Linking Aggregation in Solution, Solvation, and Solubility of Simvastatin

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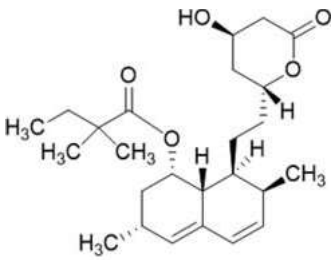
Understanding how organic compounds assemble in solution to form crystals remains a major chemical challenge.[1] The analysis of the solubility dependence on the solvent nature should, however, provide a window into how the aggregation of a particular solute is modulated by the solution environment at a particularly important point in the crystallization landscape, that of saturation.

In this work the aggregation of simvastatin (**1**), one of the most commonly prescribed antihyperlipidemic drugs, in three solvents differing in polarity and protic character (acetone, ethyl acetate, and ethanol), was analyzed through a combination of solubility versus temperature measurements and molecular dynamics (MD) simulations.



(**1**)

The results revealed a solubility order of acetone > ethyl acetate > ethanol, in the temperature range 283–308 K, with no observed changes in the crystal structure of the solid phase in equilibrium with the solution.[2,3] Solubility is generally thought to be higher if the solvent effectively solvates solute molecules that are well-separated from each other. However, an analysis of the structures of the different solutions on the basis of MD simulation results indicated that the observed solubility trend reflects a balance between the tendency for solute aggregation and the ability of the solvent to efficiently solvate the aggregate structures, regardless of their size, by effectively establishing solvent–solute interactions.

Acknowledgements: This work was supported by the Fundação para a Ciência e a Tecnologia (FCT), Portugal (projects PTDC/QUI-OUT/28401/2017, LISBOA-01-0145-FEDER-028401, UIDB/00100/2020 and UIDP/00100/2020), and by the FCT-DAAD program for cooperation in science. A postdoctoral grant awarded by the FCT to R.G.S. (SFRH/BPD/118771/2016) is also gratefully acknowledged.

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