are diverse and comparable are particularly important in the current ideas on nucleation pathways. For example, studying the nucleation behavior of homologues or a structurally similar series of systems can rely on more structural relationships, just as polymorphism has become a main focus in molecular mechanism research on nucleation.

In addition, flexible molecules are the main components of organic molecules. However, due to their relative complexity, the general research idea is to avoid their complexity and try to select simple and rigid molecules to reveal the general law. However, the study of these limited rigid molecules is insufficient for general law. Whether conformational changes can provide more structural clues remains a challenge for relevant researchers to overcome, potentially revealing unknown information.

Author Contributions: Conceptualization, P.S. and J.G.; writing, P.S.; review and editing, P.S., Z.Z., Y.H. and J.G.; funding acquisition, Z.Z. and Y.H. All authors have read and agreed to the published version of the manuscript.

Funding: This work was financially supported by National Engineering Research Center for Petroleum Refining Technology and Catalyst (RIPP, SINOPEC) (FW2313-0002)and National Key Research and Development Program of China 2021YFA1501404.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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