

# Competition between hydrogen and halogen bonding in halogenated 1-methyluracil:water systems

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## ABSTRACT

The competition between hydrogen- and halogen-bonding interactions in complexes of 5-halogenated 1-methyluracil (XmU; X = F, Cl, Br, I or At) with one or two water molecules in the binding region between C5-X and C4=O4 is investigated with M06-2X/6-31+G(d). In the singly-hydrated systems, the water molecule forms a hydrogen bond with C4=O4 for all halogens, whereas structures with a halogen bond between the water oxygen and C5-X exist only for X = Br, I and At. Structures with two waters forming a bridge between C4=O and C5-X (through hydrogen- and halogen-bonding interactions) exist for all halogens except F. The absence of a halogen-bonded structure in singly-hydrated ClmU is therefore attributed to the competing hydrogen-bonding interaction with C4=O4. The halogen-bond angle in the doubly-hydrated structures (150-160°) is far from the expected linearity of halogen bonds, indicating that significantly non-linear halogen bonds may exist in complex environments with competing interactions.

## Introduction

A halogen bond (X-bond) is a type of noncovalent interaction similar to a hydrogen bond (H-bond), but with a halogen atom taking the role of the donor. In a halogen-bonded complex, the halogen atom in one molecule interacts favorably with the negative site of another molecule, usually a Lewis base. The first description of such a complex ( $\text{H}_3\text{N}\cdots\text{I}_2$ ) dates back to the nineteenth century;<sup>[1]</sup> later it was recognised that not only dihalogens can act as electron acceptors in such donor-acceptor complexes, but also halides in which the halogen is attached to an electron-withdrawing group.<sup>[2]</sup> These interactions were initially called “electron donor-acceptor” or “charge transfer” interactions. The term “halogen bond” was coined in 1978,<sup>[3]</sup> to stress its similarity with the hydrogen bond. In recent years there has been

an explosive interest in halogen bonds, as their potential in different areas of chemistry, biochemistry and materials is becoming increasingly evident. In 2013, Desiraju *et al.*, sponsored by the Physical and Biophysical Chemistry Division of IUPAC, proposed a definition of the halogen bond, referring to the essential feature of a stabilising electrophile-nucleophile relationship where the electrophilic element is “a region associated with a halogen atom in a molecular entity”.<sup>[4]</sup> This definition also includes a set of features as a guide to whether a given interaction would be correctly characterised as a halogen bond.

It may seem strange that halogens, which are generally considered electronegative, would form noncovalent bonds with Lewis bases. Politzer *et al.* provided a theoretical explanation for this phenomenon based on molecular electrostatic potentials.<sup>[5,6]</sup> The positive regions

on the potential maps reflect a deficiency in the electron density at the end of the halogens in  $\text{CCl}_4$  and  $\text{CBr}_4$ , surrounded by a belt of negative potential. This topology explains the observation that electrophiles tend to approach a halogen in a C-X bond (where X = Cl, Br or I) in a side-on manner (nearly perpendicular to the C-X bond), whereas nucleophiles approach head-on.<sup>[7,8]</sup> The electron deficiency at the end of the halogens has been labelled a  $\sigma$ -hole. The central position of the  $\sigma$ -hole, confined by a negative belt, is the reason for the observed strong directionality of halogen bonds, with halogen-bond angles typically between 160-180°. However, Auffinger *et al.* suggested that complex environments (such as those found in biological systems) can give rise to substantially non-linear halogen bonding due to secondary polarisation of the halogen atom's electron density.<sup>[9]</sup> Zhu *et al.* observed that in some protein structures, multiple halogen-bonding interactions take place with the same halogen,<sup>[10]</sup> which necessarily cannot all be at ideal linear halogen-bond angles. Hill and Hu found significant interactions at considerably angular displaced geometries in halogen-bonded complexes of dihalogens and ammonia.<sup>[11]</sup>

Fluorine is generally not considered to form halogen bonds. This has been attributed to the high electronegativity of fluorine and its tendency to engage in significant sp hybridisation, which produces an influx of negative charge into the region where the positive  $\sigma$ -hole would be.<sup>[12,13]</sup> Some recent studies state that organic fluorines can form halogen bonds when strongly electronegative substituents are bound to the carbon.<sup>[14-17]</sup> However, it has been suggested that this type of bond should not be labelled a halogen bond, as there are fundamental differences between

these interactions and halogen bonds involving Cl, Br and I.<sup>[18]</sup> Halogen-bonding strength is usually found to increase with the size and polarisability of the halogen.<sup>[11]</sup> Usually, only the more biologically and chemically relevant Cl, Br and I halogens are considered, though theoretical studies show that astatine-containing dihalogens tend to form the strongest halogen bonds.<sup>[11]</sup>

