

Direct observation of intermediates in a thermodynamically controlled solid-state dynamic covalent reaction

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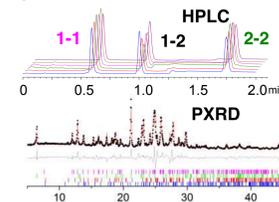
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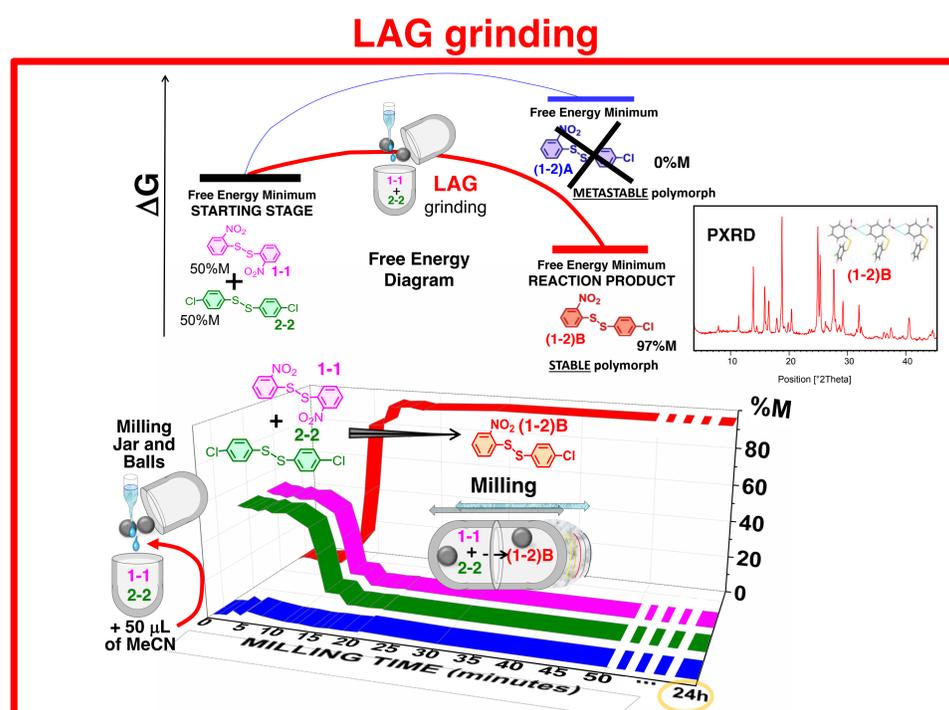
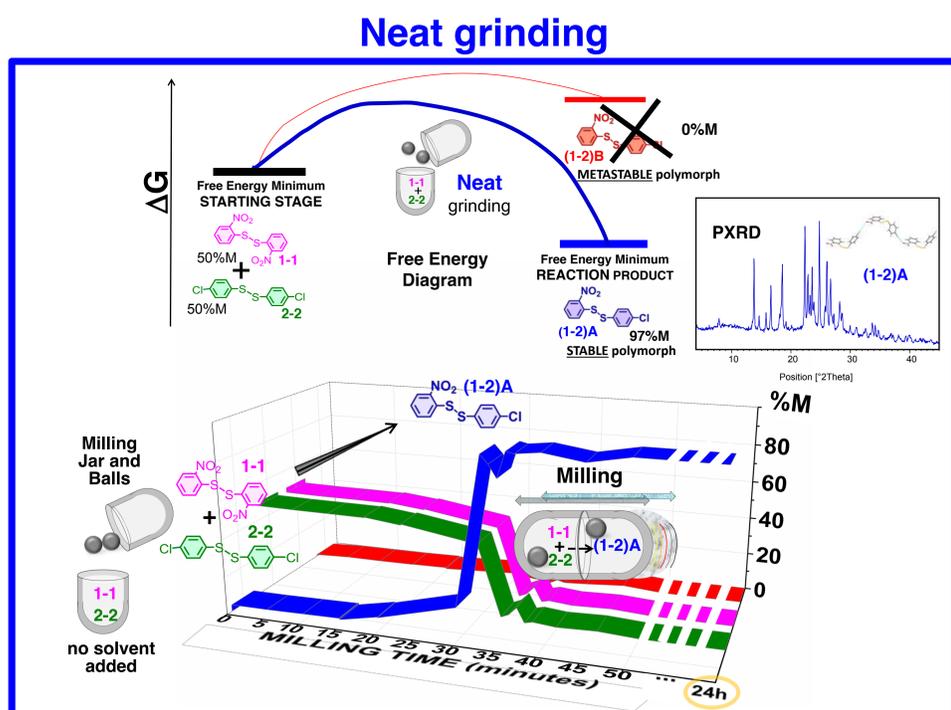
Dynamic covalent chemistry (DCC) is a powerful tool for generating new structures and studying systems chemistry driven by thermodynamics, generally in solution¹. We have recently been exploring solid-state DCC utilizing ball mill grinding technology² and have discovered that the outcome of a reaction is determined by the relative thermodynamic stabilities of the crystalline library members, yielding completely different outcomes to that obtained with the same DCC library equilibrated in solution³



