CrystEngComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *CrystEngComm*, 2019, **21**, 1091

Received 7th November 2018,
Accepted 3rd January 2019

DOI: 10.1039/c8ce01911h

rsc.li/crystengcomm

Multicomponent crystals of nitrofurazone – when more is less†

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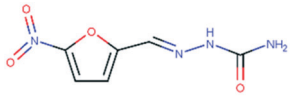
Multicomponent crystal formation of nitrofurazone, a conformationally flexible drug that is capable of forming various supramolecular synthons, was challenging when coformers were selected based on popular crystal engineering principles.

Multicomponent crystal (MCC) formation[1] of a drug, during which the molecular structure of the active pharmaceutical ingredient (API) stays intact, may lead to new solid forms of the API with improved pharmacokinetic profiles.[2] Many factors are important in MCC formation, but the most probable ones are the ability of the molecules to form supramolecular synthons with one another (preferably *via* hydrogen or halogen bonds) and similarity in shape/size and polarity.[3] Even though these guiding principles are widely accepted and applied in MCC design, their true success rate is unknown because of the scarcity of published discussions of failed cocrystallisation attempts.[4]

Nitrofurazone (5-nitro-2-furaldehydesemicarbazone, NFZ) is a broad-spectrum bactericidal with antiprotozoal and antiparasitic activities, generally administered as an alcohol solution or water soluble ointment for fresh wound treatments of domestic animals.[5] Currently, three polymorphs of NFZ are known. The first, described by Olszak *et al.*, is the α-polymorph.[6] (Cambridge Structural Database, CSD, v5.39, February 2018 (ref. 7) reference: WERVEU). Recently, Pogoda *et al.* reported the β- and γ-polymorph (WERVEU01 and WERVEU02, respectively).[8]

The polymorphic nature of NFZ represents its ability to adopt alternative packing arrangements *via* forming different synthons, and thus suggests that NFZ is potentially a good cocrystal former.[9] Its ruthenium(II) complex was synthetized and showed increased activity against Chagas disease.[10] This promising modification of the drug, the scarcity of its solid state structures and the abundance of hydrogen bonding sites of the molecule (three strong and three weaker hydrogen bond donors and five acceptors,[11] Scheme 1) directed our attention to an investigation of possible MCC formations with NFZ.

Synthon engineering principles[12] were used to (i) select a series of possible coformers with complementary functional groups to form cocrystals or molecular salts *via* the semicarbazone chain, and (ii) identify strong mineral acids to protonate the semicarbazone group and form mineral salts.[13] A CSD search, which focused on the semicarbazone chain and its fragments, was carried out and the results were analysed, with the aid of Mercury (v. 3.10.2 CSD Materials[14]), in order to investigate the intermolecular interaction preferences of NFZ. (ESI,† Scheme S1) Firstly, a general search was conducted for the occurrence of carbonyl, amine, amide, urea and semicarbazone moieties as well as the whole NFZ molecule, with certain restrictions (3D coordinates determined, no errors, only single crystal structures, not polymeric and only organics, results are shown in Scheme S2†). Then, the occurrence of synthons formed by the amide, the semicarbazone chain or the whole NFZ molecule with amides, carboxylic acids, alcohols, carbonyls and ethers was recorded (Scheme S3†). The search showed that carboxylic acids and amides can hydrogen bond to both the terminal and the vicinal amide of the semicarbazone moiety, thus experimental work was focussed on the amide–amide[15] and amide–carboxylic acid synthons,[16] using a series of carboxylic acids and substituted amides as coformers. The



Scheme 1 Nitrofurazone (5-nitro-2-furaldehydesemicarbazone, NFZ).

