Which Methods for Calculating Temperature Dependent Aqueous Solubilities and the Related Lattice Energies Work Best for Pharmaceutically Relevant Materials?

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Overview

- Lattice energy (LE) calculations support processability assessment
- Predictions of temperature dependent solubility directly support the design of unit operations, e.g. cooling crystallization [1] and wet granulation [2]
- LE calculations may yield comprehensible [3], but not necessarily more accurate [4], solubility predictions
- ADDoPT aqueous solubility modelling studies have been published [4], whilst benchmarking of lattice energy calculations has been submitted for publication [5]

Background

- Based upon certain approximations, LE can be related to experimental sublimation enthalpy (ΔH_{sub}) via (1) [4,5]
- In turn, this can be related to thermodynamic solubility ($X(T)$) and its temperature dependence [4,6]

$$\Delta H_{sub} = -LE - 2RT \quad (1)$$

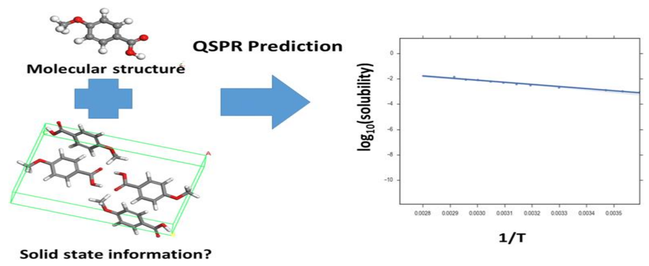
$$\Delta H_{sol} = \Delta H_{sub} + \Delta H_{solvation} \quad (2)$$

$$\Delta G_{sol} = \Delta H_{sol} - T\Delta S_{sol} \quad (3)$$

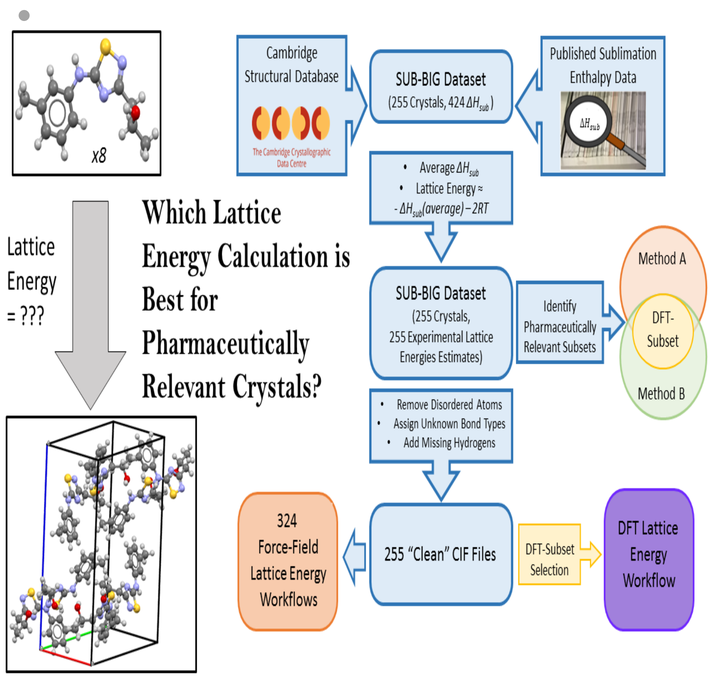
$$\Delta G^{0}_{sol} \propto -RT \log_{10} X(T) \quad (4)$$

Solubility: Model Comparison

- 882 aqueous solubility data points, at various temperatures, for 309 organic, crystalline materials
- Experimental melting point data available for modelling
- Subset of 129 materials (530 data points) integrated with crystal structures – hence force-field lattice energies available for modelling
- Other QSPR model inputs: molecular and temperature (1/T) descriptors [4]

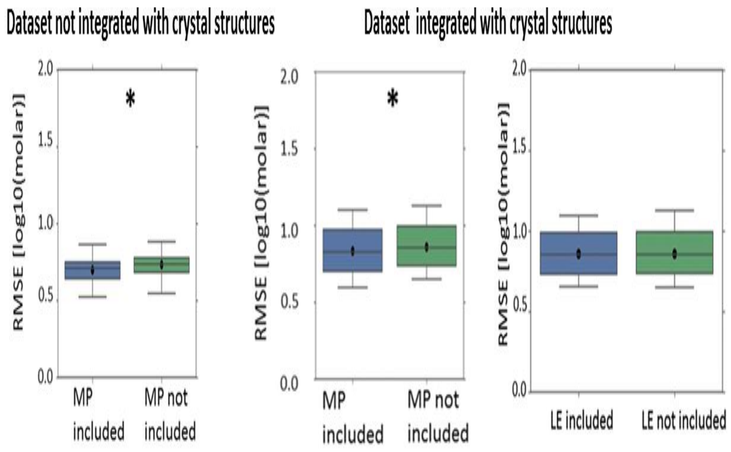


Lattice Energy: Benchmarking



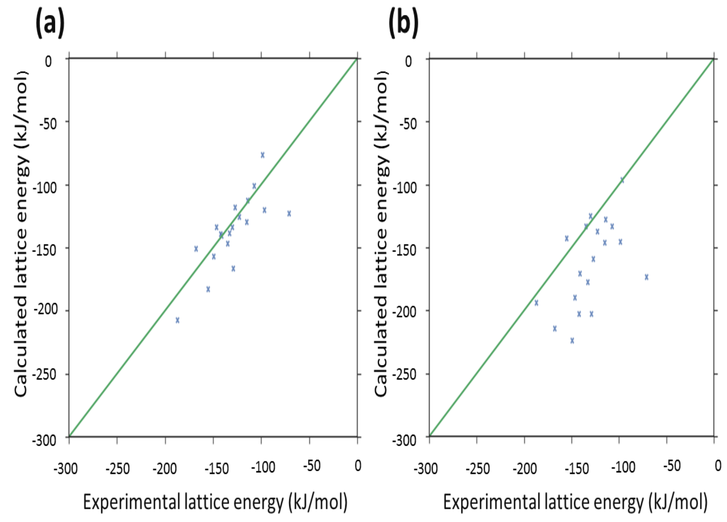
Solubility: Influence of Solid State Information

- N.B. (1) Lattice energies calculated using a provisional protocol based on COMPASS force-field, and (2) stars denote statistically significant differences



Lattice Energy: Best Force-Field Protocol vs. Dispersion Corrected DFT (PBE+TS)

- Force-field (a) calculations outperform DFT (b)



Solubility: Conclusions

- Solid state descriptors – calculated lattice energies or experimental melting points – did not greatly improve the best predictions of aqueous temperature dependent solubility
- Consideration of thermodynamics makes this surprising
- In part, this may reflect limitations of solid state descriptors, including lack of polymorph specific data
- Ongoing work at Leeds to model non-aqueous data (more than 3000 data points – 150+ solutes, 40+ solvents) using Solvation Search program derived solvation descriptors derived from molecular structures

Lattice Energy: Conclusions

- A new benchmark dataset was derived (SUB-BIG, 255 crystal structures) – this will be the largest published to date
- We can recommend a force-field protocol based upon the COMPASS II force-field [7] for calculations from the crystal structures of pharmaceutically relevant materials
- This protocol seems to outperform a basic dispersion corrected DFT protocol (PBE+TS)
- However, an evaluation on smaller, literature benchmark, datasets suggests it may not outperform some other protocols presented in the literature – so future studies should compare using our new benchmark dataset

References

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