A comparison of analogous hydrogen and halogen bonds in DNA base pairs found that hydrogen bonds are generally stronger than halogen bonds, though the strongest halogen bonds are sometimes of comparable or greater strength than the weakest hydrogen bonds.<sup>[19]</sup> Riley *et al.* found that halogen bonding in  $\text{NCBr}\cdots\text{OCH}_2$  is of comparable magnitude as hydrogen bonding in  $\text{NCH}\cdots\text{OCH}_2$  (interaction energies of -4.37 and -4.50 kcal mol<sup>-1</sup>, respectively).<sup>[20]</sup> A study investigating the effect of substitution of aromatic hydrogens with electron-withdrawing fluorines on halogen bonding involving aromatically-bond halogens and carbonyl oxygens revealed the tunability of halogen bonds.<sup>[21]</sup> Such substitutions can dramatically increase the strengths of the halogen bonds, potentially making them of comparable strength as hydrogen bonds. In systems where there is possibility of both halogen- and hydrogen-bond formation, there may therefore be competition between the two differing interactions. In the current study we look at hydrogen- and halogen-bond formation in 5-halogenated 1-methyl-uracil:water systems, with the halogen varying from fluorine to astatine (see Fig. 1). Halogenated uracils play important roles in biology. The 5X-uracils with X = F, Cl, Br or I are employed to increase the sensitivity of DNA against ionising radiation.<sup>[22-24]</sup> and play roles in cancer treatment. 5-Bromouracil is a known mutagen; the last years

our group has been interested in the mutagenic mechanism of this base, including the role of hydration.<sup>[25-27]</sup> Ho *et al.* have shown that a halogen bond formed between a brominated uracil and an oxygen on a phosphate group can be engineered to direct the conformation of a DNA Holliday junction.<sup>[28]</sup> The heaviest halogen, astatine, is radioactive and all of its isotopes have short life times. The second longest-lived isotope is <sup>211</sup>At, which is of interest for medicinal applications as it can be used to diagnose and treat cancer. 5-Astatouracil has been synthesised as a possible carrier to direct <sup>211</sup>At to specific sites in the body.<sup>[29]</sup>

## Methods

The 5-halogenated 1-methyluracil:water (XmU-H<sub>2</sub>O with X = F, Cl, Br, I or At) systems were built using GaussView<sup>[30]</sup> and all calculations were performed using Gaussian 09.<sup>[31]</sup> For each system, we attempted to optimise a C5-X•••Ow halogen-bonded minimum as well as a C4=O4•••Hw1 hydrogen-bonded minimum (see Figure 1 for atom labeling). The minima found were used as starting points for scan calculations in which the C5-X•••Ow angle was varied in step sizes of 5°, while all other dimensions were allowed to freely optimise. For FmU-H<sub>2</sub>O and ClmU-H<sub>2</sub>O, only a hydrogen-bonded minimum was found. For all other systems, the transition state structure between the hydrogen- and halogen-bonded minima was obtained using the Synchronous Transit-Guided Quasi-Newton (STQN) Method<sup>[32,33]</sup> (invoked by the QST2 and QST3 keywords), or by a simple transition state optimisation (using the TS keyword), starting from the highest-energy structure in the flexible scan. For all fully-optimised structures the nature of the stationary point (minimum or transition state) was confirmed by calculation of harmonic

vibrational frequencies. Gaussian's default convergence criteria were used for the scan calculations, whereas "tight" convergence criteria were used for complete optimisations. All calculations were performed using the M06-2X<sup>[34]</sup> density functional. By default we employed the "ultrafine" integration grid (99 radial points and 590 angular points per shell), though in two cases the frequency calculations were done with the "superfine" grid, which is a (150,974) grid for the first two rows of the periodic table and (225,974) for later elements, as explained below. For systems incorporating fluorine, chlorine or bromine the 6-31+G(d) Pople basis set<sup>[35]</sup> was employed, while for the iodine- or astatine-containing systems the aug-cc-pVDZ-PP basis set, which includes small-core energy-consistent relativistic pseudopotentials (PP)<sup>[36]</sup>, was employed to incorporate relativistic effects. The full optimisations were performed using the counterpoise (CP) procedure<sup>[37]</sup> to remove basis set superposition error (BSSE). CP-corrected single-point energies were performed at the partially optimised geometries from the scans. Structures were visualised using GaussView and Molden.<sup>[38]</sup>

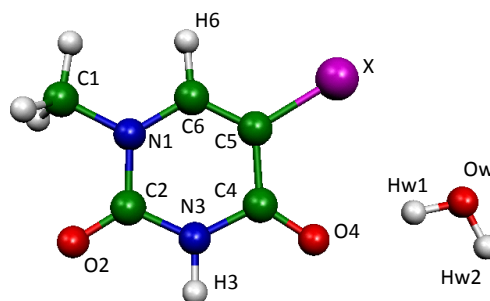


Figure 1. Atom labeling for the XmU-H<sub>2</sub>O (X=F, Cl, Br, I or At) systems. X is the halogen.

Electrostatic potential surfaces were created for the M06-2X/6-31+G(d) optimised structures of

the XmU (X = F, Cl, Br, I or At) molecules using GaussView. The electrostatic potentials were mapped on the  $0.0004 \text{ e}^-/\text{au}^3$  electron density surfaces.

CP-corrected M06-2X/6-31+G(d) or M06-2X/aug-cc-pVDZ-PP geometry optimisations were also performed for XmU-(H<sub>2</sub>O)<sub>2</sub> (X = F, Cl, Br, I or At) systems, with one water at the halogen-bonding site and the other water molecule hydrogen-bonding with C4=O4.