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† Electronic supplementary information (ESI) available: Contains full results of CSD search and experimental details of XRD, TG, DSC, FTIR analysis. Structural data for single crystals were deposited under CCDC 1877008–1877010. Results of conformational analysis and computational work are included. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8ce01911h

CSD search also indicated possible synthon formation between the NFZ molecule and typical organic solvent molecules with hydrogen bond donor or acceptor functionalities. However, all these crystallisation attempts resulted in the formation of polymorphs α, β or γ, exclusively (Table S1†).‡ It is interesting to note that, in these structures, the NFZ molecules form a variety of non-centrosymmetric synthons amongst the semicarbazone chains (Fig. S1†). Thus, the coformer should have the ability to compete with the formation of these favoured amide synthons. Therefore, strong mineral acids were also applied as coformers (Table S3†).[17] Eventually, crystallisation of NFZ with perchloric acid (chloric(VII) acid, $HClO_4$), phosphoric acid (phosphoric(V) acid, H_3PO_4), and propionic acid (propanoic acid, C_2H_5COOH) resulted in multicomponent crystals.

MCCs of NFZ

The single crystal data for the three multicomponent crystals 4NFZ·$[H_3O^+][ClO_4^-]$, NFZ·H_3PO_4 and NFZ·PA are summarized in Table S4† and their bulk properties were analysed using PXRD, DSC, TGA and FTIR spectroscopy (details are given in the ESI†).

Poor quality crystals of 4NFZ·$[H_3O^+][ClO_4^-]$ were obtained after 3 months (Fig. S2†). The compound crystallised in the triclinic $P\bar{1}$ space group with four NFZ molecules, one H_3O^+ ion and one ClO_4^- ion in the asymmetric unit. The acid donated its proton to a water molecule and subsequently formed a hydronium ion. The four symmetrically independent NFZ molecules form a virtually 4-fold arrangement around the hydronium ion (Fig. 1a). The molecular units of NFZ are labelled A, B, C and D in the ASU. The four NFZ molecules hydrogen bond together *via* four N15–H15···O13 interactions that may be described by the $R_4^4(16)$ graph set. The central hydronium ion also hydrogen bonds to each NFZ molecule forming $R_3^2(8)$ synthons.

The four, almost coplanar NFZ molecules and the hydrogen bonded hydronium ion, dubbed as the tetramer, is the basic building unit of the crystal. The neighbouring tetramers are coplanar and held together *via* hydrogen bonds formed between the nitro oxygen atoms and the semicarbazone moieties, N11–H11···O2, described by the $R_2^2(18)$ graph set (Fig. 1b). Relevant hydrogen bonds are listed in Table S5.† The perchlorate anions are embedded between the tetramer's tails, but no strong hydrogen bonds are observed between the ions and the surrounding molecules (Fig. 1c). The major structural function of the ClO_4^- anions is to connect the layers of tetramers together in the third dimension *via* weak hydrogen bonds (Fig. 1d).

The formation of 4NFZ·$[H_3O^+][ClO_4^-]$ was unexpected for multiple reasons. Firstly, based on the pK_a difference between $HClO_4$ (p$K_a \approx -10$) and NFZ (pK_a = 11.79),[18] proton transfer was expected to happen.[19] Hence, the crystallisation was carried out in dilute acid that contains water. Protonation of the water molecule was not surprising, because water is a stronger base than NFZ. The other interesting feature of the 4NFZ·$[H_3O^+][ClO_4^-]$ structure is its unusual stoichiometry and unique combination of Z', Z'' and Z^r values (1, 6 and 3, respectively).[20]

