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Role of Weak Hydrogen Bonds and Halogen Bonds in 5-Halo-1,3-dimethyluracils and Their Cocrystals - A Combined Experimental and Computational Study

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KEYWORDS: 5-halo-1,3-dimethyluracils; halogen bonding; hydrogen bonding; X-ray diffraction; quantum chemical calculations; spin component scaled local MP2

ABSTRACT: Seven single crystals containing either *N*,*N*-dimethyluracil (DMHU) or one of its 5-halogenated derivatives (DMXU; X = F, Cl, Br, I) were prepared using *N*,*N*-dimethylformamide as the crystallization solvent. Single crystal X-ray diffraction and quantum chemical calculations carried out at the spin component scaled local MP2 level of theory were then used to study the intramolecular halogen and non-conventional hydrogen bonds present in the structures. The results were compared to and contrasted with the previously reported data for uracil and its halogenated derivatives. In particular, the intermolecular interactions in DMIU were compared to the halogen and hydrogen bonds in 5-iodouracil that, in contrast to DMHU and its derivatives, displays conventional hydrogen bonds involving its strong N-H donor sites. The crystallographic and computational analyses showed that, while non-conventional hydrogen bonds are present in both DMHU and DMXU, halogen bonds could only be identified in DMBrU and DMIU, in which case they play an important role in directing the resulting crystal structures.

INTRODUCTION

The 5-halogenated derivatives of uracil (XUs) have received increased interest in the last two decades due to their biological and pharmaceutical importance.[1,2] For instance, XUs are employed as antitumor, antibacterial and antiviral drugs, and they are known to exert profound effects in a variety of microbiological and mammalian systems as they can be readily incorporated into DNA.[3,4] XUs have also gained special attention in the well-established area of cocrystals of active pharmaceutical ingredients as pharmaceutically acceptable coformers.[5] The biological and pharmaceutical importance of XUs is partly based on their capability to form supramolecular assemblies through halogen (XBs) and hydrogen bonds (HBs),[6-13] but they also have a variety of other features that can be used to control the organization of molecules at the supramolecular level.[14]

Both XBs and HBs are defined as net attractive interactions between an electrophilic (electron poor) region of a molecular entity and a nucleophilic (electron rich) region at the same or a different molecular entity. In XBs and HBs, the electrophilic site is associated with halogen and hydrogen atoms, respectively. HBs in halogenated uracils have been investigated extensively by different research groups.[6-13] In biological systems, the different 5-halouracils, similar in size to thymine (5-methyluracil), are expected to exhibit base pairing which closely mimics the Watson-Crick thymine-adenine duplex stabilization in DNA. However, the variation of halogen from fluoro to iodo may substantially affect the chemical and electronic properties of the nucleobase, and therefore its incorporation into DNA and *in vivo* activity.[15-17] For example, as shown by computational investigations,[18] the substitution of the methyl group in thymine by fluorine atom influences the acidity of the two amidic N-H sites in the heterocyclic ring by decreasing their pK_a values, hence, increasing the strength of Watson-Crick base pairing.[19]

The biological utility of XBs and conventional HBs has been widely studied and their structural competition is well documented.[20-23] In particular, Ho and co-workers first searched the Protein Data Bank (PDB) for short XBs between halogenated proteins and nucleic acids, and this survey yielded 113 hits in which XBs were found to direct ligand-protein binding and molecular folding.[6] Despite the work already performed, there remains a need to investigate small biomolecular systems where XBs and non-conventional HBs, such as C-H···O, are simultaneously present, as the latter interactions are ubiquitous in many small molecule crystal structures[24,25] and advantageously used for enhancing the efficiency of weak base pairing in DNA.[26-33]

Due to our continuing interest in the potential of pyrimidine nucleobases for crystal engineering strategies underpinned by multiple HBs[34-45] and our involvement in studies of systems exhibiting halogen bonding *via* alternative donors (halogen atom not polarized by fluorine) and acceptors (such as anions),[46-59] we were interested in search for systems that could be used to investigate the role of concurrent XBs and non-conventional HBs in the control of sequence, structure and flexibility of DNA halogenated within the natural tract. For this purpose, 5-halogenated derivatives (DMXU; X=F, Cl, Br, I) of *N*,*N*-1,3-dimethyluracil (DMHU) and their mixed cocrystals are ideal candidates because of several advantageous properties.

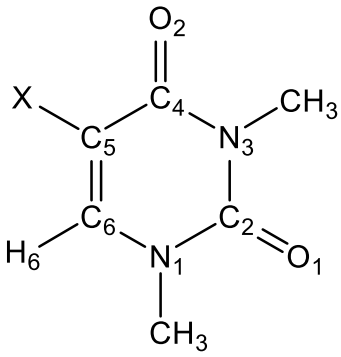
DMXUs can be considered as simple models of halouridine, in which deoxyribose attaches to uracil at the N1 atom, and where the *N*-methylation at the 1- and 3-positions leads to the absence of strong N-H hydrogen bond donors.[60-62] The halogen atom at the 5-position can act as a XB donor since it is polarized by the adjacent electron-withdrawing carbonyl group. In addition, the two oxygen atoms in the C=O group are nucleophilic and can act as halogen bond acceptors, if not saturated by conventional HBs. The difference in the intrinsic basicity of the two carbonyl

moieties, caused by the substituent at the 5-position,[63-66] can account for a variety of hydrogen bonded motifs involving conventional HBs.[14,40] Due to the electron-deficient moieties in the heterocyclic ring, the less acidic hydrogen atoms at the sp^3 hybridized carbons[67,68] are able to form weak C-H···O interactions and, to a smaller extent, also C-H···X interactions.[69-72]

