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Co-crystal or salt? A cautionary tale when inferring proton disorder solely from X-ray and computational data

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We can define cocrystals and salts by considering if a proton has transferred between the acid and base components in a structure.[1] In a cocrystal, the proton stays on the acid. While in a salt, the proton transfers to the base. Despite this, as Childs et al. (2007) state in their paper on the "*salt-cocrystal continuum*": "*the extent of proton transfer in the solid state is not predictable and a continuum exists between the two extremes.*"[1]

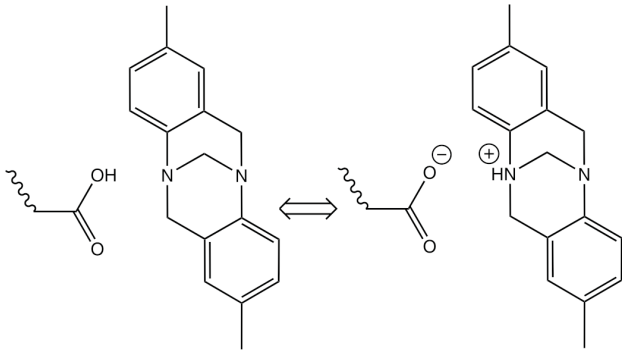
During the `sixth blind test of organic crystal structure prediction methods' (Reilly et al. 2016), one of the target structures was a 1:1 cocrystal of 3,5-dinitrobenzoic acid and Tröger's base (3,5-DNBA:TB).[2] All 14 predictions of the structure of 3,5-DNBA:TB predicted a cocrystal.[2]

However, following this blind test further X-ray data of 3,5-DNBA:TB were collected by Wheeler & Breen (2016*b*).[3] This provided evidence that the proton may in fact be disordered over two sites.[2] Reilly et al. (2016) states that: "*More variable-temperature studies and neutron diffraction may resolve whether the proton disorder is a dynamic, temperature-related effect.*"[2]

To study this potential hydrogen disorder, an accurate determination of the hydrogen atom positions is required. Therefore, we collected Laue neutron single crystal diffraction data, at 150 K on the KOALA Laue diffractometer at the Australian Centre for Neutron Scattering.

Laue neutron data are presented, showing that the proton being examined is not disordered over two sites. The Fourier difference map shows clear single site occupancy of the hydrogen closer to the oxygen atom. This demonstrates the need for neutron data to confirm or deny whether a hydrogen is disordered or not.

Further Laue neutron data were collected for a related two-component material, with potential two-site proton disorder based on X-ray data: 1:1 3,5-bis(trifluoromethyl)benzoic acid and Tröger's base (3,5-BTFBA:TB). Again, the Laue neutron data presented show that this proton is not disordered over two sites. Therefore, we recommend that one should be cautious when inferring that a structure contains disordered protons, solely based on X-ray and computational data.



Co-crystal Salt

References:

[1] Childs, S. L. et al. (2007). Mol. Pharmaceutics, 4(3), 323-338.
[2] Reilly, A. M. et al. (2016). Acta Cryst. B72, 439-459.
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