

Computational Prediction of Effects of Pressure on Organic Crystal Structure

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The importance of polymorphism in crystal structures of organic molecules has been well recognized for many years. Interestingly, recent experimental studies [1] have provided indications of the effectiveness of high pressure as an additional means for exploring this polymorphism. The present paper represents an examination of the extent to which lattice energy minimisation methods can be used to complement the experimental investigations. The computational algorithm [2] employs the results derived from quantum mechanical calculations to construct accurate and efficient conformationally dependent intramolecular and intermolecular models used during crystal structure optimisation.

We focus our study on a molecule of pharmaceutical interest - piracetam (2-oxo-1-pyrrolidine acetamide). Five distinct polymorphs have been identified experimentally for this model system, two of which have been observed only at high pressure [1]. One of the latter polymorphs, Form V, is produced by the application of pressure to the most stable form at ambient conditions (Form II), which results in a direct reversible single-crystal to single-crystal transformation, a major characteristic of which is the shearing of the unit cell by ~10 degrees.

The lattice energy minimisation of Form V at ambient pressure resulted in a Form II crystal. This appears to be in agreement with the fact that Form V has not been observed experimentally at low pressures. Above the transition pressure, we were able to obtain both forms as stable lattice energy minima. However, the lattice energy of Form V is predicted to be slightly higher than that of Form II at all coexistence pressures, which is at variance with the experimental observation.

The Form II to Form V reversible transition under pressure variation was studied by both pressurising Form II and decompressing Form V. The transition pressure predicted by the model is generally higher than that observed experimentally, but the degree of overestimation is reduced when the molecular distortions under packing forces are modelled to greater detail.

Finally, a set of low-energy structures generated by an earlier theoretical study [3] along with the experimentally resolved forms have been pressurised in steps of 1 GPa from 0 to 9 GPa. It is shown that there is considerable re-ranking and increasing energy separation between hypothetical crystal structures as the pressure is raised. As a result, the number of independent, energy plausible structures is not the same at different pressures. This indicates that performing a search for crystal structure prediction at a single pressure will not generally be sufficient for identifying all energy plausible structures that may occur at different regions of the phase diagram.

References:

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- [2] Kazantsev, A. V. et al.; in preparation
- [3] Nowell, H. and Price, S. L.; *Acta Cryst.*, B61, 558, (2005)