At the moment, DMHU and DMXUs are not well studied in the solid state. A search of crystal structures containing DMHU or DMXU units (excluding metallic elements and including polymorphs and their mixed co-crystals) with the Cambridge Structural Database (CSD, version 5.36 with updates to May 2015)[73] gave only five unique hits with X = H, F, Cl (CSD refcodes: DMURAC, DMURAC01, KAMSAS, KAMSEW and LAKJUC). Adopting a cutoff value of 0.9 for the interaction ratio R_{XB},[54] the ratio between the X···A (A = acceptor) contacts showing linear C-X···A disposition (bond angle > 155°) and the sum of van der Waals (vdW) radii,[74] there was no crystallographic evidence that the existing fluoro and chloro derivatives form XBs. On the other hand, from the measured differences in sublimation enthalpies in 5-halouracils and in their 1,3-dimethyl derivatives, it was recently speculated that DMBrU and DMIU can act as XB donors/acceptors in the solid state, the strength of the XB increasing, as expected, from bromine to iodine.[75]

In this work, we crystallized DMHU (**1**) and six DMXUs (**2**-**5**), both pure and mixed from *N*,*N*-dimethylformamide (DMF) to investigate their structures in the solid state and explore the balance between non-conventional HBs and XBs in pyrimidine halonucleobases. Of the investigated systems, DMHU can be regarded as a reference molecule for C-H···O interactions in the DMXU series as a monoclinic polymorph. A systematic analysis using single crystal X-ray diffraction and quantum chemical calculations was performed for all investigated species to

examine the intermolecular interactions present in the observed structures. The obtained data was also compared to the previously reported results for uracil and its halogenated derivatives.[46]



1 (DMHU) X = H
2a (DMFU) X = F
2b (DMHU/DMFU) X = H or F
3 (DMClU$_W$) X = Cl
4a (DMBrU) X = Br
4b (DMBrU/DMIU) X = Br or I
5 (DMIU) X = I

Scheme 1. Chemical structures of systems **1-5**.

EXPERIMENTAL

Materials. 1,3-dimethyluracil (DMHU), 5-fluoro-1,3-dimethyluracil (DMFU), 5-bromo-1,3-dimethyluracil (DMBrU) and 5-iodo-1,3-dimethyluracil (DMIU) were all purchased from Aldrich (98-99% purity). The 5-chloro-1,3-dimethyluracil (DMClU, 95% purity) was obtained from Ukrorgsyntez. All compounds were purified by successive sublimation under reduced pressure. Organic solvents used in crystallizations were dried before use.

Crystallizations. The same crystallization method was used for **1-5**. Equal amount (0.1 mmol) of each pure compound was dissolved in hot DMF and the resulting solutions were stirred at 70°C for 18 h under reflux and filtered. For **2b** and **4b**, equimolar amounts of DMHU and DMFU or DMBrU and DMIU, respectively, were used instead of pure compounds. Colorless transparent single crystals of suitable size were obtained from slow room-temperature evaporation of the solutions during two to three weeks and used for subsequent X-ray diffraction studies. Unfortunately, any attempts to produce good quality crystals of the orthorhombic form of DMHU or the anhydrous DMClU by repeating the crystallization conditions using different solvents, or mixtures of solvents in different ratios, were unsuccessful.

Single Crystal X-ray Diffraction Studies. The intensity data were collected using Oxford Diffraction Xcalibur S CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.710689 Å) at room temperature. Data reduction was performed using the CrysAlisPro software package.[76] Solution, refinement and analysis of the structures were done using the programs integrated in the WinGX system.[77] The crystal structures were solved by direct methods using SIR2002[78] and refined by the full-matrix least-squares method based on F^2 using SHELXL-2014/7.[79] For all structures, non-hydrogen atoms were refined anisotropically. The hydrogen atoms were located from the difference Fourier map and refined freely. Carbon-bound H atoms were placed in calculated positions [C-H = 0.97 Å, U_{iso}(H) values equal to 1.2 U_{eq}(C) for aromatic or 1.5 U_{eq}(C) for methyl H atoms] as riding atoms. Free rotation about the local threefold axis was then allowed for all methyl groups. Geometrical calculations were performed using PLATON[80] and all figures were prepared with the Mercury 3.5.1 program package.[81] Crystal data and refinement details of **1-5** are summarized in Table 1, while full crystallographic data has been deposited to the Cambridge Crystallographic Data Centre (CCDC 1426930-1426936). These data can be obtained free of charge via www.ccdc.cam.uc.uk/data_request/cif.

For the monoclinic form of DMHU (**1**),[60] a different choice of the unit cell from that previously published was made in order to get β angle closer to 90°.[82] The isomorphic DMFU (KAMSAS, **2a**) and (1:1) DMHU/DMFU (KAMSEW, **2b**) structures have previously been reported in the enantiomorphous space group $P2_12_12_1$ (No 19).[83] An inspection of the atomic coordinates table in the original paper clearly showed that the x coordinate values were only slightly deviating from the symmetry element at x = ¼. Consequently, the structures **2a** and **2b** were re-investigated in the centrosymmetric space group *Pnma* (No 62). The (1:1) DMHU/DMFU structure **2b** exhibits F(5) and H(5) disorder. This disorder has been treated

assigning equal values (0.5) to site occupancy factors of both atoms. In the isomorphic DMBrU (**4a**) and (1:1) DMBrU/DMIU (**4b**) structures, each molecule in the asymmetric unit is disordered between two orientations generated by a two-fold axis passing along the O1-C2-C5-R fragment (R = Br and Br/I), *i.e*. the oxygen and hydrogen atoms *ortho* to the halogen atom are positionally disordered. This disorder was treated assigning equal values (0.5) to the site occupancy factor of each component in the two orientations.

