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Crystal-stabilisation of an elusive 4,6-pyrimidinedione dimer

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Abstract—The formation of a disproportionation dimer of 4,6-pyrimidinedione **1**, 2-(4,6-dioxo-5-pyrimidinyl)-4,6-dioxo-1,2,3,5,5-pentahydropyrimidine **2**, results from the reactivity of the inner-salt tautomers or ions of **1**, contrasting to the general properties of nucleobases which are all stable in the lactam or dilactam molecular forms. The observation of dimer **2**, indefinitely stable in the crystalline state, reveals an unusual chemical reactivity strongly dependent on the H-tautomeric forms of the substrate and product.

The tautomeric conversions of nucleobases are of crucial importance for their chemical and biological functions. This particularly concerns the behaviour of natural pyrimidines,[1,2] their role for base-pair matching, mutations,[3] DNA repair, activity of enzymes[4] and their agricultural[5] or pharmaceutical applications.[6] In order to better understand the reactions specifically related to tautomeric transformations, we have studied the reactivity of a nucleobase analogue which cannot assume a dilactam form. Recently, we have shown that 4,6-dihydroxypyrimidine **1**, an analogue of uracil (2,4-dihydroxypyrimidine), crystallises from aqueous solution at room temperature in molecular and ionic polymorphs.[7] In polymorph **1**α, the molecules are in the lactam–lactim form, while in the unprecedented ionic polymorph **1**β, division of the molecules into cations and anions was observed. The conversion into ions can be regarded as a first step leading to the dimerisation reaction of **1**. Here, we report on its product — a disproportionation dimer, which until now has not been observed. Its occurrence throws new light on the reactivity and transformations of 4,6-pyrimidinedione tautomers, their possible functions, properties, as well as formation of higher aggregates. The molecular structure of the dimer is unusual and intriguing, and it has been observed only in the solid state, in which it is very stable. It illustrates the role of crystal-environment and hydrogen-bonding for the formation and stabilisation of otherwise unstable molecules.

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Polymorphs **1**α and **1**β can serve as a text-book example of the structure-correlation method:[8] the ionisation of **1**β results from instabilities of molecules **1** preceding their imminent dimerisation. The electrostatic attraction of ions in solution should promote the reaction. Indeed, when recrystallizing **1** from aqueous solution we have found long and very thin pale-yellow or colourless needles occasionally appearing. The habit of these new crystals was clearly different from those of polymorphs **1**α and **1**β: yellow skew monoclinic prisms, and orange plates with sphenoidal habit, respectively. Moreover, by exposing an aqueous solution of **1** directly to sunlight, we managed to obtain a 100% yield of these needles. Their structure determined by X-ray crystallography,[9] revealed that they are semi-hydrated dimers of **1**: 2-(4,6-dioxo-5-pyrimidinyl)-4,6-dioxo-1,2,3,5,5-pentahydropyrimidine **2**, as shown in Figure 1.

The extraordinary feature of **2** is that it reveals two different reaction sites of the identical substrate monomers, and that the dimer is disproportionated ($C_4H_5N_2O_2$)–($C_4H_3N_2O_2$) with one moiety zwitterionic. This structure appears to be a natural consequence of the ionic forms of molecule **1** observed in the solid state,[7] or of the inner-salt of **1** occurring in aqueous solution.[10] The forms observed in polymorphs **1**α and **1**β can be regarded as a means of realisation of the crystal packing involving the OH–O and NH–N hydrogen bonds of molecules **1**. The preference for the inner-salt form arises essentially from the linked amide and cyclic β-diketone units, which separately would possess a pK_a greater than 12, and pK_a less than 6, respectively. Thus, an inner salt is the prevailing form of any α-amino acid in general,

