DETERMINING MOLECULAR CONFORMATION IN ORGANIC CRYSTALS USING COMBINED SOLID STATE NMR – CRYSTAL STRUCTURE PREDICTION (CSP) APPROACH

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Many organic crystals are notoriously challenging to characterize structurally at the atomic level due to their tendency to crystallize as microcrystalline powder. Here, we demonstrate the benefits and limitations of using crystal structure prediction (CSP) calculations in combination with solid-state NMR spectroscopy to fully describe crystalline structures of so far uncharacterized polymorphic forms of pharmaceutical-like systems. Such molecules usually display fairly high level of flexibility, resulting in a large number of possible molecular conformations which have to be accounted for in a CSP search.[1] While solid-state NMR spectroscopy can successfully assist in limiting this search space, a bunch of ambiguities in the interpretation of experimental data often lessens its usefulness. We show how a combined theoretical and experimental approach used in a step-by-step manner helps in circumventing the disadvantages of each of the methods alone. With it, we were able to describe polymorphic forms of furazidin and meloxicam,[2] as well as of two new cocrystals of linezolid (Figure 1a) and of a monohydrate of a cyclic dipeptide (Figure 1b). Using this set of examples, together with cases in which the CSP-NMR approach failed to deliver a decisive answer, lessons can be learned about the existing boundaries and weak points of this method.

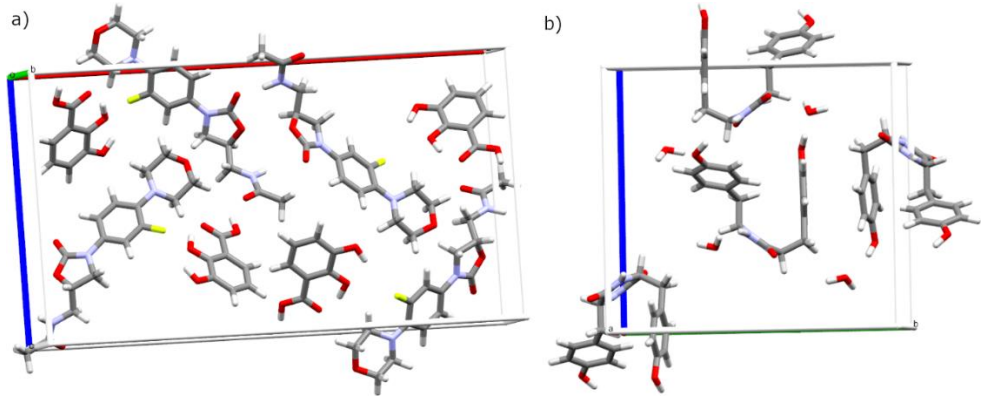

Figure 1. Crystal structures of linezolid:2,3-dihydroxybenzoic acid cocrystal (a) and a monohydrate of cyclic-L-Tyr-L-Tyr dipeptide revealed by combined solid-state NMR – crystal structure prediction approach.

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REFERENCES

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[2] M. K. Dudek , P. Paluch, E. Pindelska, *Acta Cryst. B* **2020**, 76, 322–335.