Cartesian coordinates of all optimised minima and transition states can be found in the Supporting Information.

## Results and Discussion

### XmU-H<sub>2</sub>O (X = F, Cl, Br, I, At)

Since the pioneering work by Politzer *et al.*<sup>[5,6]</sup>, many studies have used molecular electrostatic potential maps to demonstrate the  $\sigma$ -hole in possible halogen-bond donors, see for example references.<sup>[9,11,12,16,17,19,39-44]</sup> Figure 2 shows the electrostatic potential surfaces of the halogenated methyluracil molecules studied in this work. These show the absence of a clear  $\sigma$ -hole for FmU, whereas the  $\sigma$ -hole is clearly increasing in size from ClmU to AtmU.

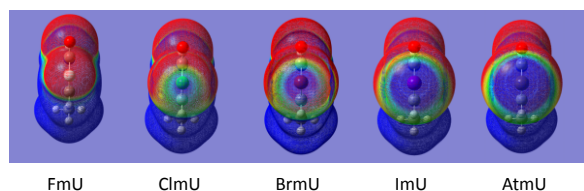


Figure 2. Molecular electrostatic potential maps (mapped on the  $0.0004 \text{ e}^-/\text{au}^3$  electron density

surface) for the XmU (X = F, Cl, Br, I, At) molecules. Blue and red represent positive and negative regions of electrostatic potential, respectively (from  $6.93\text{E-}3$  to  $-6.93\text{E-}3 \text{ E}_h/\text{e}$ ).

For all XmU-H<sub>2</sub>O systems we found a minimum with the water molecule hydrogen bonding to C4=O4. In these, the water binds to the base in a similar fashion as found for U-H<sub>2</sub>O<sup>[45]</sup> (see Figure 3A): the water molecule is in the plane of the methyluracil ring; one water hydrogen points to O4 of methyluracil, whereas the water oxygen points to the halogen (note that in U-H<sub>2</sub>O, only the water located in the binding site flanked by C5-H5 and C4=O4 is coplanar with the uracil ring; in the other minima the free water hydrogen is pointing out of the plane<sup>[45]</sup>). For comparison, we have also optimised the equivalent minimum for 1-methyluracil:H<sub>2</sub>O (mU-H<sub>2</sub>O) with M06-2X/6-31+G(d), which contains a weak C5-H5...Ow hydrogen bond in addition to the O4...Hw-Ow hydrogen bond (see Figure 3A). Compared to mU-H<sub>2</sub>O, for which the O4...Hw-Ow angle is  $154^\circ$ , the hydrogen-bond angle is much more linear in the halogenated systems, and becomes more linear going down the periodic table: the O4...Hw-Ow angle ranges from  $173^\circ$  for FmU-H<sub>2</sub>O to  $179^\circ$  in AtmU-H<sub>2</sub>O. This is accompanied by an increase in the C4=O4...Hw angle (from  $125^\circ$  for FmU-H<sub>2</sub>O to  $137^\circ$  for AtmU-H<sub>2</sub>O). These trends are presumably related to the increasing size of the halogen going from F to At and show that the C5-X...H<sub>2</sub>O interaction is not attractive in this orientation.

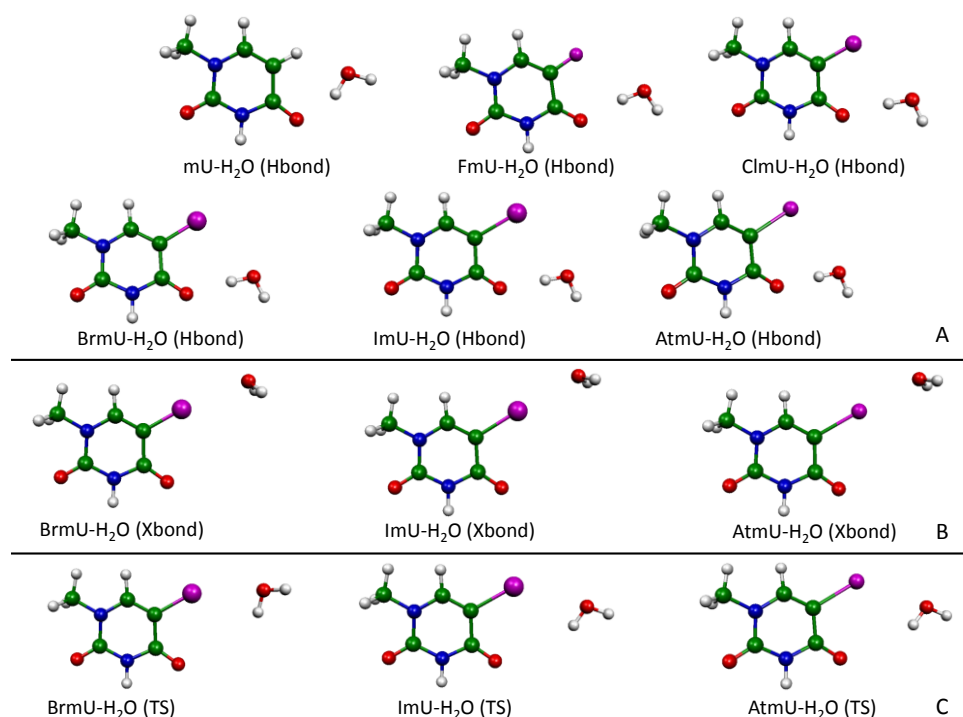


Figure 3. Minima and transition states for the  $XmU-H_2O$  ( $X = F, Br, Cl, I, At$ ) systems. The corresponding  $mU-H_2O$  minimum is also shown. A. Hydrogen-bonded minima. B. Halogen-bonded minima. C. Transition states between the hydrogen- and halogen-bonded minima.