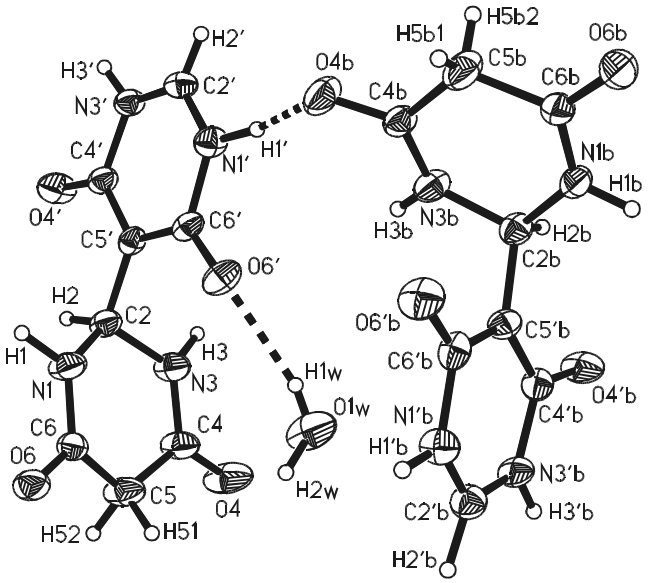
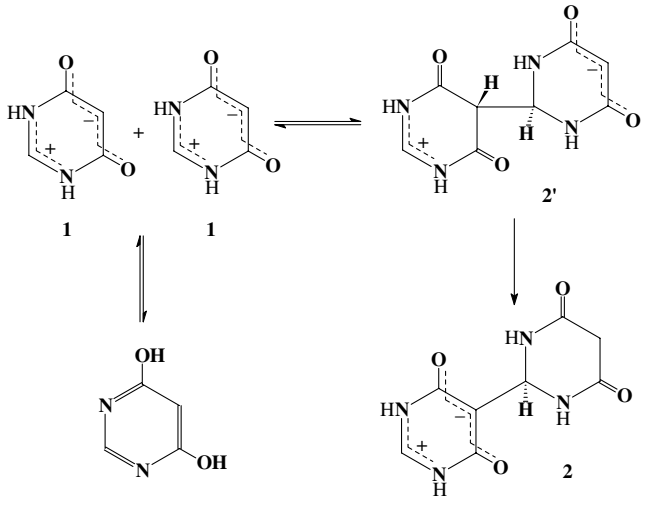


Figure 1. The asymmetric part of the unit cell of the $\mathbf{2}\cdot\frac{1}{2}H_2O$ crystal consists of two dimers **2** and one H_2O molecule. Only two of numerous hydrogen bonds (see the text) have been shown as dashed lines.

and specifically of **1**, in aqueous solution. Therefore the reaction path leading to dimer **2**, postulated in Scheme 1, starts from the inner salt of **1**. The amidine and malonyl carbons of the inner-salt molecules **1** would be attracted electrostatically and their proximity would lead to the formation of the C5′–C2 covalent bond binding the monomers. The formation of this covalent bond in the postulated manner implies the intermediacy of **2′** (Scheme 1). The formation of the C5′–C2 bond compensates the charges of the bonded amidine and malonyl carbons; however, due to the opposite charges at the transannular remote carbons, dimer **2′** retains the inner salt character, and a very high dipole moment. The dipole moment can be considerably reduced, from about 32 D (estimated for the extended molecular conformation observed in the crystal), to 13 D (107×10^{-30}–43×10^{-30} cm, respectively), if the H-atom from C5′ transfers to C5 and in this way the disproportionation dimer **2** observed in the crystalline state is formed.



Scheme 1. Reaction path of 4,6-pyrimidinedione **1** dimerisation, leading to the large dipole-moment dimer **2′**, and then its conversion to the low dipole-moment H-tautomer **2**.

Analogous reactions could lead to trimer, tetramer and higher aggregates of **1**; however, only dimer **2** has been evidenced. Moreover, dimer **2** is stable only in the crystalline form, suggesting that the dimerisation may be a topochemical reaction on the crystal surface.

Compound **2** is very stable in the crystalline state, and it has existed in this form for over two years in our laboratories, and resisted an elevated temperature of 200 °C for hours. However, in mass spectrometry, only traces of **2** were detected in *m*-nitrobenzyl alcohol, glycerol and triethanolamine solutions.[11] Moreover, apart from **1**, in equilibrium the protonated $(\mathbf{1}+H)^+$ and deprotonated $(\mathbf{1}-H)^-$ ions were also identified in D_2O by ^1H NMR spectroscopy, but dimer **2** was not considered at that time.[12] Our ^1H NMR and ^{13}C NMR high resolution studies revealed no differences in the spectra between the solutions obtained by dissolving **1**α, **1**β and **2**. At the same time, **2** on reaction with $POCl_3$ or methylation with Me_2SO_4 gave the same products as were obtained from chlorination or methylation of **1**. While the formation of dimer **2** can be readily monitored by solid-state IR, either in KBr pellets or Nujol suspension (Fig. 2), no differences in the IR spectra were noted between dissolved **1**α, **1**β and **2**.

Thus the factors stabilising the structure of dimer **2** appear to be inherent to its crystal structure. The crystal structures of polymorphs **1**α and **1**β apparently differ from solvate $\mathbf{2}\cdot\frac{1}{2}H_2O$ by the types and patterns of H-bonds. Hydrogen bonds OH–O and NH–N are formed in **1**α and **1**β, while the dimer **2** molecules are each sixfold NH–O bonded to other dimers, and the water molecule is threefold OH–O and single NH–O bonded to the dimers (Fig. 3). Thus, heteronuclear NH–O hydrogen bonds prevail in **2**, which is a consequence of the lactam tautomeric form of each dimer, and its four >NH amine H-donor and four =O ketone H-acceptor sites.

