

# Ionic Disparity of Identical Molecules in Polymorphs

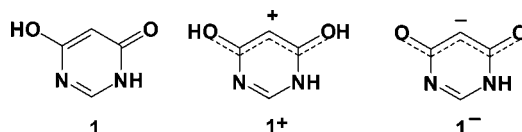
Andrzej Katrusiak\*<sup>†</sup> and Anna Katrusiak<sup>‡</sup>

Faculty of Chemistry, Adam Mickiewicz University, Grunwaldzka 6, 60-780 Poznań, Poland, and Faculty of Pharmacy, Karol Marcinkowski University of Medical Sciences, Grunwaldzka 6, 60-780, Poznań, Poland

katran@amu.edu.pl

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## ABSTRACT



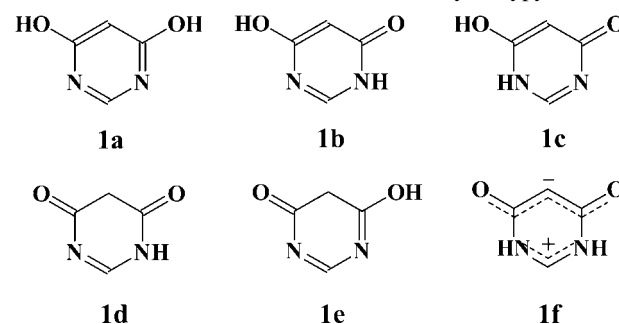
Formation of ionic pairs of identical molecules, extremely common in Nature but exceptional for diffractometric observations in the crystalline state, has been found in one of two polymorphs of a nucleobase analogue, 4,6-pyrimidinedione (**1**). The occurrence of the neutral and ionic polymorphs of **1** in many respects resembles neutral–ionic transitions of electron-donor/acceptor complexes. The ionization affects the reactivity of **1** and illustrates general properties of H-tautomers with low-disproportionation energy.

The crucial role of mesomeric and tautomeric forms of nucleobases for the formation and replication of DNA was already recognized by the discoverers of the DNA structure. The H-tautomerism pertains to the basic problems of mismatched base pairs, mutations, DNA repairs, activity of enzymes,<sup>1</sup> pursuit of the origins of life,<sup>2</sup> and practical applications of nucleobases and their analogues in agriculture<sup>3</sup> or in medicine as antiviral and anticancer drugs.<sup>4</sup> Nucleobases and DNA are prone to photochemical reactions damaging the genetic code;<sup>5</sup> however, the role of specific H-tautomers for these reactions is difficult to observe directly. 4,6-Dihydroxy-pyrimidine (**1**) is an analogue of uracil (2,4-dihydroxypyrimidine) and of other nucleic acid bases. The tautomeric forms of **1** were investigated over a half-century ago by Short and Thompson, who suggested that **1** existed in the form of a lactam-lactim tautomer in the solid state.<sup>6</sup> It

is shown in this report that molecules **1** adjust their structure to their surrounding conditions and interconvert into relatively stable anions and cations. The ionization is due to the small disproportionation energy (i.e., the energy difference between the anion and cation). This allows each pair of molecules to exist in one of three states, cation-anion, neutral-neutral, and anion-cation. Memory devices based on such tertiary systems can be 50% more advantageous than those applying polarization of molecules in bistable ferromagnetic or ferroelectric materials.

Isolated molecule **1** (Scheme 1) is usually associated with the dilactim (**1a**), lactam-lactim (**1b**), dehydrolactam-*N*-hydrolactim (**1c**), lactam-dehydrolactam (**1d**), or dehydro-

**Scheme 1.** Neutral H-Tautomers of 4,6-Dihydroxypyrimidine



<sup>†</sup> Adam Mickiewicz University.

<sup>‡</sup> Karol Marcinkowski University of Medical Sciences.

