Poster

Rich polymorphic landscape of binary systems of meloxicam with imidazole and pyrazole

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Meloxicam (MLX) is an anti-inflammatory drug used to treat arthritis. It is an interesting molecule prone to form diverse polymorphic forms, solvates, salts with organic and inorganic acids and basis, as well as cocrystals. We have recently reported a reliable and repeatable protocol for the crystallization of three elusive forms of MLX [1], with some of the attempts involving crystallization additives, such as pyrazole (POL) and imidazole (IMI). Here, we report a discovery and crystallization of several new binary phases of MLX with the said additives. Interestingly, only two of those were accessible through solution crystallization, while three remaining forms were obtained either through mechanochemical grinding or melting.

MLX with POL forms two 1:1 cocrystals, form 1, which can be crystallized by slow evaporation from hexafluoroisopropanol or dichloromethane solutions, and form 2, obtained by neat mechanochemical grinding. Both MLX:POL cocrystals can be obtained by heating/melting at different temperatures and at different heating times with different molar ratios of the starting components. For MLX and IMI three different binaries were obtained: 1:1 salt obtained through grinding in the presence of acetonitrile, 1:2 cocrystal obtained by melting, and 1:1 salt-cocrystal, which can be crystallized from dichloroethane (DCE) solution or by grinding in the presence of DCE. ^{15}N and ^{13}C CPMAS NMR measurements allowed for the determination of the protonation states of the coformers, as well as the tautomeric form of MLX present in the crystals.

Interestingly, two crystal structures of MLX:POL cocrystals solved by single crystal X-ray diffraction share a common hydrogen bond motif, with hydrogen atoms located as shown in Figure 1a. However, the respective ^{15}N CPMAS NMR spectra for the two polymorphs are noticeably different (Figure 1b). Calculations of the ^{15}N chemical shielding constants for both crystal forms using periodic DFT enabled to reconcile these differences. In form 2 the protonation state seen in the NMR experiment is in agreement with the structure solution from scXRD, but in form 1 there is an exchange between two tautomeric forms, taking place in the NMR timescale, but invisible for the X-ray diffraction experiment.

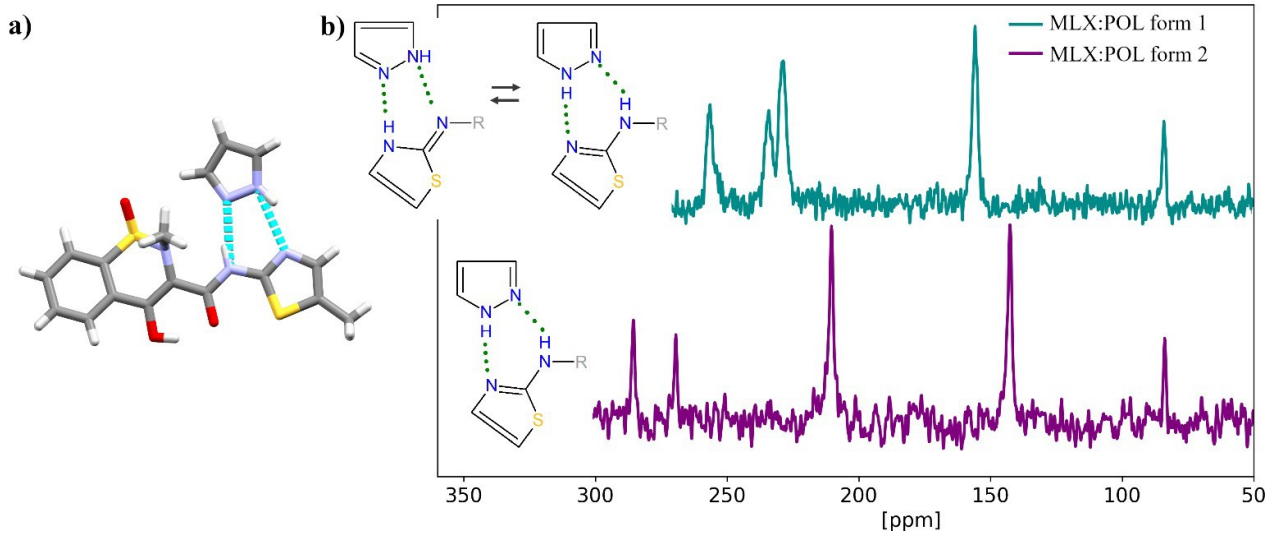

Figure 1. a) Hydrogen bond motif observed in both polymorphs of MLX:POL cocrystal; (b) ^{15}N CPMAS NMR spectra for MLX:POL cocrystals together with the corresponding protonation states of two interacting molecules.

[1] Jeziorna, A., Paluch, P., Zając, J., Dolot, R. & Dudek, M. K. (2023). *Cryst. Growth Des.*, **23**, 5998.

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