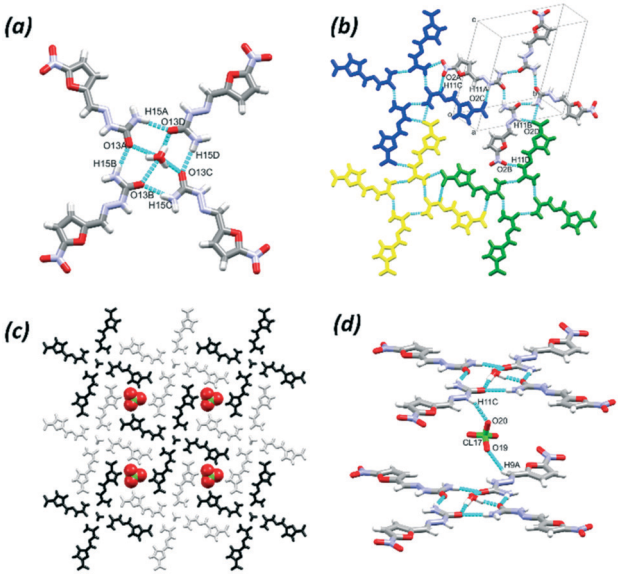

Fig. 1 ASU of 4NFZ·$[H_3O^+][ClO_4^-]$ without the perchlorate ion (a), hydrogen bonds between the neighbouring NFZ molecules to hold the tetramers together (b), embedded perchlorate ions in the layer of tetramers are presented in space fill (c) and hydrogen bonding of ClO_4^- between the layers of tetramers (d).

Crystals of NFZ·H_3PO_4 were obtained after 4 months. Unlike the perchlorate cocrystal salt, NFZ·H_3PO_4 crystals are elongated, not clustered, and their brittleness is observed when handled (Fig. S3†). The compound crystallised in the triclinic $P\bar{1}$ space group with one NFZ and one phosphoric acid molecule in the ASU (Fig. 2a). Obtaining NFZ·H_3PO_4 in its current form, *i.e.* a solvate, was also unexpected since the pK_a difference between the phosphoric acid (pK_a = 2.02) and the NFZ (ΔpK_a = 9.77) does suggest salt formation. More interestingly, the crystallisation was carried out in dilute acid, thus, we expected a similar chemical outcome seen in the 4NFZ·$[H_3O^+][ClO_4^-]$ structure. The typical amide–amide synthon formation was blocked by the inclusion of the phosphoric acid and O18–H18···O13 and N14–H15···O19 hydrogen bonds were formed, creating $R_2^2(8)$ synthons. Conversely, *via* N11–H11···O13 interactions, an amide dimer formed with the aid of the hydrazone moiety between the neighbouring NFZ molecules. The coplanarity of the neighbouring NFZ molecules gave rise to quadruple hydrogen bond formation between the adjacent NFZ·H_3PO_4 units with the aid of C9–H9···O18 hydrogen bonds. The other prominent contacts formed between adjacent NFZ molecules are the hydrogen bonds between the nitro and the amine functional group *via* an N14–H15···O3 interaction, with less ideal geometry, and an N14–H14···O2 interaction (Fig. 2b). The sheets of NFZ molecules are bonded together *via* phosphoric acid dimers formed *via* O19–H19···O17 interactions (Fig. 2c). Details of the hydrogen bonds are shown in Table S6.† The packing of NFZ·H_3PO_4 is layered, as a consequence of the planar molecular shape, and the role

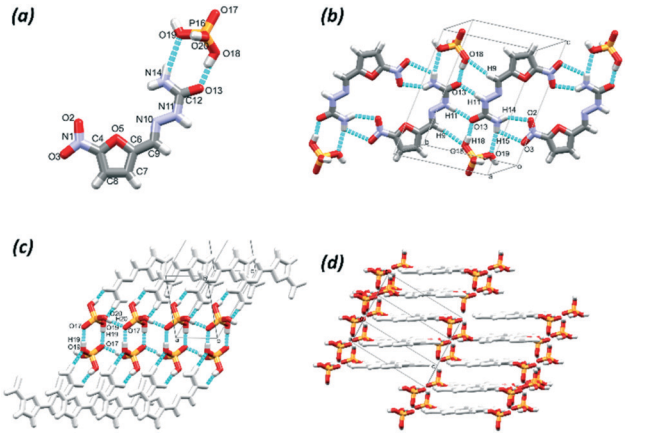

Fig. 2 The ASU of NFZ·H_3PO_4 (a), hydrogen bonding between the coplanar NFZ molecules and the adjacent phosphoric acids (b), hydrogen bonding between adjacent phosphoric acid molecules (c) and the packing showing the layered nature of the structure (d).

of the phosphoric acids is to connect the planar structures in the third dimension. (Fig. 3d).