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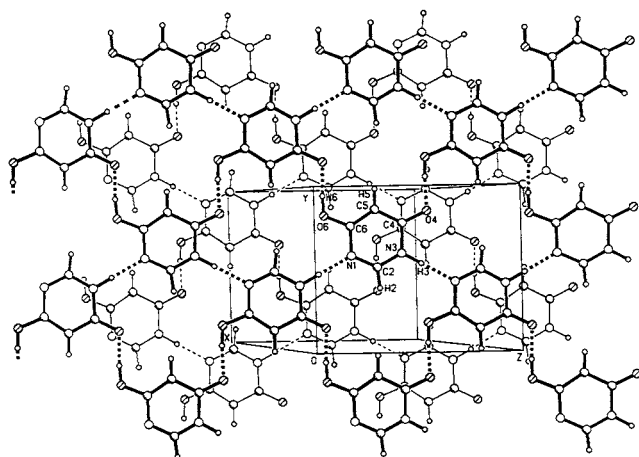
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lactam-lactim (**1e**) tautomers; a zwitterionic form (**1f**) was also proposed.<sup>7</sup> Our ab initio calculations in the 6-31G\* base showed that form **1d** is insignificantly (by 0.06 kcal/mol) more stable than **1b**, 1.2 kcal/mol more stable than **1a**, and 15.2 kcal/mol more stable than **1c**. Tautomers **1d** and **1e** have only one H-donor and three H-acceptors, while two donors and two acceptors are present in the other tautomers. Thus, tautomer **1b** is favored by hydrogen bonds, and indeed it has been observed in the prevailing of two concomitant polymorphs, **1a**.<sup>8</sup> In polymorph **1a**, molecules **1b** are hydrogen bonded into sheets by OH--O and NH--N bonds, as shown in Figure 1. The donor–acceptor distances in these



**Figure 1.** Autostereogram<sup>12</sup> of the structure of polymorph **1a** viewed perpendicular to the H-bonded sheets. The H-bonds are shown as dashed lines.

H-bonds are 2.520(2) and 2.794(2) Å, respectively. The motif of the H-bonded networks can be described by graph  $C_1^1(4)R_4^4(18)$ .<sup>9</sup>

The other polymorph, **1β**,<sup>10</sup> has a pattern of H-bonded planar sheets similar to that in **1a**, shown in Figure 2. According to Etter et al.,<sup>8</sup> the H-bond motif is essentially identical to that of **1a**, but the refined method of Bernstein et al.<sup>11</sup> differentiates the graph of **1β** due to two symmetry-independent formula units in this polymorph. Thus, at the

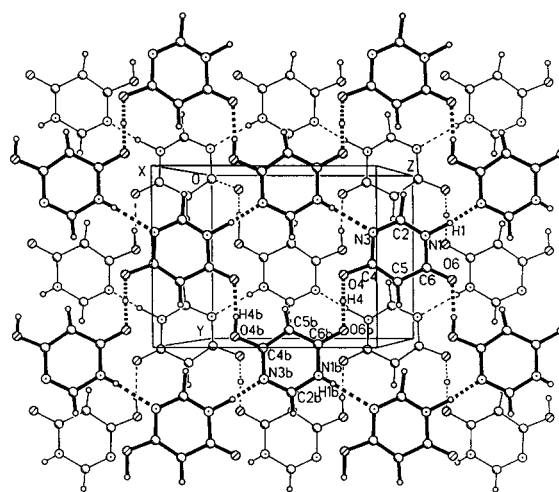
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(8) Crystal structure data for polymorph **1a**:  $C_4H_4N_2O_2$ ,  $M_r = 112.09$ , yellow prisms, crystal sample  $0.28 \times 0.15 \times 0.09$  mm, monoclinic, space group  $Cc$ ,  $a = 7.666(2)$ ,  $b = 7.692(2)$ ,  $c = 9.545(2)$  Å,  $\beta = 124.74(3)^\circ$ ,  $V = 462.5(2)$  Å<sup>3</sup>,  $Z = 4$ ,  $T = 295$  K,  $D_x = 1.610$  g/cm<sup>3</sup>,  $\lambda(\text{Cu K}\alpha) = 1.54178$  Å, reflections collected 1498 out to  $2\theta_{\text{max}} = 140.24^\circ$ , independent reflections 773,  $R_{\text{int}} = 0.0377$ ; all H-atoms from  $\Delta F$  maps and refined with  $U_{\text{iso}}$ ; GOF = 1.089,  $R = 0.0372$  (for  $I > 2\sigma$ ) and 0.0383 for all data.