Computational details. Geometries of DMXU dimers (**6-9**; X = F, Cl, Br, I) and tetramers (**10** and **11**; X = I) were optimized without symmetry constraints using the spin component scaled second-order local Møller-Plesset perturbation theory[84] in conjunction with the density fitting approximation,[85,86] SCS-DF-LMP2. Initial geometries for **7**, **8** and **9-11** were taken from the crystal structures of LAKJUC, DMBrU (**4a**) and DMIU (**5**), respectively, whereas the geometry of the dimer **6** was constructed from the crystal structure of **5** by replacing iodine with fluorine.

In all SCS-DF-LMP2 calculations, the Pipek-Mezey localization approach was used to construct localized molecular orbitals while the Boughton and Pulay procedure was employed in domain definition.[87,88] Domains were determined at large intermolecular distance and individual monomers were identified automatically to minimize the basis set superposition error (BSSE).[89] Spin component scaling factors 6/5 and 1/3 were used for antiparallel and parallel spins, respectively. All calculations used the aug-cc-pVTZ correlation consistent basis sets for all other nuclei except iodine for which the small core ECP basis set, namely aug-cc-pVTZ-PP,[90-92] was used. Auxiliary basis sets of triple-ζ valence quality were employed in density fitting to speed up all calculations.[93-95]

All quantum chemical calculations were done with the Molpro 2012.1 program package;[96,97] for visualization of optimized geometries, the program Mercury 3.5.1 was employed.[81]

Table 1. Crystallographic Data of **1-5**.

	DMHU (1)	**DMFU (2a)**	**DMHU/ DMFU (2b)**	**DMClU$_w$ (3)**	**DMBrU (4a)**	**DMBrU/ DMIU(4b)**	**DMIU (5)**
Empirical formula	$C_6H_8N_2O_2$	$C_6H_7FN_2O_2$	$C_6H_{7.5}F_{0.5}N_2O_2$	$C_6H_7ClN_2O_2 \cdot H_2O$	$C_6H_7BrN_2O_2$	$C_6H_7Br_{0.5}I_{0.5}N_2O_2$	$C_6H_7IN_2O_2$
Crystal data							
M_r	140.14	158.14	149.0	192.60	219.05	242.54	266.04
Crystal system space group	Monoclinic $P2_1/n$	Orthorhombic *Pnma*	Orthorhombic *Pnma*	Monoclinic $P2_1/m$	Orthorhombic *Cmcm*	Orthorhombic *Cmcm*	Monoclinic $P2_1/c$
a (Å) b (Å) c (Å)	3.9784 (7) 12.4126 (19) 13.4615 (19)	12.6168 (15) 6.6071 (12) 8.4748 (12)	12.4755 (18) 6.6703 (13) 8.4189 (14)	8.3281 (17) 6.4411 (11) 8.7961 (15)	6.8271 (7) 8.8170 (9) 13.0307 (13)	7.0173 (11) 8.9629 (10) 13.0296 (17)	8.8984 (7) 12.8142 (9) 7.8925 (7)
α (°)	90	90	90	90	90	90	90
β (°)	92.233(13)	90	90	117.86 (2)	90	90	114.619(10)
γ (°)	90	90	90	90	90	90	90
V (Å^3)	664.26 (18)	706.46 (18)	700.6 (2)	417.16 (15)	784.38 (14)	819.50 (19)	818.14 (13)
Z	4	4	4	2	4	4	4
F(000)	296	328	312	200	432	468	504
μ (mm^{-1})	0.11	0.13	0.12	0.43	5.19	4.41	3.87
Crystal size (mm)	0.12 × 0.10 × 0.07	0.11 × 0.09 × 0.08	0.13 × 0.10 × 0.09	0.15 × 0.12 × 0.10	0.14 × 0.11 × 0.09	0.12 × 0.09 × 0.08	0.10 × 0.08 × 0.06
ρ_{calc} (Mg m^{-3})	1.401	1.487	1.413	1.533	1.855	1.966	2.160
Data collection							
No. of measured, independent and observed [$I>2\sigma(I)$] reflections	8774 1433 824	14022 1167 839	8927 825 631	8565 1435 981	7969 756 615	8949 761 698	24207 1968 1735
R_{int}	0.047	0.041	0.039	0.043	0.045	0.038	0.053
$(\sin\theta/\lambda)_{max}$ (Å^{-1})	0.639	0.714	0.639	0.725	0.745	0.735	0.660
Refinement							
$R[F^2> 2\sigma(F^2)]$	0.048	0.055	0.072	0.040	0.030	0.022	0.034
$wR(F^2)$	0.140	0.161	0.167	0.108	0.071	0.056	0.080
GOF on F^2	1.05	1.11	1.17	1.03	1.12	1.16	1.19
No. of parameters	93	70	72	81	44	48	102
No. of restraints	0	0	2	0	1	1	0
$\Delta\rho_{max}$/ $\Delta\rho_{min}$ (e Å^{-3})	0.16/ −0.19	0.21/ −0.17	0.15/ −0.16	0.25 / −0.32	0.55 / −0.45	0.39 / −0.34	0.97/ −0.63

RESULTS AND DISCUSSION

Structures of DMHU and DMXUs. Previous crystallographic studies have shown that DMHU has two polymorphic forms: the $P2_1/n$ monoclinic, DMURAC,[60] and the less stable P*mcn* orthorhombic, DMURAC01.[61,62] As already mentioned, this molecule is of particular interest for the scope of the present study for which reason the monoclinic form **1** was reinvestigated to increase the precision of the geometric parameters, *viz.* σ(C-C) = 0.002Å (*cf.* 0.005Å in the original report).