For the systems incorporating Br, I or At, an  $X\cdots Ow$  halogen-bonding minimum was found; we also located the transition states connecting the halogen- and hydrogen-bonded minima. The structures are shown in Figure 3 (parts B and C). In all halogen-bonded minima, the water hydrogens are pointing above and below the plane of the methyluracil, and are tilted towards the O4 atom of the base. This orients the water oxygen's lone pair towards the halogen. One might expect an equivalent minimum with the water hydrogens tilted away from the O4 atom (exposing the other oxygen lone pair to the halogen). However, we did not manage to locate such a minimum. Presumably, favorable interaction between the water hydrogens and the O4 atom of methyluracil is

responsible for this. The halogen-bonded minima show near-linear halogen bonds (The  $C5-X\cdots Ow$  angle is 173, 177 and 178°, for the systems containing Br, I and At, respectively—see Table 1). The  $C5-X\cdots Ow$  angles for the Br-, I- and At-containing transition states are between those of the corresponding hydrogen- and halogen-bonded minima. Whereas this distance is closer to that of the hydrogen-bonded minimum for BrmU- $H_2O$ , it is closer to the halogen-bond minimum for ImU- $H_2O$ . The  $X\cdots Ow$  distance decreases from 3.02 to 3.01 and 2.94 Å for Br, I and At, respectively. The halogen-bond distances are within the sum of the van der Waals radii of the halogen and oxygen, which are 3.37, 3.50 and 3.54 for Br, I and At, respectively (see Table 2). These values

indicate a stabilising interaction at the halogen-bonding geometry for  $X = \text{Br}, \text{I}$  and  $\text{At}$ . Table 2 shows a trend towards smaller ratios for the internuclear distance divided by sum of the vdW radii (vdW-ratio), giving further strength to the proposition that the halogen-bond strength increases as the halogen group is descended.

All structures were confirmed to be minima or transition states by calculating harmonic vibrational frequencies. In two cases, we did not obtain the expected number of imaginary frequencies: the hydrogen-bonded  $\text{ClmU-H}_2\text{O}$  frequency calculation yielded one negative frequency, whereas the calculation of the transition between the hydrogen- and halogen-bonded  $\text{ImU-H}_2\text{O}$  minima yielded two negative frequencies. The spurious frequency was in both cases related to out-of-plane motion of the water hydrogens. Tighter geometry optimisation did not solve the problem. We manage to get rid of the spurious imaginary frequency by calculating the frequencies using the “superfine” integration grid. We verified that the superfine grid yields the same geometries for these two systems. Tests for some of the other stationary points using the superfine grid did not change the results.

While searching for the hydrogen-bonded minima described above, we found two other types of minima with a direct interaction between the water molecule and the halogen: (1) an out-of-plane minimum with the water molecule located above the plane of methyluracil and binding to O4 and (2) a minimum in which the water binds to the base through  $\text{C6-H6}\cdots\text{Ow}$  and  $\text{C5-X}\cdots\text{Hw}$  interactions. We refer to these as “out-of-plane” and “second hydrogen-bonded” minimum, respectively. Such minima exist for all halogens (see Figure 4), but not for non-halogenated methyluracil. The out-of-plane minimum does not exist for non-halogenated methyluracil presumably because the water prefers to form two hydrogen bonds with the base, which can only be achieved if the water (or, at least, one of the  $\text{Ow-Hw}$  bonds) is in the plane of the base (cf. the  $\text{mU-H}_2\text{O}$  hydrogen-bonded structure in Figure 3A). The second hydrogen-bonded minimum does not exist for non-halogenated methyluracil as the C5 atom does not contain a hydrogen-bond acceptor (H instead of halogen).

Table 1. C5-X•••Ow angle (in degrees) for the H-bonded and X-bonded minima and the transition state between them

1Stationary point	X=F	X=Cl	X=Br	X=I	X=At
H-bonded minimum	81	107	104	98	97
X-bonded minimum	--	--	173	178	178
Transition state	--	--	153	136	129

Table 2. X•••Ow distances R(X-Ow), sums of vdW radii ( $\Sigma$  vdW radii) and the ratio between them (vdW-ratio) for the X-bonded minima. All distances in Å

System	R(X-Ow)	$\Sigma$ vdW radii <sup>[a]</sup>	vdW-ratio <sup>[b]</sup>
BrU-H <sub>2</sub> O	3.02	3.37	0.90
IU-H <sub>2</sub> O	2.96	3.50	0.85
AtU-H <sub>2</sub> O	2.94	3.54	0.83

[a] Sum of van der Waals radii.<sup>[46,47]</sup> The van der Waals radius of oxygen is 1.52 Å.<sup>[47]</sup> [b] The ratio of R(X-Ow) and  $\Sigma$  vdW radii.