Crystals of NFZ·PA were obtained after a longer period (*ca.* 5–7 months). They appear to have a rectangular morphology with a dark brown colouration (Fig. S4†). The compound crystallised in the $P2_1/c$ space group with four symmetrically independent NFZ and PA molecules in the ASU (Fig. 3a) with no proton transfer observed. The ASU may be divided into two sections that contain two NFZs and two PA molecules, each based on the connective hydrogen bonds. These NFZ pairs form dimers with each other through the terminal amide groups *via* N14A–H14B···O13B and N14B–H14D···O13A interactions between molecules A and B, and N14C–H14F···O13D and N14D–H14G···O13C contacts between molecules C and D, respectively. Also, each of the NFZ molecules form vicinal amide–acid heterosynthons with one PA *via* the respective O15–H15···O13 and N11–H11···O17 hydrogen bonds. Therefore, the ASU may be subdivided into two tetrameric units, each formed from two hydrogen-bonded NFZ molecules and two related PA molecules. Three additional interactions were noted between molecules A and C (C7A–H7A···O2C and N14A–H14A···O3C) as well as between molecule C and the PA molecule related to B (C8C–H8C···O15B(PA)). The NFZ·PA structure, similar to 4NFZ·[H_3O^+][ClO_4^-], has unusual stoichiometry and a unique combination of Z', Z'' and Z^r values (4, 6 and 2, respectively). The geometric details of the most prominent intermolecular interactions are listed in Table S7.† The tetramers form sheets in the *ac* plane (Fig. 3b), but no strong interactions can be found between the parallel layers (Fig. 3c). The layered nature of this structure is a plausible explanation for why the crystallisation of the NFZ·PA crystals was extremely time consuming and challenging.

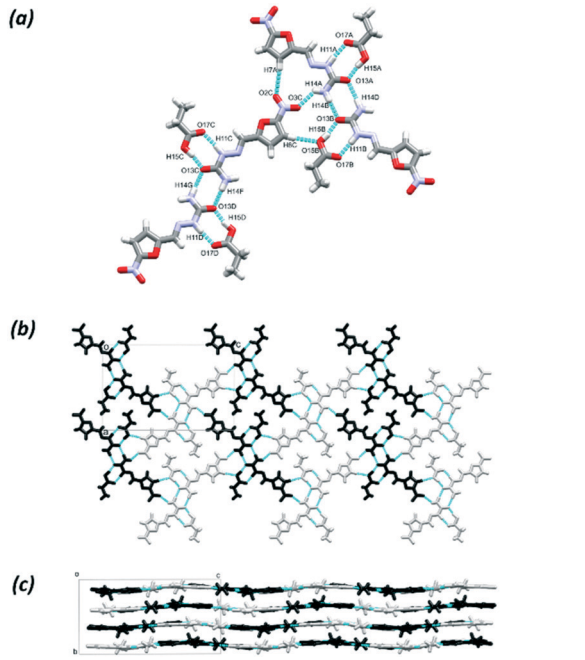

Fig. 3 ASU of NFZ·PA (a), packing of hydrogen bonded tetramers viewed down *b* (b) and down *a* (c).

The NFZ conformers observed in these three structures are planar and tend to form hydrogen bonds in the plane of the molecule. Therefore, growing crystals, *i.e.* 3D structures, can be challenging if there are no functional groups that would form interactions into the third dimension.

In the case of 4NFZ·[H_3O^+][ClO_4^-], the perchlorate anion is linking the layers of NFZ molecules in the third dimension. The same role may be described for the phosphoric acid molecules in NFZ·H_3PO_4. In the NFZ·PA crystal the layers are held together by weak interactions only. PA is the only carboxylic acid that successfully competed with the amide dimer formation and formed an MCC with NFZ. To further understand this outcome, interaction energies for synthons formed in the polymorphs and NFZ·PA were calculated§ [21–29] and compared to fragments taken from the crystal structures (Fig. S5†). The strongest interaction was found when NFZ hydrogen bonds to the PA molecule. The stability of the vicinal amide–acid synthon, the one observed in NFZ·PA, was more obvious after geometry optimization (Fig. S6†). This would suggest that the formation of this synthon may be preferred over the amide–amide homosynthon, and subsequently support our initial idea of using carboxylic acids as coformers for NFZ.