In the crystal structure of **1**, the asymmetric unit contains a single molecule that forms HBs to five molecules at adjacent asymmetric units to create R^2_2 (10) symmetry-related dimers, R^1_2 (6) dimers and R^2_3 (10) trimers (Fig.1a).[98,99] In addition, C-H···O HBs connect both the methyl groups and the two aromatic HB donor sites with the two available HB acceptor sites. The equivalence of the two carbonyl groups can be justified by the complete utilization of the two O atoms in the C-H···O interactions.[34, 100]

The molecular disposition is different in the orthorhombic form of DMHU, DMURAC01, which could account for the observed difference in stability.[61] In DMURAC01, the adjacent molecules are linked to head-to-tail chains via C-H···O HBs and the antiparallel arrangement of these chains forms a two-dimensional array of adjoining $R^4_4(20)$ hydrogen bonded rings (Fig. 1b), thus leaving one methyl and one aromatic C-H group unused for HB formation and both carbonyl oxygen atoms partially unsaturated. The hydrogen bonding motif therefore originates from intermolecular contacts between the less hindered methyl group and the amide carbonyl oxygen O2 atom, which alternates with contacts between the C6 atom and the urea carbonyl O1 atom.

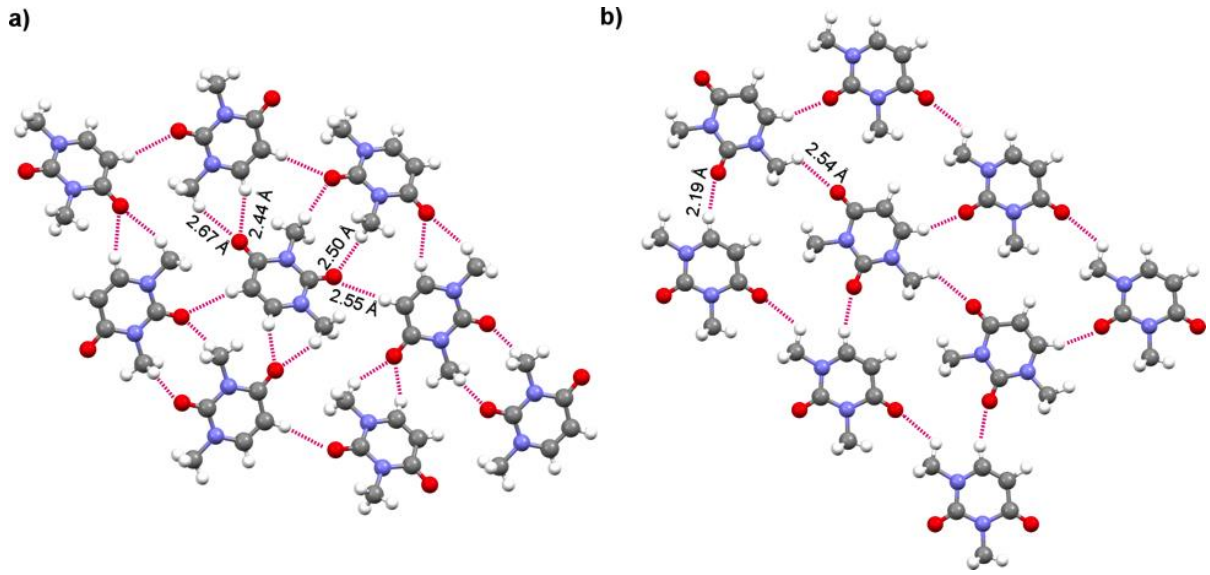


Figure 1. Nine asymmetric units of monoclinic **1** (a) and orthorhombic DMURAC01 (b) showing the HBs (C-H···O, red).[61]

The orthorhombic P*mcn* DMHU is isomorphic and isostructural with **2a** and **2b** in space group P*nma* (Fig. 2). For this reason, the discussion of the hydrogen bonding scheme of **2a** and **2b** compounds follows the above description. We note that no indication of intermolecular C-H···F HBs were observed in either of the two structures. Furthermore, neither **2a** nor **2b** shows any indication of XBs.

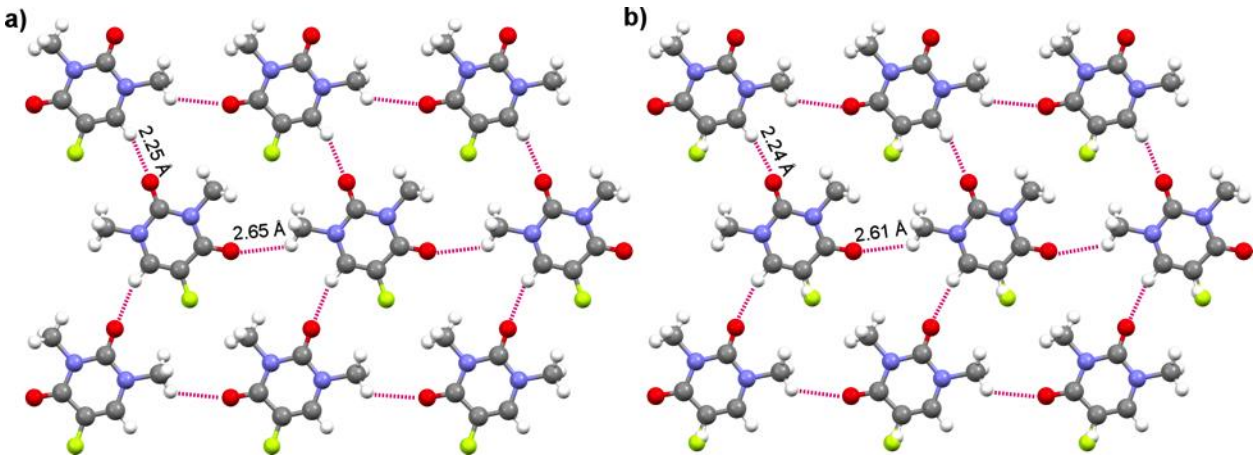


Figure 2. Nine asymmetric units of **2a** (a) and **2b** (b) showing the HBs (C-H···O, red). Both disordered components are shown for **2b**.

