Nucleation behaviour of racemic and enantiopure histidine

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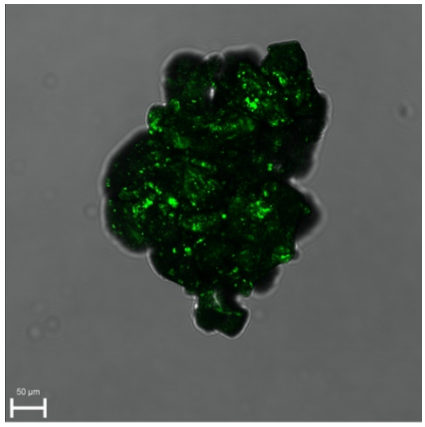
In this study, racemic and enantiopure histidine have been selected as model compounds, as control over nucleation is a possible pathway to accomplish chiral resolution through crystallisation. We aim to compare the nucleation behaviour of the racemic and enantiopure materials. To the best of our knowledge, this kind of studies is rare.

Nucleation of DL- and L-histidine has been examined using induction time measurements and their nucleation rates have been deduced.[1] Results indicate a much slower nucleation for the racemic form compared to the pure enantiomer form. The effect of temperature and supersaturation on the nucleation rate is also described. Classical nucleation theory (CNT) is used to determine the interfacial energy, the nucleation energy barrier, and the nucleus size for both compounds, although a large discrepancy is found between the measured nucleation rates and those theoretically calculated, indicating that CNT may not apply. Second harmonic generation analysis demonstrates the presence of non-centrosymmetric domains embedded within the racemic crystals, as indicated by the green domains in the figure on the right. This may at least provide a partial reason, why CNT may not apply, as it demonstrates that nucleation processes can be highly complex phenomena in which the initially nucleating form (the green non-centrosymmetric domains) loses out to the faster growing, racemic form, that appears through secondary nucleation and growth, and which may occur on the nuclei of the initially nucleating, chiral form.



The large difference between the nucleation rates for the pure enantiomer and the racemic compound have so far not led to satisfactory preferential crystallization; however, improving control over the nucleation conditions may lead to more efficient preferential crystallisation and symmetry breaking in the histidine system.

[1] L.C. Harfouche, S. Clevers, G. Coquerel, Ivo B. Rietveld, *CrystEngComm*, **2021**, 23, 8379-8385.