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Review

A review of the effect of multiple conformers on crystallization from solution and strategies for crystallizing slow inter-converting conformers

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ABSTRACT

The effect of multiple conformers in solution on nucleation, growth rate and polymorphism is reviewed and methods for crystallizing substances present as slow inter-converting conformers in solution are proposed. Review of the previous art indicated that for fast inter-converting conformers, nucleation and polymorphism are favored but no effect is expected on crystal growth rate as crystal forces are expected to modify the conformation of the integrating species onto the crystal surface. On the other hand, nucleation rates and propensity for polymorphism are expected to be lowered for systems with slow conformational inter-conversion kinetics. In addition, for such systems, the effect of crystal forces on conformational change upon crystallization is decreased which results in an impediment of crystal growth. This effect is more pronounced if the species that crystallizes is a minor conformer in solution. Strategies for crystallizing slow inter-converting conformers, including the evaluation of the propensity for nucleation of specific conformers via calculation of the intrinsic supersaturation, are presented. This latter method was used to determine crystallization conditions of a drug candidate present as slow inter-converting conformers in solution.

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1. Introduction

A common characteristic of organic molecules is their ability to adopt multiple conformations due to their inherent high degree of freedom compared to inorganic substances. In theory, for solution organic chemistry, conformational change always occurs because in most cases organic molecules contain at least one degree of freedom such as a covalent bond which permits free rotation. Therefore, it is intuitive to expect that in most cases, organic molecules exhibit conformational changes in solution.

Indeed as noted by March (1992), free rotation around σ-bonds occurs readily in organic compounds which leads to an infinite number of very short-lived conformers that are not distinguishable by analytical methods. Solution NMR remains the most useful analytical technique to detect multiple conformations in solution if the conformation change is longer than the NMR timescale, as reported by Kessler (1970), Oki (1983) and Binsch (1975). In addition to rotation, conformation change in solution can also be due to other less common causes, such as lone electron pair inversion which is mainly concerned with substances containing nitrogen and phosphorus. Typically this type of inter-conversion occurs rapidly due to the low energy barrier required (Block et al., 1991; Kohmel et al., 1991). Furthermore, molecular folding is a remote type of conformational change (Hill et al., 2001) that is considered as secondary configuration and is beyond the scope of this paper.

Rotation around single bonds can be temporarily hindered by steric blockage or by stabilization via intra-molecular H-bonds and/or other non-covalent bonds. In this case, conformations can be locked for a long enough time that they can be detected by techniques such as NMR. The term atropisomer was first introduced by Kuhn (1933) to denote conformations in which rotations are "frozen". It was further nuanced by Laplante et al. (2011a, 2011b) into two classes based on the effect of the species' half-life on drug developability: atropisomers with long half-life and better drug/target specificity are more prone to development as they can provide targeted action before converting to less active atropisomers. On the other hand, developability is compromised for atropisomers with better activity but short half-life as they can convert to less active atropisomer (and possibly be eliminated) before reaching their target.

Currently, atropisomers are defined as conformers having a half-life of 1000 s or more. Studies addressing isolation of atropisomers have increased recently due to growing evidence of improved potency of specific atropisomers under physiological conditions (Laplante et al., 2011a, 2011b; Xing et al., 2009. Vrudhula et al., 2007; Bringmann et al., 2005; Zhou et al., 2004; Albert et al., 2004; Fukuyama and Asakawa, 1991). In contrast, few reports can be found in the literature about the effect of relatively rigid conformations such as atropisomers in solution on nucleation, polymorphism and on crystallization kinetics.

In the following sections, we will present a succinct bibliography of the accounts of the literature on the effect of multiple conformers on nucleation, crystal growth and on the propensity for polymorphism. We will then propose strategies that can be useful in the development of crystallization recipes for substances present as slow inter-converting conformers in solution. Lastly, we present an approach to identify routes to first crystals based on the calculation of supersaturation with respect to a given conformer (*i.e.* the intrinsic supersaturation, ISS).

2. Effect of multiple conformations on nucleation and polymorphism

With respect to nucleation and propensity for polymorphism, an interesting question is: How does multi-conformation affect nucleation and polymorphism of organic molecules? To date, there is no evident consensus in the literature regarding the effect of the existence of several conformers for a given molecule on its nucleation behavior. Two general ideas were proposed, namely, multiple conformations can either enhance nucleation and polymorphism, or inhibit them.

The first school of thought proposes that multiple conformations are expected to increase the barrier to nucleation and decrease the propensity for polymorphism. Yu et al. (2000a) presented a general rule of thumb for predicting which conformer in solution is expected to crystallize depending on the crystal structure. If a conformer favors intermolecular Van der Waal interactions, the resulting polymorph would be of a closed-packed lattice. On the other hand, if the conformation facilitates intermolecular H-bonding, a structure with low-packing density is expected because of the orienting effects of H-bonds. Conformers with high dipoles can lead to structures with either parallel or anti-parallel dipoles. These authors also believe that systems with higher degrees of freedom (*i.e.* high number of conformers) are likely to be more difficult to nucleate. This is attributed to the lower effective concentration of the conformer that crystallizes. Because of the presence of all other conformers, the conformer that crystallizes is diluted in solution, which in turn gives a low supersaturation. The other conformers can act as "impurities" and inhibit key solute integration sites on the crystal surface. This rationale leads to the expectation that systems with multiple conformations have a decreased nucleation rate. Jeffrey and Kim (1970) adhere to this school of thought and reported that minor conformers of relatively rigid alditols have low probability for nucleation due to restricted flexibility and low population in solution. Hurshouse et al. (2009) also adhere to this school and believe that nucleation is likely retarded if multiple conformers are present in solution. Threlfall et al. (2013) reported that conformational multiplicity may retard nucleation in some cases. However, these authors did not investigate the mechanisms implicated in the decrease of nucleation rates due to the presence of multiple conformers. Recently, we reported a similar behavior of slow nucleation of substances present as multiple inter-converting conformers in solution (Derdour et al., 2011). In this case, spontaneous nucleation was impossible at 20 °C and solution NMR, solubility measurements, and *ab initio* calculations indicated that the conformer that crystallizes is likely to be the minor species in solution. We proposed that slow nucleation kinetics is expected for a system with high energy barrier between conformers (>10 kcal/mol), and where the crystal is packed with a high energy conformer. According to Oki (1983), slow inter-converting conformers can be isolated at ambient conditions if the energy barrier to conformational is 23 kcal/mol or higher. These levels of energy barrier lead to species half-life of over 1000 s, which is sufficient to isolate the conformations by chromatography. In this situation, separation via nucleation/crystallization can be possible if conformers have self-assembly patterns that lead to a sustained crystal lattice and if they are not present in very small proportions in solution (*i.e.* very minor conformers). This behavior was also reported by Kitamura (2002, 2003, 2009) who attributed the temperature dependence of nucleation outcome of L-glutamic acid to the variation of conformers' concentrations in solution with temperature. This author indicated that this effect is more likely to occur for systems with high energy difference between conformers which translate into high energy barrier of transition between conformers in solution.

The second school of thought considers that the presence of multiple conformations in solution favors nucleation and polymorphism. Buttar et al. (1988), Starbuck et al. (1999) and Nangia (2008) noted that for most organic compounds, energy difference between different conformers is of the same order of magnitude as the difference in lattice energy between polymorphs (<2 kcal). Therefore strained conformers, *i.e.* conformers with higher energy, can crystallize if the resulting crystal lattice provides a better recognition pattern and/or stronger anchoring sites, resulting in low lattice energy.

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