In the previously reported structure of DMClU, LAKJUC,[101] the compound crystallizes in the monoclinic space group $P2_1/n$ with only one molecule in the asymmetric unit. In the crystal, each molecule is hydrogen bonded to three adjacent molecules to form symmetry-related dimers via C-H···O HBs in which one methyl group and the aromatic HB donor site point to the two carbonyl oxygen atoms O1 and O2 of adjacent molecules, respectively (Fig. 3a). The structure also shows short C-Cl···O intermolecular contacts [3.266(3) Å] that practically coincide with the cutoff value for XBs (3.27 Å). No appreciable intermolecular C-H···Cl HBs are present in the structure.

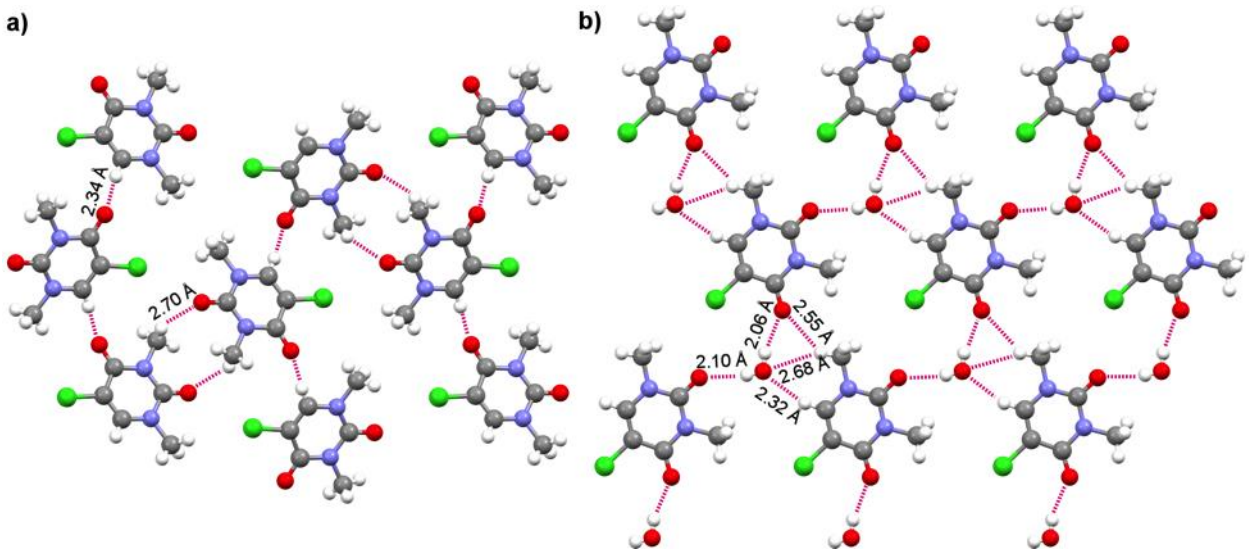


Figure 3. Nine asymmetric units of LAKJUC (a) and **3** (b) showing the HBs (C-H···O and O-H···O, red).[101]

The asymmetric unit of **3** comprises one DMClU and one water molecule, both laying on a mirror plane in the monoclinic space group $P2_1/m$. In the crystal structure, the water molecules play a strategic role in the overall organization and, being not involved in XB interactions, are free to participate as both donors and acceptors in conventional and non-conventional HBs (Fig. 3b). As a result, each water molecule operates as a bridge between head-to-tail parallel chains of **3** formed by C-H···O HBs involving the less hindered methyl group and the amide carbonyl oxygen O2. Thus, these interactions contribute to form a two-dimensional array of adjoining hydrogen bonded rings of $R^4_5(20)$ graph-set motif. As with the structure of anhydrous LAKJUC, no relevant intermolecular HBs or XBs involving the chlorine atom of DMClU were observed.

The crystallographic investigation of DMBrU **4a** showed the crystals to be isomorphic with those of the 1:1 DMBrU/DMIU cocrystal **4b** in the orthorhombic space group C*mcm*. The structure of **4a** has a short and linear C-Br···O (2.95 Å) unit, whereas two short and linear C-Br···O and C-I···O (2.90 Å and 3.01 Å, respectively) units are found in **4b** (Fig. 4). The XB ratios

R_{XB} vary between 0.86 and 0.88. The observed XBs connect adjacent molecules in head-to-tail antiparallel chains involve the urea carbonyl oxygen O1 as the XB acceptor. Weak C-H···O HBs connect the methyl groups and the aromatic C-H units to the O2 oxygen atom flanking the aforementioned XBs.