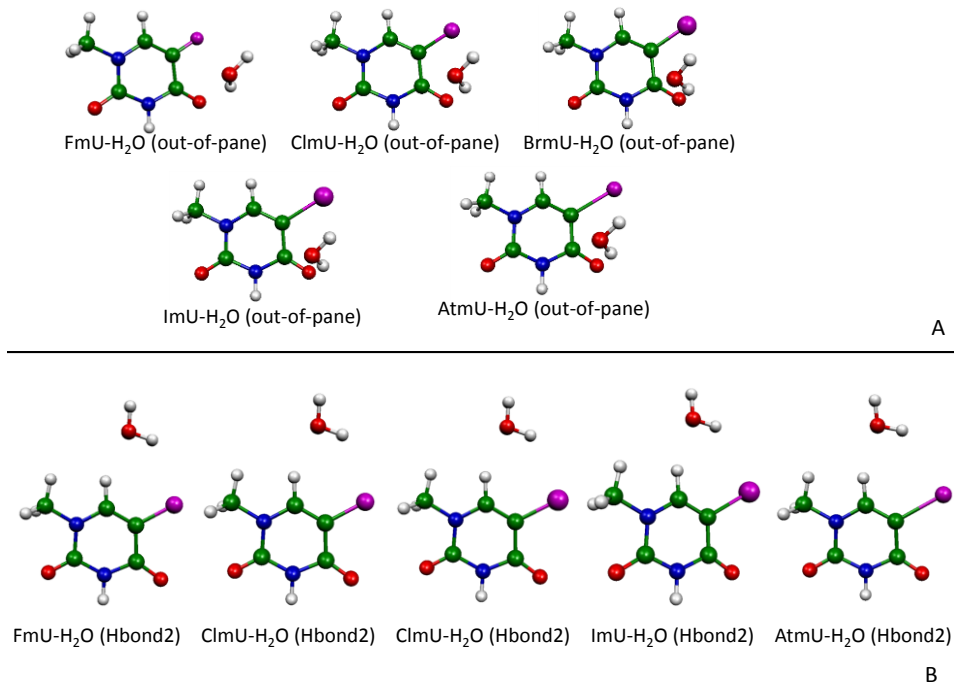


Figure 4. Out-of-plane and second hydrogen-bonded (Hbond2) minima for the  $XmU-H_2O$  ( $X = F, Br, Cl, I, At$ ) systems.

Table 3 shows the CP-corrected interaction energies for the different types of minima and, for the systems for which also a halogen-bonded minimum was located, the transition states connecting the halogen- and hydrogen-bonded minima. In all cases, the halogen-bonded minimum has a smaller interaction energy than the hydrogen-bonded minimum. The halogen-bond strength increases going down the halogen group, with astatine forming a halogen bond of comparable strength to the  $O4\cdots Hw$  hydrogen bond, with an energetic difference of only  $1.0 \text{ kJ mol}^{-1}$ . Note that the hydrogen-bond strength does not increase going down the halogen group; the strongest hydrogen bond is formed in the  $BrmU-H_2O$  system ( $-25.2 \text{ kJ mol}^{-1}$ ), whereas the weakest occurs in the  $ImU-H_2O$  system ( $-23.2 \text{ kJ mol}^{-1}$ ).

The non-halogenated hydrogen-bonded minimum has a considerably larger interaction energy than its halogenated counterparts, due to the presence of a second ( $C5-H5\cdots Ow$ ) hydrogen bond. Tian and Li studied different types of bonding (halogen,  $\pi$  and hydrogen bonding) for complexes formed between the superalkali  $Li_3S$  and the  $XCCH$  molecule ( $X = F, Cl, Br$  or  $I$ )<sup>[44]</sup>. They also found that, while the halogen-bonding interaction increases with increasing atomic number of the halogen, the hydrogen-bonding interaction shows little dependence on the nature of  $X$  in  $XCCH$ , in agreement with our observations. For  $Li_3S\cdots XCCH$ , the halogen-bonded minimum is more favorable than the hydrogen-bonded minimum already for  $X = Br$ .

Table 3. Interaction energies (in  $\text{kJ mol}^{-1}$ ) of minima and transition states (between H-bonded and X-bonded minima)

Stationary point	X=H	X=F	X=Cl	X=Br	X=I	X=At
H-bonded	-35.8	-24.3	-24.4	-25.2	-23.2	-24.3
X-bonded	--	--	--	-12.2	-16.4	-23.3
Transition state	--	--	--	-11.7	-11.6	-13.5
Out-of-plane	--	-24.7	-24.5	-24.8	-22.4	-22.0
Second H-bonded	--	-25.2	-23.8	-24.7	-23.0	-22.3

Only a very low energy barrier,  $0.5 \text{ kJ mol}^{-1}$ , impedes the halogen-bonded geometry in the bromine-containing system from converting to the more energetically favorable hydrogen-bonded geometry. Hence, the halogen bond is presumably only metastable. The barriers for conversion from the halogen- to hydrogen-bonded systems are larger for the iodinated and

astatinated systems ( $4.8 \text{ kJ mol}^{-1}$  and  $9.8 \text{ kJ mol}^{-1}$ , respectively).