One dimer **2** molecule forms eight hydrogen bonds in the crystal, and each of its moieties is involved in four H-bonds, as with **1**α and **1**β. It is plausible that the structure of **2** is stabilised both by the strong proton affinity of the nitrogens and by intermolecular NH—O= bonds. Without these H-bonds, O4′ or O6′ could carry a hydrogen, which would lead to the H—O4′—C4′=C5′, or H—O6′—C6′=C5′ moieties, respectively. It appears that their formation would not destabilise the C5′–C2 bond.

The crystal structure of dimer **2** illustrates the conformational properties of the C2–C5′ bond linking the monomers. The mutual positions of the moieties described by torsion angles N1–C2–C5′–C6′ are of 56.7(4)° and 68.9(4)° in two symmetry-independent dimers **2**. The dimensions of the dehydrogenated ring of **2** [e.g., lengths N1′–C6′ and N3′–C4′ of 1.410 Å characteristic for the single N_{sp^2}–C_{sp^2} bonds[13] and the non-planar endocyclic

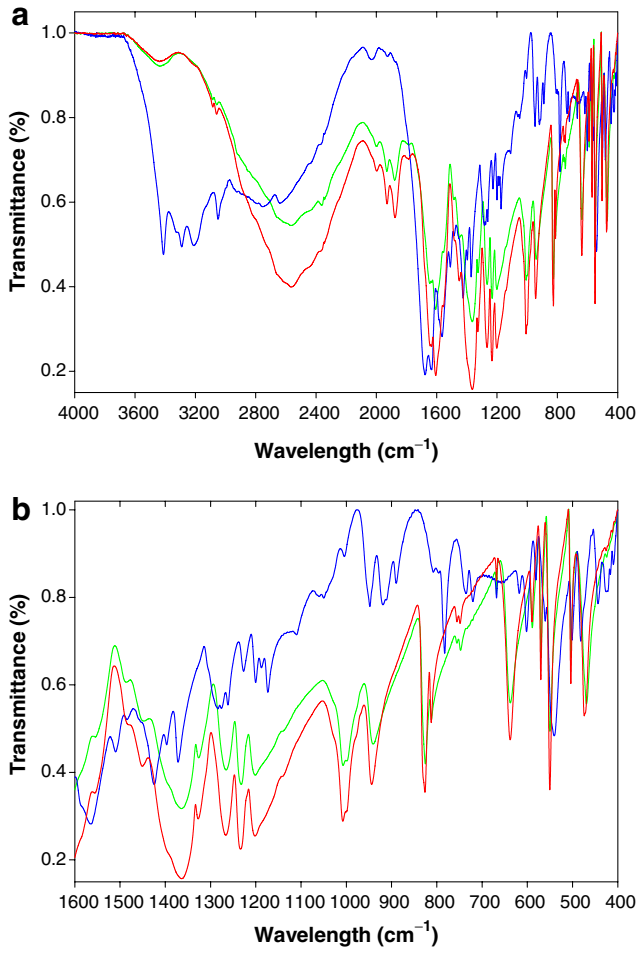


Figure 2. Superimposed FT-IR spectra of polymorphs **1**α (green), **1**β (red) and crystalline **2**·$\frac{1}{2}$H$_2$O (blue), all in KBr pellets (a) and (b) the extended 1600–400 cm^{-1} range of these plots.