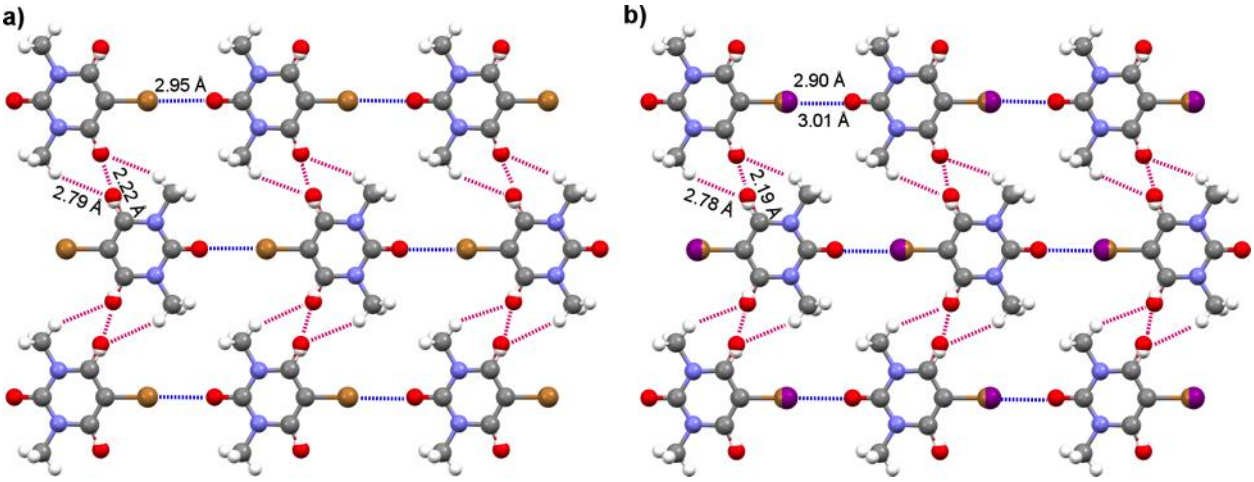


Figure 4. Nine asymmetric units of **4a** (a) and **4b** (b) showing the HBs (C-H···O, red) and XBs (blue). Both disordered components of **4a** and **4b** are shown.

The structure of DMIU (**5**) has one molecule in the asymmetric unit in the monoclinic $P2_1/c$ space group and shows nearly linear (173.7 (4)°) C-I···O XBs similar to those found in **4a** and **4b**, *i.e.* between the iodine atom and the urea carbonyl oxygen O1 on molecules at adjacent asymmetric units (Fig. 5). The I···O XB is 3.04 Å and the XB ratio R_{XB} is 0.84. The small deviation from linearity of the XB can be attributed to the concomitant C-H···O1 HBs that are not in the same plane with the XBs. Consequently, the hydrogen bonding pattern in **5** differs from that in **4a** and **4b** in that head-to-tail antiparallel chains are linked through adjunctive C-H···O HBs between the more hindered methyl group and the O1 oxygen atom.

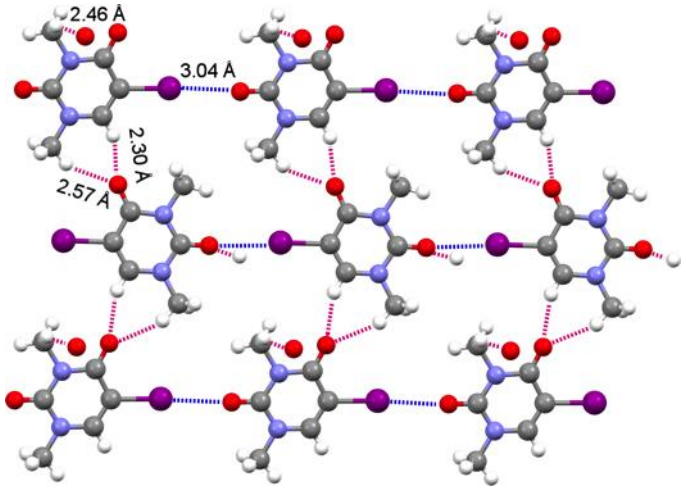


Figure 5. Nine asymmetric units of **5** showing the HBs (C-H···O, red) and XBs (blue).

In the structures of **4a**, **4b** and **5**, the halogen atoms do not take part in intermolecular HBs. For comparison, we note that XBs and HBs are present in 5-iodouracil (IU) cocrystallized with four different polar solvents, but IU acts simultaneously as a halogen bond donor/acceptor only in two complexes (VIXROL and VIXRAX),[46] *i.e.* when the ring carbonyl oxygens do not take part in HBs. In pure IU and 5-bromouracil (BrU), the crystal packing is controlled entirely by conventional HBs as the molecules do not manifest XBs.[14,40]

In the XB and HB survey by Ho and co-workers,[6] and in a later survey performed on more than 600 hits,[11] it has been shown that, when HBs and XBs share a common oxygen atom, the C=O···X angle is commonly found close to 120°.[6] This result is consistent with lone-pair directionality similar to that frequently observed for hydrogen donors involved in conventional and unconventional hydrogen bonding to sp^2 hybridized oxygen atoms.[102-104] In contrast to the above, the C=O···X interactions in **4a**, **4b** and **5** are linear. A nearly linear C=O···X disposition has also been found when XB and HB donors do not share a common acceptor, *i.e.* in the crystal structure of the complexes of IU with formamide (VIXROL, <C=O···X = 156°) and 1,4-diazabicyclo[2.2.2]octane (VIXRAX, <C=O···X = 168°).[46]

Computational studies of DMXUs dimers and tetramers. Geometry optimizations were carried out for dimers and tetramers of DMXU (**6-11**; X = F, Cl, Br, I) at the SCS-DF-LMP2/aug-cc-pVTZ level of theory. The SCS-DF-LMP2 method was chosen since it describes all forces involved in the formation of HB and XBs (electrostatic, polarization, charge transfer and dispersion) while giving virtually basis set superposition free interaction energies.[84-86,105] Moreover, as we have previously applied the same method to investigate the interaction energies of halogen and hydrogen bonded 5-iodouracil,[46] the calculated numbers are fully comparable between the two studies.

The optimized structures of dimers **6-9** are shown in Figure 6, whereas the key intermolecular distances and angles are listed in Table 2. We note that the optimized geometries of the model dimers are in reasonable agreement with the crystallographic data (where available), taking into account the flatness of the potential energy hypersurfaces with respect to XBs and HBs, and the complete neglect of lattice effects in calculations.