(9) Etter, M. C.; MacDonald, J. C.; Bernstein, J. *Acta Crystallogr., Sect. B* **1990**, *46*, 256–262.

(10) Crystal structure data for polymorph **1β**:  $C_4H_4N_2O_2$ ,  $M_r = 112.09$ , deep-yellow plates, crystal sample  $0.25 \times 0.13 \times 0.08$  mm, monoclinic, space group  $P2_1$ ,  $a = 6.6080(10)$ ,  $b = 7.709(2)$ ,  $c = 9.497(2)$  Å,  $\beta = 109.05(3)^\circ$ ,  $V = 457.3(2)$  Å<sup>3</sup>,  $Z = 4$ ,  $T = 295$  K,  $D_x = 1.628$  g/cm<sup>3</sup>,  $\lambda(\text{Mo K}\alpha) = 0.71073$  Å, 1612 reflections collected out to  $2\theta_{\text{max}} = 50^\circ$ , independent reflections 1517,  $R_{\text{int}} = 0.024$ ; all H-atoms from  $\Delta F$  maps and refined with  $U_{\text{iso}}$ ; GOF = 1.208,  $R = 0.0507$  (for  $I > 2\sigma$ ) and 0.0606 for all data.

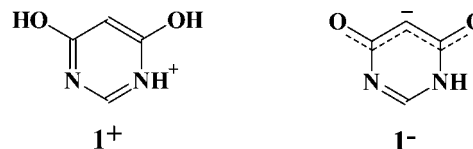


**Figure 2.** Polymorph **1β** structure viewed analogously as in Figure 1. Cationic **1b**<sup>+</sup> is labeled like neutral **1b**, while the labels of the symmetry-independent **1b**<sup>-</sup> have been differentiated by adding the letter *b*.

first-level graph, four dimer descriptors are introduced, and the defining integers of the chain patterns of the second level are doubled:  $DDDD C_2^2(12)C_2^2(8)R_4^4(18)$ . But the most striking feature of **1β** is that the molecules are differentiated into positive **1**<sup>+</sup> and negative **1**<sup>-</sup> ions.

In the shorter of the two symmetry-independent OH--O bonds in **1β** [2.488(4) compared to 2.548(3) Å], atom H(4) is shifted toward the midpoint between the oxygen atoms: 1.18(5) Å away from O(4)<sup>-</sup> and 1.35(5) Å toward O(6b)<sup>+</sup>. The H-shift is consistent with the well-known correlation between O...O and O–H distances<sup>13</sup> and also with the much more precisely determined elongation of the acceptor O(6b)=C(6b) bond to 1.292(5) Å, compared to 1.227(5) Å in the other symmetry-independent O(6)=C(6) acceptor carbonyl. Thus, the positive charge of 0.42 e associated with H(4) is shifted away from one of the oxygens toward the other (Scheme 2). The other H atoms in the OH--O and NH--N

**Scheme 2.** Pair of Half-Zwitterions of 4,6-Dihydroxypyrimidine



bonds in **1β** have been located within errors at 1 Å from their donors, although H(1) has been also found to be shifted slightly toward N(3b) of **1**<sup>+</sup>.

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(12) Katrusiak, A. *J. Mol. Graphics Modell.* **2001**, *19*, 362–366.