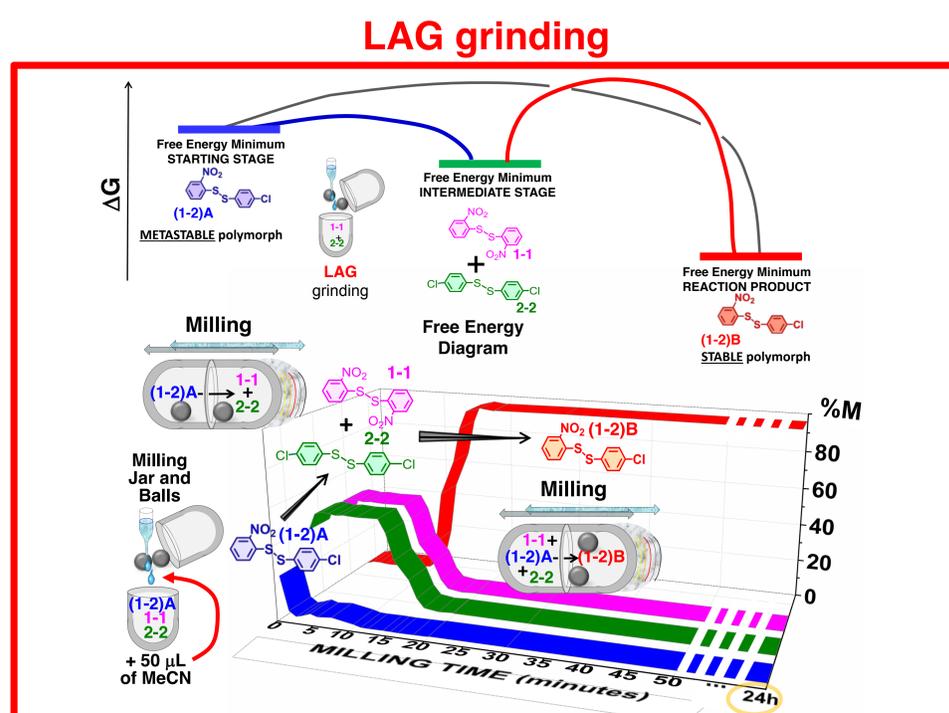
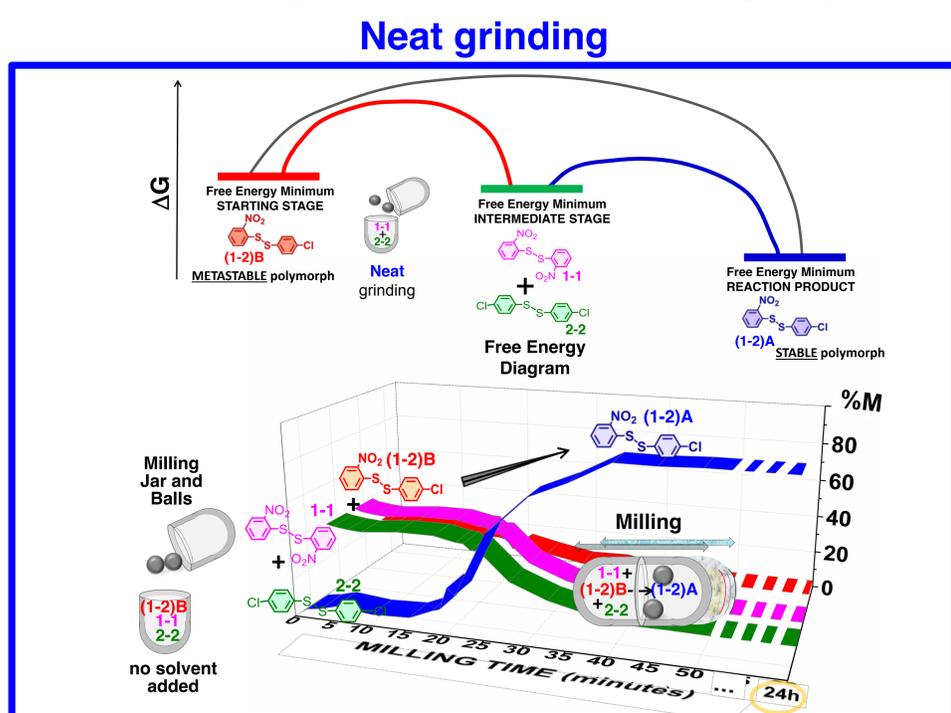
We present here the first polymorph interconversion study using solid-state DCC. This system exhibits unexpected and rich behavior, including the observation that under appropriate conditions the interconversion of two polymorphs proceeds through covalent chemistry: the starting material undergoes a disulfide exchange reaction to generate intermediates that undergo further reaction to yield a different polymorph of the original. Furthermore, this route is facilitated by one of the two intermediates. The chemical composition has been analysed by HPLC while the solid state composition has been obtained by the Rietveld refinement of PXRD data.



Solid-state DCC synthesis: stable and metastable polymorphs of 1-2 heterodimer under Neat and LAG conditions



Seeding with metastable polymorph: remarkable kinetic observations



Conclusions

- Solid-state DCC experiments are highly reproducible as analysed by HPLC and Rietveld refinement of PXRD patterns which are in excellent agreement.
- The milling process produces nanosized crystals. At high surface/volume ratio the contribution of the surface solvated structure to the stability of a certain polymorph is significant. While at the microsize (1-2)B is the stable polymorph (slurry experiments), at the nanosize (milling) the experimental conditions dictates the selection of which polymorph is formed.
 - Under Neat grinding conditions (no added solvent) polymorph (1-2)A is always exclusively formed.
 - Under LAG conditions (50 μ L MeCN) polymorph (1-2)B is always exclusively formed.
- On milling, the **metastable** polymorph is **always** transformed into the **stable** polymorph.
- This **metastable** to **stable** polymorph transformation occurs through two simultaneous and competing routes: (a) straightforward polymorph interconversion; (b) sequential polymorph interconversion through reversible covalent chemistry intermediates (i.e. 1-1 and 2-2).
- The experimental results can be explained **only** by a balance between kinetic and thermodynamic control.

Acknowledgements

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