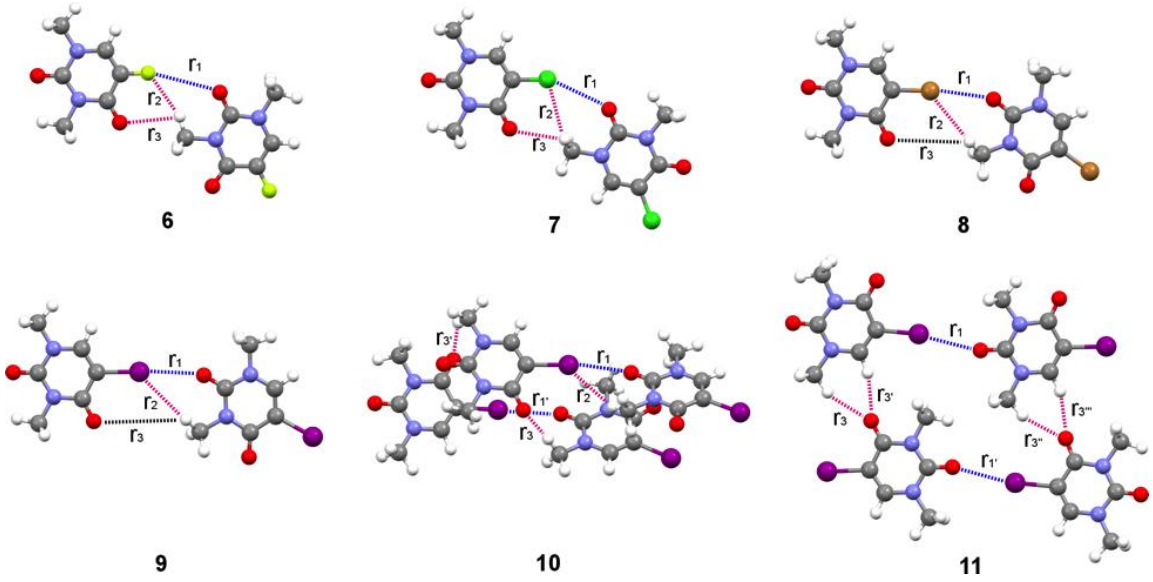


Figure 6. Optimized geometries of dimers **6-9** and tetramers **10-11** showing HBs (C-H···O, red) and XBs (blue). Bond distances r_1-r_3 are given in Table 2.

Table 2. Optimized X···O (r1), X···H (r2) and O···H (r3) distances, and C=O···X bond angles in **6-11**.[a]

dimers	r_1 [Å]	r_2 [Å]	r_{vdW}(X···H)[b]	r_3 [Å]	r_{vdW}(O···H)[b]	C=O···X [°]
6	3.64 [4.596(3)]	2.62	2.67	2.94	2.72	129.5 [102.8(3)]
7	3.35 [3.266(3)][101]	3.16	2.95	2.87	2.72	138.1 [145.3(2)][101]
8	3.11 [2.949(4)]	3.15	3.05	4.38	2.72	148.1 [180]
9	3.14 [3.039(3)]	3.3	3.18	4.54	2.72	151.5 [172.3(3)]
tetramers	r_1, $r_{1'}$ [Å]	r_2 [Å]	r_{vdW}(X···H)[b]	r_3-$r_{3'''}$ [Å]	r_{vdW}(O···H)[b]	C=O···X [°]
10	3.11, 3.10[3.039(3)]	3.15	3.18	2.44, 2.39 [2.466]	2.72	148.5, 154.8 [172.0(3)]
11	3.12, 3.15[3.039(3)]	-	3.18	2.31-2.54 [2.229, 2.570][c]	2.72	162.5, 165.3 [172.0(3)]

[a]Experimental values in square brackets. [b] Sum of van der Waals radii. r_3 = 2.54 Å, $r_{3'}$ = 2.34 Å, $r_{3''}$ = 2.40 Å, $r_{3'''}$ = 2.31 Å.[78]

It is evident from the data in Table 2 that the F···O distance in the dimer **6** is very long (3.64 Å), which indicates that the interaction between monomers would be repulsive at shorter distances and that DMFU is reluctant to form XBs. This was to be expected as the crystal structure of **2a** showed no indication of XBs. The X···O distances in dimers **7-9** are all significantly shorter than that in **6**, which suggests that halogen bonding is plausible when X is a heavier atom. However, the DMClU monomers in the dimer **7** interact also by non-conventional HBs as evidenced by the calculated O···H distance (2.87 Å) that is close to the sum of vdW radii and significantly shorter than that found for either **8** or **9** (> 4 Å). The structural parameters in Table 2 further suggest that X···H HBs could play a minor role in the formation of DMClU, DMBrU and DMIU dimers, although these interactions, if they take place, are very weak. A common descriptor in the optimized structures of **7-9** is the non-linearity of the C=O···X angles that differs from the features observed in the crystal structures of **4a** and **5**, and is more in line with lone-pair directionality discussed above. For this reason, the C-X bonds in the dimers **8** and **9** are significantly nonparallel even though the molecules form linear chains in the crystal structures of **4a** and **5**.