Conformational analysis

The known crystal forms of NFZ represent well the conformational flexibility of the molecule. To understand if this carries any advantage during MCC formation, conformational analysis was carried out with the aid of the CSD and DFT computations.

The conformation of the semicarbazone moiety can be described by three torsion angles (τ_1: O5–C6–C9–H9, τ_2: H9–C9···N11–H11 and τ_3: H11–N11···N14–H14, Fig. S7†). Because of the planar nature of the NFZ molecule, the most prominent descriptors occurring in our analysis are *synperiplanar*

(*sp*) and *antiperiplanar* (*ap*);[30] the combination of the three torsion angles gave 8 possible molecular conformers for NFZ. The α-polymorph has the *ap-sp-sp* conformer while the γ- and β-polymorphs are built from the *sp-sp-ap* conformer. (Table S8†) All four independent NFZ molecules in 4NFZ·[H_3O^+][ClO_4^-] and NFZ·PA crystallised in the *sp-sp-ap* conformation. However, the conformation of NFZ in the NFZ·H_3PO_4 crystal structure can be classified as *ap-sp-ap*. These descriptors reveal the appearance of a new molecular conformation of NFZ that was not observed before in any of its crystal structures. To evaluate the occurrence of this conformation in semicarbazone chains, geometrical data of this moiety was collected by searching the CSD with the aid of ConQuest[31] (applied criteria: only single crystal structures, 3D coordinates determined, no errors, not polymeric and only organic structures). Sixty structures, with 166 motifs were found, listed in Table S9† and summarized in Fig. 4. The most popular combination of the torsion angles was the *sp-sp-ap* conformer and the second most popular conformer was *ap-sp-ap*. The currently known NFZ structures fit well into this distribution. The occurrence of the relatively popular *ap-sp-ap* conformer in NFZ·H_3PO_4, combined with the multipotent hydrogen bonding potential of the molecule, can be an indication of the existence of another polymorphic form of NFZ (It was noted that during the crystallisations, in some cases, the DSC and the PXRD analysis of the obtained solid forms indicated the formation of polymorphic mixtures and occasionally the solid forms could not be identified as any of the known polymorphs or their mixtures.[32])

The solid state findings were tested by conducting conformational analysis of the NFZ molecule with gas phase DFT calculations.§[21–29] The 8 lowest energy conformers and their relative energies are shown in Fig. S8.† The *sp-sp-ap* conformer, which was observed in polymorphs β and γ as well as in two of the MCCs and concurrently showed the highest occurrence in the CSD (Fig. 4), was found to have the lowest relative energy. The energy of the *ap-sp-ap* conformer had the second lowest energy and this conformation of the semicarbazone moiety was observed in 38 of the 166 hits as well as in NFZ·H_3PO_4. The *ap-sp-sp* conformer had the highest energy of the pool of conformers calculated. This conformer appears in the α-form that is particularly difficult to obtain, and had a significantly lower occurrence in the CSD. (It has to be noted that a recent study by Thompson and Day[33] showed that molecules with large conformational flexibility often adopt high energy conformers when crystallising and compensate the energetically unfavoured conformation with the formation of inter- and intramolecular interactions.)