The shifted charge results in statistically significant changes in molecular dimensions of **1b**: the bond orders in electron-deficient **1b**<sup>+δ</sup> become slightly reduced and on average 0.010 Å longer than those in **1b** in polymorph **1α**, while the order of electron-rich bonds shifts toward double bonds in **1b**<sup>-δ</sup>. Hence, the bonds in **1b**<sup>-δ</sup> are on average 0.007 Å shorter than those in **1b**. The ionic character of **1β** is confirmed also by the smaller formula volume of **1β** than **1α** due to additional electrostatic cohesion, by the deeper coloring of **1β** due to more delocalized electrons, and by the considerably slower sublimation of **1β** samples compared to that of **1α**. Polymorph **1β** is pseudosymmetric (approximating space group *P2<sub>1</sub>/c*), with the glide-plane symmetry broken due to the differentiation of the ions, but the structure resisted transformation to the molecular form even when heated to 350 K. No changes of the location of the H-atoms were observed in **1α** or **1β** down to 90 K. In other words, the forms of **1** observed in polymorph **1β** can be considered as a pair of half zwitterions (compare zwitterion **1f** of Scheme 1 and the ions shown in Scheme 2). This would imply that the N(1b)H--N(3<sup>i</sup>) is partly charge assisted, and indeed it is shorter than the other NH--N hydrogen bond: 2.787(4) Å compared to 2.815(3) Å, respectively (compare Figure 2 and Scheme 2).

The formation of cations and anions of identical molecules is of fundamental importance for many physical, chemical, and biological processes and occurs frequently in systems as simple as water and ice or as complex as living tissue. However, such a spontaneous formation of ions usually does not involve all molecules comprised within a crystal but affects only scarce molecules distributed stochastically, and the structures of ions thus formed are inaccessible for direct observation.

The protonated (**1**<sup>+</sup>) and deprotonated (**1**<sup>-</sup>) molecules were identified in equilibrium with other forms of **1** in the D<sub>2</sub>O solution by <sup>1</sup>H NMR spectroscopy.<sup>14</sup> Although in principle the different ions can be stabilized by different environments in crystals, in **1β**, the ions are embedded in similar pseudo-symmetric surroundings. All of this indicates that the ionic forms are strongly favored and characteristic of **1**. To our knowledge, until now, only one case of such a spontaneous differentiation in the crystalline state was postulated for phosphorus pentachloride forming neutral PCl<sub>5</sub> molecules in vapor and for crystals built of PCl<sub>4</sub><sup>+</sup>·PCl<sub>6</sub><sup>-</sup> ions.<sup>15</sup> However, phosphorus pentachloride does not form molecular crystals. Neutral- to ionic-phase transitions have been more recently observed in (electron-donor):(electron-acceptor) systems.<sup>16</sup> Although these are not identical molecules that

transform into anions and cations, these phase transitions demonstrated structural effects of a net charge transfer of a few tenths of an electron, similar in magnitude to those in polymorph **1β**, as well as other features like volume contraction upon transition or pairing of the ions of opposite charges. Also, we are aware of only two examples of disparity of molecules and their zwitterionic counterparts, evidenced in polymorphs of *o*-aminobenzoic acid<sup>17</sup> and of 2-amino-3-hydroxy-6-phenylazopyridine.<sup>18</sup> Thus, to our knowledge, **1** is the first pure substance capable of forming molecular and ionic polymorphs.

Polymorphs **1α** and **1β** can serve as a textbook example of the structure-correlation method:<sup>19</sup> the partial ionization of **1β** indicates instabilities of molecule **1b**, which in solution, along with the electrostatic attraction of ions, would promote dimerization. Indeed, we have observed in aqueous solution the reaction of asymmetric dimerization yielding 2-(4',6'-dihydroxy-5'-pyrimidinyl)-4,6-dioxo-1,2,3,5,5-pentahydropyrimidine. This unusual product evidences two different active sites in **1**.

The variety of forms of **1** observed in its polymorphs and in solution demonstrates that analogues of pyrimidine bases can transform to an extent not considered even for their most "exotic" tautomers.<sup>20</sup> Knowledge of these compounds is essential for predicting their multiple functions or pharmaceutical activity of analogous medicines.<sup>4</sup> The neutral–ionic polymorphism of **1** provides straightforward evidence for the properties and transformations of nucleic acid bases and peptides<sup>21</sup> that otherwise could be elusive for sophisticated experiments or theoretical investigations.

**Supporting Information Available:** Crystal data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. *CCDC 164907* (**1α**) and *CCDC 164908* (**1β**). Copies 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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