Although we are mainly interested in the hydrogen- and halogen-bonded minima, because of their potential competitiveness, we also list the interaction energies of the out-of-plane and second hydrogen-bonded minima. The three hydrogen bonded minima are of



comparable strength, with interaction energies ranging from 22 to 25 kJ mol<sup>-1</sup>.

Figure 5 shows the interaction energy of the XmU-H<sub>2</sub>O systems investigated as a function of the C5-X•••Ow angle. The FmU-H<sub>2</sub>O and ClmU-H<sub>2</sub>O systems show similar profiles, with a minimum where the hydrogen-bonded minimum occurs and no minimum at (near-)linear C5-X•••Ow angles (where the halogen-bonded minimum would occur if it existed). The BrmU-H<sub>2</sub>O, ImU-H<sub>2</sub>O and AtmU-H<sub>2</sub>O profiles show two minima: a deep hydrogen-bonded minimum around 100° and a shallower halogen-bonded minimum at 180°. In agreement with Table 3, the halogen-bonded potential well becomes deeper for increasingly heavier halogens. The BrmU-H<sub>2</sub>O profile is different depending on whether the scan was started from the hydrogen- or halogen-bonded minimum. When starting from the hydrogen-bonded minimum, the water remains in the plane of the methyluracil ring when the angle is increased towards 180°. Above ~160°, this is a less favorable arrangement than that adopted by the halogen-bonded minimum. When starting from the halogen-bonded minimum, the water remains initially in the position it adopts in the halogen-bonded minimum (water hydrogens on either side of the methyluracil ring), but when the C5-X•••Ow angle drops below 118°, the water molecule reorients itself to be in the plane of the methyluracil ring. This is accompanied by a drop in energy (Figure 5). Something similar happens in the ImU-H<sub>2</sub>O scans: starting from the halogen-bonded minimum, the water first remains in the halogen-bonded orientation, then reorients itself into the hydrogen-bonded orientation from ~120° downwards. Then, for C5-X•••Ow angles below ~100°, the water starts going out of the plane of the methyluracil ring, apparently

on a pathway towards the out-of-plane minimum. In the AtmU-H<sub>2</sub>O scans the cross-over point from hydrogen- to halogen-bonded orientation in the scan started from the hydrogen-bonded minimum occurs at approximately the same angle (~160°) as the cross-over point from halogen- to hydrogen-bonded orientation in the scan started from the halogen-bonded minimum. The two curves merge seamlessly at the cross-over point. Like for ImU-H<sub>2</sub>O, in the AtmU-H<sub>2</sub>O scan from the halogen-bonded minimum, the water starts going out of the plane of the methyluracil ring for C5-X•••Ow angles below ~100°.

As discussed above, the hydrogen-bonded minima correspond to structures in which the water molecule is coplanar with the aromatic ring, whereas the halogen-bonded geometries place the Hw atoms either side of the plane of the aromatic ring. Hence hydrogen bonding and halogen bonding are competing factors in determining the position of the water molecule. These competing influences on the geometry of the system arise from the directionality of hydrogen bonding and (especially) halogen bonding.

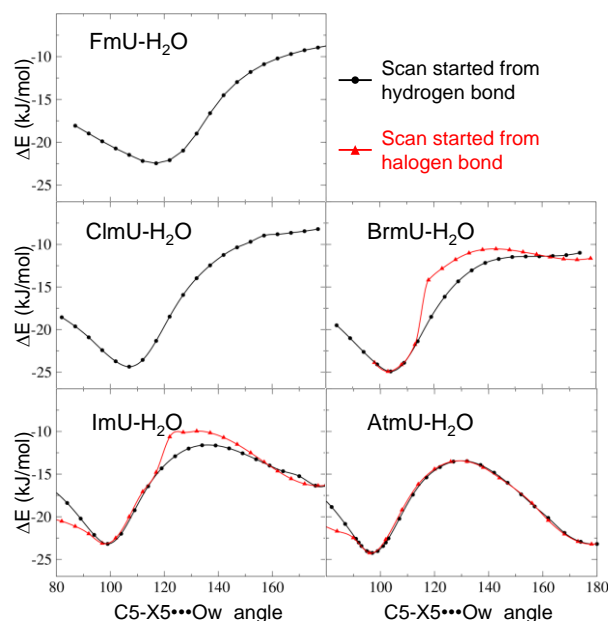


Figure 5. Interaction energies (in  $\text{kJ mol}^{-1}$ ) of the  $\text{XmU-H}_2\text{O}$  ( $X = \text{F, Cl, Br, I, At}$ ) systems as a function of the  $\text{C5-X}\cdots\text{Ow}$  angle (in degrees).