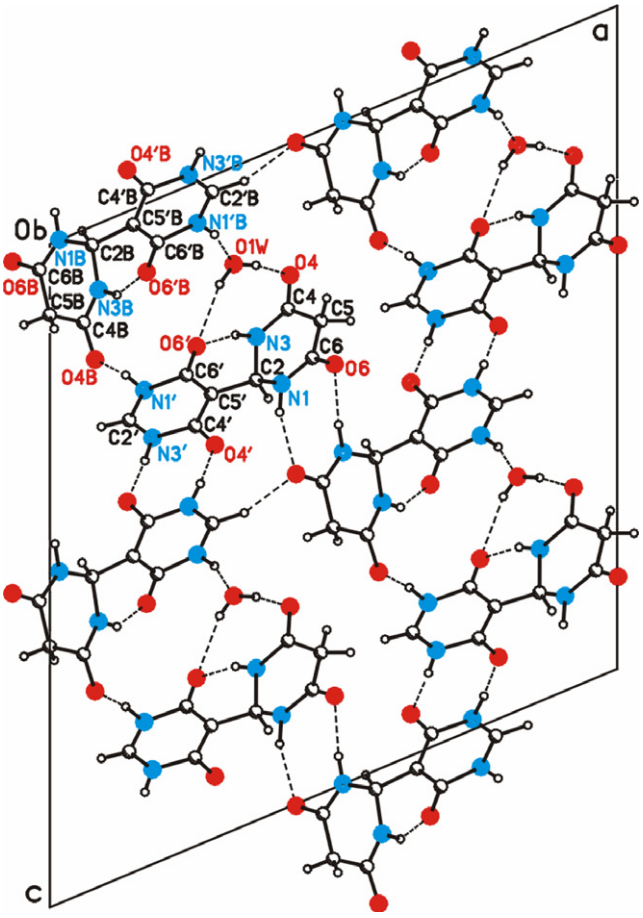


Figure 3. The molecular packing and the hydrogen bonding (dashed lines) in the **2**·$\frac{1}{2}$H$_2$O structure, viewed down the crystal direction [*y*]. The oxygen and nitrogen atoms of the symmetry-independent part of the unit cell have been labelled only.

torsion angle N3′–C4′–C5′–C6′ of 5.6(5)°] indicate that there is a considerable mesoionic[14] contribution to the resonance structure of the ring. The conformations of the hydrated rings can be described as a flattened twist-boat distorted towards a 1,3-diplanar conformation in dimer **2**(a), and a flatter distorted sofa with atom N3 off the ring plane in dimer **2**(b). The N1–C6 and N3–C4 bonds, of 1.320(3) Å, are shortened in the hydrogenated moieties, indicating a partial N_{sp^2}=C_{sp^2} character of these bonds.[13]

Covalently bonded purine-pyrimidine analogues were predicted and synthesised, for example in the structure of 7-(4,6-dioxo-5-pyrimidinyl)theophylline dihydrate.[15]

The ionic structures observed for **1** and dimerisation reactions, such as this leading to dimer **2**, are highly unlikely for nucleobases. It appears that the proton affinity of the nitrogens is the factor that contributes most to the ionisation and subsequent dimerisation of **1**. It is specific to **1** that none of its H-tautomers can be present in the di($^-$O–C=NH$^+$) form. Meanwhile **1**, unable to attain a dilactam form, is prone to reactions which would satisfy the affinity of both its nitrogen atoms. The only means to reach the dilactam form is a disproportionation reaction, such as the dimerisation of **1** described in this paper. Thus molecules analogous to **1** unable to reach a lactam or dilactam form in the monomeric state are potential candidates for a similar disproportionation dimerisation, and for forming even larger aggregates.

Characterisation of dimer **2**: $C_8H_8N_4O_4$ (224.16); mp >360 °C; δ_H (300 MHz; DMSO-d_6): 5.21 (s, 1H), 8.01 (s, 1H); δ_C (75 MHz; DMSO-d_6): 89.98, 149.90, 164.30, 164.32: MS see Ref. 11.

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9. Crystal data for 2-(4,6-dioxo-5-pyrimidinyl)-4,6-dioxo-1,2,3,5,5-pentahydropyrimidine **2**: $C_8H_8N_4O_4\cdot\frac{1}{2}H_2O$, $M_r = 233.19$; light-yellow needles, crystal sample 0.32·0.03·0.01 mm, monoclinic, space group *Cc*, $a = 19.334(4)$, $b = 4.9350(10)$, $c = 20.896(4)$ Å, $\beta = 112.86(3)^\circ$, $V = 1837.2(6)$ Å^3, $Z = 8$, $T = 295$ K, $\rho_x = 1.686$ g cm^{-3}, $\mu(\text{Cu K}_\alpha) = 1.213$ mm^{-1}, $\lambda(\text{Cu K}_\alpha) = 1.54178$ Å, 1475 reflections collected (all independent out to $2\theta_{max} = 130^\circ$, $R_{int} = 0.024$; goodness-of-fit 1.035, $R = 0.0257$ (for $I > 2\sigma_I$) and 0.0544 for all data). X-ray data for **2** were measured on a KUMA KM-4 diffractometer; to compensate for the very small crystal size, a variable scan speed with very slow limits of 0.20–5.0° min^{-1} was applied. The structure was solved by direct methods using SHELXS-86[16] and refined by full-matrix least squares on all F^2's with SHELXL-97.[17] All H-atoms were located from ΔF maps and refined with U_{iso}, all other atoms were refined with anisotropic thermal parameters. The crystal data of $\mathbf{2}\cdot\frac{1}{2}H_2O$ have been deposited with the Cambridge Crystallographic Database Centre as supplementary publication No. CCDC 164909. A copy can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44(12) 23336 033, e-mail: deposit@ccdc.cam.ac.uk.
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