The interaction energies (at 0 K) calculated for **7**, **8** and **9** are −15.2, −10.1 and −13.4 kJ mol^{-1}, respectively. It is clear that the interaction energy of **7** (X = Cl) is anomalously low as it also takes into account the rather strong contribution from the nonconventional C-H···O HB as well as from the Cl···H HB. Consequently, the XB in **7** is expected to be very weak. In contrast, XBs dominate the interaction between DMBrU and DMIU molecules in dimers **8** and **9**, for which reason the calculated interaction energies can be used as upper estimates of XB strengths in **8** and **9**. A comparison of the data to our previous calculations shows that, regardless of the substituent at positions 1 and 3 (H or methyl), IU and DMIU dimers have equal interaction energies.[13] However, as already mentioned, the absence of methyl groups in IU allows it to form stronger interactions with solvent molecules, such as with MeF (−18.4 $kJmol^{-1}$) and DMF (−19.5 $kJmol^{-1}$), or HBs with itself (−27.4 kJ mol^{-1}) or with solvents, for example with MeF (−22.5 kJ mol^{-1}), *via* N-H sites. It is therefore not surprising that IU shows much less tendency for XB formation, whereas its *N*-methylation to DMIU makes halogen bonding the preferred interaction mode.

Quantum chemical calculations were also performed for two more realistic tetramers, **10** and **11**, whose structures resemble the packing of DMIU in the crystal structure of **5**. The tetramers were investigated in order to estimate the overall contribution of XBs to the total interaction energy and therefore the crystal structure of **5**. Overall, the optimized structures of **10** and **11** are in satisfactory agreement with the crystallographic data (Fig. 6 and Table 2), giving a reasonable description of the observed intermolecular interactions. In this context, it should be mentioned that the tetramer **11** shows a nearly linear arrangement of DMIU molecules with C=O···X angles that deviate less than 10° from the experimental data (*cf.* > 20° for the structure of the dimer **9**). A comparison of the optimized structures of **9** and **11** suggests that the more linear arrangement

of adjacent molecules in the tetramer results from delicate interplay of XBs with the C-H···O HBs between adjacent chains. Obviously, for any given crystal, the overall structure always reflects a compromise among all possible intermolecular and intramolecular interactions.

The calculated total interaction energies for **10** and **11** are −108.8 and −77.8 kJ mol^{-1}, respectively.[106] Hence, considering that the interaction energy of a single XB in the dimer **9** is −13.4 kJ mol^{-1}, it can be estimated that the two XBs in **10** and **11** account for roughly 20 – 30 % of the total intermolecular interactions. Thus, the network of XBs is a major, but not entirely dominant, contributor to the intermolecular interactions in the crystal packing of DMIU in **5**. The role of halogen bonding is best exemplified by comparing the crystal structures of **4a** and **5** to that of LAKJUC: the absence of C=O···X XB in the latter leads to a very different arrangement of molecules in the solid state and complete breakup of the linear chains observed in the structures of both **4a** and **5**.

CONCLUSIONS

The focus of the present study was to explore the competition and cooperation between non-conventional hydrogen bonds (C-H···O) and halogen bonds (C-O···X) in pyrimidine nucleobases which where halosubstituted at the 5-position. Hence, seven crystal structures consisting of either DMHU (**1**) or its halogenated derivatives DMXUs (**2-5**) were prepared in *N*,*N*-dimethylformamide. All examined structures showed non-conventional hydrogen bonding but only three of them (**4a**, **4b** and **5**) were found to contain halogen bonds. In addition to X-ray analyses, quantum chemical calculations at the SCS-DF-LMP2/aug-cc-pVTZ level of theory were performed for dimers and tetramers of DMXUs (**6-11**) to get insight into the strengths of the observed interactions. The results obtained for compounds **1-5** were also compared to the

data previously reported for complexes of pure and halogenated uracils. The following conclusions may be drawn:

(1) No halogen atom mediated hydrogen bonds were observed in any of the investigated structures. The dominant role of non-conventional hydrogen bonds in the crystal structures of **1**-**3** arises from *N*-methylation that prevents the formation of strong hydrogen bonds between two uracil units. However, conventional hydrogen bonding to strong donor solvents remains a possibility. An illustrative example is the structure of **3** that contains one molecule of water per molecule of DMClU.

(2) Of all crystal structures investigated, halogen bonding is present only in systems **4a**, **4b** and **5**, with the urea carbonyl oxygen O1 acting as the acceptor. Thus, steric hindrance plays no role in the choice of carbonyl oxygen atoms in halogen bond formation, which can be rationalized with the comparable vdW radii for a methyl group (2.0 Å), iodine (1.98 Å) and, to lesser extent, bromine (1.85 Å).

(3) The halogen bonds in **4a**, **4b** and **5** are all rather weak, as exemplified by the observed reduction from the sum of vdW radii of the contact atoms (from 12 to 14%) and the calculated SCS-DF-LMP2/aug-cc-pVTZ interaction energies (all less than 15 kJ mol^{-1}). Despite of this, halogen bonding plays an important role in determining the crystal packing of all three compounds, acting alongside non-conventional hydrogen bonds. The delicate interplay of these two interactions also explains the linearity of C=O···X interactions in **4a**, **4b** and **5**, as illustrated by theoretical calculations for related dimers and tetramers. In comparison, pure 5-bromouracil and 5-iodouracil favour the formation of conventional

hydrogen bonds over other interactions, due to the presence of strong hydrogen bond donor N-H sites.

(4) In DMXUs, selectivity is observed in the choice of the basic sites O1 and O2 for C-H···O hydrogen bonds. Almost always the most acidic site (aromatic C-H) forms hydrogen bonds with the urea carbonyl oxygen O1, provided that the latter is not engaged in halogen bonding. The only exception is observed in the crystal structure of DMClU. As DMHU does not show as clear selectivity in its crystal structures, it can be concluded that halogenation of the structure at the 5-position most likely enhances the basicity of the O2 site. A related behavior has been reported for cyclic uracil-water and thymine-water complexes in which the most stable hydrogen bond is formed between the O site characterized by the smallest basicity and the N-H site with the highest acidity.[107,108]

ASSOCIATED CONTENT

Supporting Information. Full crystallographic data and *xyz*-coordinates of optimized structures are available free of charge via the Internet at http://pubs.acs.org.

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