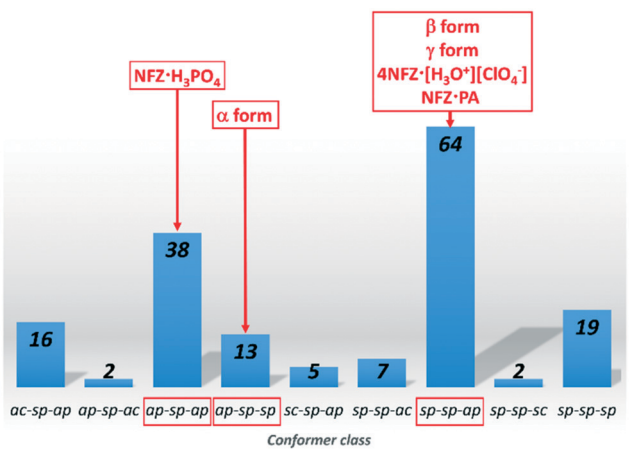

Fig. 4 Distribution of conformer classes of the semicarbazone moiety.

Conclusions

At first sight, nitrofurazone is an ideal compound to be used for multicomponent crystal formation because of its multipotent hydrogen bonding ability and conformational flexibility. The three known polymorphs are good representations of these properties. As it turns out, the two listed properties are more likely limiting factors in the case of NFZ.

The CSD search and the large amount of failed multicomponent crystal formation experiments support the observation that complex molecules with many hydrogen bonding possibilities may exhibit highly unpredictable behaviour during cocrystallisation experiments.[4,34] Also, the conformational flexibility does not add any advantage to the crystallisation in the case of NFZ, because it results in the formation of mainly planar molecules that are notoriously difficult to crystallise.[32] Successful cocrystallisations of NFZ happened only when coformers with the ability to form strong interactions in the third dimension ($HClO_4$ and H_3PO_4) were applied. The excessively time consuming crystallisation of NFZ·PA represents the challenges when layered structures are formed. The observed unique crystallographic descriptors (Z', Z'' and Z^r) for 4NFZ·[H_3O^+][ClO_4^-] and NFZ·PA suggest a problematic crystallisation process of these molecules in three dimensions.[20]

Conflicts of interest

The authors declare that they have no conflict of interest.

Acknowledgements

The financial assistance of the National Research Foundation (NRF Pretoria, South Africa, Unique Grant Numbers 105969 and 115091) towards this research is hereby acknowledged. Opinions expressed and conclusions arrived at, are those of the authors and are not necessarily to be attributed to the NRF. The authors acknowledge the Centre for High Performance Computing (CHPC), South Africa, for providing computational resources to this research project.

Notes and references

‡ The structures of the β and the γ-polymorphs were recollected at 173 K and were deposited to the CSD for completeness (CCDC 1877436–1877437). The room temperature WERVEU, WERVEU01 and WERVEU02 structures and the low temperature crystal structures of the polymorphs, labelled as β-LT and γ-LT, respectively, (Table S2†) are basically the same.

§ All density functional theory (DFT) calculations were done using ORCA 4.0.[21] Single molecule conformers and synthons not present in the crystal structures were optimized using the PBE0 (ref. 22) hybrid density functional and the def2-TZVP basis set.[23] The D3 dispersion correction of Grimme with the Becke–Johnson damping function was added.[24] This level of theory is denoted as PBE0-D3(BJ)/def2-TZVP. The resolution of identity approximation was applied to Coulomb integrals (RI-J), using the universal def2 auxiliary basis set of Weigend.[25] HF exchange was calculated numerically using the chain-of-spheres algorithm (RIJCOSX).[26] All optimized structures were local minima (confirmed through the absence of imaginary frequencies in the vibrational spectrum). Synthon fragments taken from the crystal structure were used directly without further optimization. Conformational energies were calculated using the spin-component-scaled, double hybrid, dispersion corrected DSD-PBEP86 (ref. 27) functional with the large def2-QZVPP basis set.[23] Coulomb and exchange integrals (RIJK), as well as two-electron integrals involved in calculation of the perturbative correction to the correlation energy, were approximated using the appropriate auxiliary basis sets.[28] Interaction energies were also calculated at the DSD-PBEP86/def2-QZVPP level of theory using the approximations described above and corrected for the basis set superposition error (BSSE) using the counterpoise procedure.[29]

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