#### $\text{XmU-(H}_2\text{O)}_2$ ( $X = \text{F, Cl, Br, I, At}$ ).

Figure 6 shows the  $\text{XmU-(H}_2\text{O)}_2$  structures obtained by placing two water molecules between the  $\text{C5-X}$  and  $\text{C4=O4}$  sites. For  $X = \text{Cl}$  to  $\text{At}$ , a minimum was found where the two waters form a bridge between the two functional sites; one water interacts with the base through a halogen bond, whereas the other forms a hydrogen bond with  $\text{C4=O4}$  (Figure 6A). Such a structure was not found for  $\text{FmU-(H}_2\text{O)}_2$ . Instead, the geometry optimisation converged towards a minimum in which the water dimer is located above the methyluracil plane, with one of the waters forming an  $\text{OH}\cdots\text{O}$  hydrogen bond with  $\text{O4}$  and the second water hydrogen-bonding to the first one. Thus, even if the competing  $\text{C4=O4}$  site is saturated with a hydrogen bond, water still does not form a halogen bond with  $\text{C5-F}$ . However,  $\text{ClmU}$ , which like  $\text{FmU}$  does not form a halogen bond with one water, does form a halogen bond with a water dimer. The absence of a halogen-bonded  $\text{ClmU-H}_2\text{O}$  structure can therefore be attributed to the competing hydrogen-bonding interaction

with  $\text{C4=O4}$ . Once this interaction is blocked by a water molecule, the chlorine is apparently happy to form a halogen bond with a second water molecule. Substitution of uracil hydrogens by strongly electron-withdrawing groups, as investigated in Ref. <sup>[21]</sup>, may potentially increase the  $\sigma$ -hole on chlorine to such an extent that the halogen-bonded minimum becomes stable in  $\text{ClmU-H}_2\text{O}$ .

All  $\text{XmU-(H}_2\text{O)}_2$  complexes have a minimum-energy structure with the water dimer above the methyl uracil plane (Figure 6B). Such a minimum also exist for non-halogenated methyluracil, though there are some differences. In the halogenated structures, the water molecule hydrogen-bonding with  $\text{O4}$  is tilted towards the halogen; the hydrogen that is not hydrogen-bonding with  $\text{O4}$  is pointing to the halogen, presumably interacting with its negative ring. In non-halogenated methyluracil, the water molecule that is hydrogen-bonding with  $\text{O4}$  is tilted towards the  $\text{N3-H}$  functional group, presumably forming a favorable  $\text{N-H}\cdots\text{O}$  interaction (with an  $\text{N-H}\cdots\text{O}$  angle of  $114^\circ$ ).

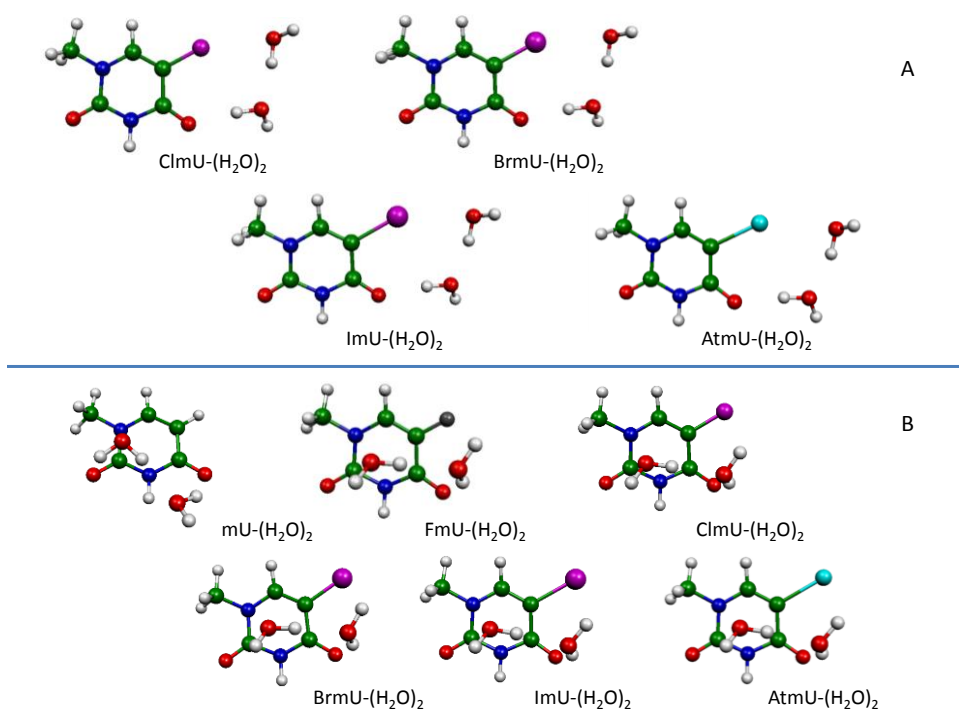


Figure 6. Structures of the  $XmU-(H_2O)_2$  minima optimised in this work. A. Water dimer located between C5-X and C6=O6. B. water dimer located above the methyluracil ring.

Table 4 shows the interaction energies and structural parameters, including the vdW-ratio for the structures with the water dimer bridging the C5-X and C4=O4 functional groups. The interaction energies of these structures increase from X = Cl to At, though there is only a very minor increase in interaction energy from X = Br to X = I ( $0.20 \text{ kJ mol}^{-1}$ ). The vdW-ratio is below 1 for all of these, indicating a true halogen bond, and decreases from X = Cl to X = At. Note that the halogen-bond angle, C5-X...Ow is significantly less linear ( $150\text{--}160^\circ$ ) than in the singly-hydrated halogen-bonded systems. This is presumably because of the need to accommodate the water-water and water-uracil hydrogen bonds, as well as the halogen bond. This shows that significantly non-linear halogen bonds may exist if competing interactions are

present. This is consistent with research by Shields *et al.*,<sup>[48]</sup> who studied the properties of several R-Br...B (where B is a negative site) halogen-bonded complexes as a function of the R-Br-B angle. They found that the interaction energy changes very gradually from  $180^\circ$  to about  $160^\circ$ , but then falls off much more rapidly after about  $150^\circ$ . Also shown in Table 4 are the interaction energies of the complexes with the water dimer above the methyluracil ring, which contain two hydrogen bonds. These are considerably more stable than the corresponding structures featuring one hydrogen bond and a halogen bond, confirming the greater strength of hydrogen compared to halogen bonds.

Table 4. Interaction energies (in  $\text{kJ mol}^{-1}$ ) and geometric parameters (distances in  $\text{\AA}$ ; angles in degrees) for the  $\text{XmU}-(\text{H}_2\text{O})_2$  systems

System	Water dimer located between the C5-X and C6=O6 sites						Above ring
	$\Delta E$	R(X-Ow)	R(O6-Hw)	C5-X•••Ow	$\Sigma$ vdW radii <sup>[a]</sup>	Ratio <sup>a</sup>	$\Delta E$ <sup>[b]</sup>
U-(H <sub>2</sub> O) <sub>2</sub>	--	--	--	--	--	--	-83.73
FU-(H <sub>2</sub> O) <sub>2</sub>	--	--	--	--	--	--	-79.82
ClU-(H <sub>2</sub> O) <sub>2</sub>	-64.79	2.92	1.93	159	3.27	0.89	-87.84
BrU-(H <sub>2</sub> O) <sub>2</sub>	-68.84	2.98	1.94	155	3.37	0.88	-90.00
IU-(H <sub>2</sub> O) <sub>2</sub>	-69.04	3.03	1.98	150	3.50	0.87	-83.78
AtU-(H <sub>2</sub> O) <sub>2</sub>	-74.94	2.97	1.99	150	3.54	0.84	-82.89

[a] See footnote, Table 2. [b] Water dimer located above the methyluracil plane.

## Conclusions

We investigated hydrogen and halogen bonding in the region between C5-X and C4=O4 in 5-halogenated 1-methyluracil:water ( $\text{XmU}-\text{H}_2\text{O}$  with X = F, Cl, Br, I or At) using M06-2X/6-31+G(d). In all systems the water molecule was found to form a hydrogen bond with the C4=O4 functional group. Structures stabilised by a halogen bond between the water oxygen (Ow) and the halogen were only found for X = Br, I and At. Transition states between the halogen- and related hydrogen-bonded systems were located, and relaxed potential energy curves for conversion between the halogen- and hydrogen-bonded systems were created by varying the C5-X•••Ow angle between its values for the two competing minima. The hydrogen-bonded minima are more stable for all systems. However, the interaction energies of the halogen-bonded minima systematically increase down the halogen group (interaction energies of  $-12.2 \text{ kJ mol}^{-1}$ ,  $-16.5 \text{ kJ mol}^{-1}$  and  $-23.3 \text{ kJ mol}^{-1}$  for X = Br, I and At, respectively), and the interaction energy of the halogen-bonded  $\text{AtmU}-\text{H}_2\text{O}$  system is only  $1 \text{ kJ mol}^{-1}$

smaller than that of its hydrogen-bonded counterpart. There is also a strong trend down the halogen group towards greater barrier heights (between the halogen-bonded minimum and the transition state). From the small barrier height for  $\text{BrmU}-\text{H}_2\text{O}$  it is clear that this system can only be expected to be meta stable, even at very low temperatures.

We found two other minima with the water molecule in direct interaction with the halogen: an out-of-plane minimum with the water molecule located above the plane of the base and binding to O4 and a minimum in which the water binds to the base through C6-H6•••Ow and C5-X•••Hw interactions. These minima exist for all halogens but not for unhalogenated methyluracil.

We also investigated structures with two water molecules in the region between C5-X and C4=O4. All systems except  $\text{FmU}-(\text{H}_2\text{O})_2$  form structures where the two waters form a bridge between the two functional sites; one water interacts with the base through a halogen bond, whereas the other forms a hydrogen bond with C4=O4. The absence of a halogen-bonded

structure in singly-hydrated ClmU can therefore be attributed to the competing hydrogen-bonding interaction with C4=O4. This shows that halogen-bonding potential in molecular complexes can be reduced by nearby hydrogen bonds. The halogen-bond angle in the doubly-hydrated structures (150–160°) is far from the expected near-linearity of halogen bonds, indicating that significantly non-linear halogen bonds may exist in complex environment where competing interactions are present.

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**Keywords:** halogen bond, hydrogen bond, methyluracil, density functional theory, M06-2X

((Additional Supporting Information may be found in the online version of this article.))

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## GRAPHICAL ABSTRACT

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"Competition between hydrogen and halogen bonding in halogenated 1-methyluracil:water systems"

Density functional theory calculations reveal competition between halogen- and hydrogen-bonding interactions in complexes of halogenated methyluracil and water.

