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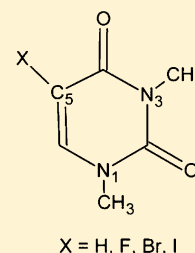
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Sublimation Enthalpies of 5-Haloderivatives of 1,3-Dimethyluracil

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ABSTRACT: Vapor pressure of solid 1,3-dimethyluracil, 5-fluoro-1,3-dimethyluracil, 5-bromo-1,3-dimethyluracil, and 5-iodo-1,3-dimethyluracil were determined by Knudsen effusion method. The sublimation enthalpies and entropies at the average temperatures of the experimental ranges were calculated from the dependence of vapor pressure by the temperature. Utilizing estimated gas–solid differences of molar heat capacity, the standard ($p^\circ = 0.1$ MPa) molar enthalpy, and entropy of sublimation corrected at 298 K were obtained. The differences in sublimation enthalpies of the haloderivatives of 1,3-dimethyluracil, which follow the sequence in polarizability of the halogen substituents in 5 position, can be used to reveal the weak bonding between the electron-rich atoms and the highly polarizable halogen atoms in these compounds. Our results suggest the possibility that 5-iodo-1,3-dimethyluracil and 5-bromo-1,3-dimethyluracil, but not 5-fluoro-1,3-dimethyluracil, can act as halogen bond donors in the crystal.



1. INTRODUCTION

Hydrogen bonding (HB), which is of vital importance in biology, is the most prominent directional interaction responsible for supramolecular construction and has been the subject of century-long interest. To the contrary, although the ability of halogen atoms to form short nonbonded contacts in crystals has been known for a long time,¹ halogen bonding (XB) is a recently defined concept.² So far, XB has received less attention in the literature than HB; however, there is increasing evidence that molecular interactions involving halogen compounds are topical in biology, materials science, and crystal engineering.^{3,4}

XB is a stabilizing directional interaction arising from a nucleophile–electrophile pairing between an electron donor species (i.e., halide anions or atoms carrying an available lone pair as N, O, or S) and a halogen atom. Halogen polarizability is the key factor in XB and the strongest interactions are formed by the most easily polarizable halogens. Therefore, the strength of the XB is expected to decrease in the order $I > Br > Cl \gg F$. Remarkably, several examples of XB have been culled from a survey of halogenated proteins and nucleic acids in the Protein Data Bank, including an unusually strong $Br^{\cdots}O$ interaction (2.7 Å, ~ 0.8 times the sum of van der Waals radii) that involves 5-bromouracil and stabilizes a Holliday junction.⁵

Enthalpy of sublimation, $\Delta_c^\circ H$, is considered the experimental thermodynamic quantity describing the stability of the crystal structure and quantifies the strength of the intermolecular interactions in the crystal.⁶ Inspired by this, as part of our continuing study of the relationships between molecular structure and crystal environment in crystal engineering of DNA/RNA canonical and epigenetic (naturally modified) bases,^{7–16} we expanded the focus of our thermodynamic study on the sublimation of pyrimidine nucleobases^{17,18} to 5-haloderivatives of 1,3-dimethyluracil (5-XDMU; X = F, Br, I; Figure 1). [5-Chloro-1,3-dimethyluracil (5-ClDMU), purchased from Ukrorgsyntez with assessed molar fraction purity of approximately 0.95, was unsuccessfully purified by successive

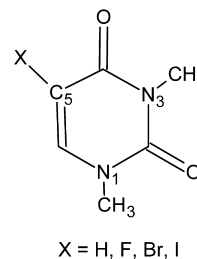


Figure 1. Structural formula of 5-halosubstituted-1,3-dimethyluracils (5-XDMU; X = F, Br, I).

sublimation under reduced pressure as well as by repeated recrystallization from different solvents (water, DMF, DMSO) and was not included in the present study.]

5-XDMUs, when compared to 1,3-dimethyluracil (DMU), are ideal candidates to ascertain the potential role of XB for molecular recognition of DNA/RNA bases. Indeed these compounds, due to the N-methylation in the 1 and 3 positions, lack strong hydrogen bond donors (N–H) but hold C=O groups that do not participate in conventional hydrogen bonds.^{19–21} Because only electrophilic halogens form XB when approaching an atom carrying an available lone pair, hence the halogen atom in 5-XDMUs, which is bonded to an sp^2 hybridized carbon and becomes polarized due to the adjacent electron-withdrawing carbonyl group, can act in the C–X as XB donor (electron acceptor). The oxygen atom in the C=O of the heterocyclic ring is the counterpart of the intermolecular interaction, and can act as XB acceptor (electron donor).

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2. EXPERIMENTAL SECTION

2.1. Experimental Apparatus. The Uguine-Eyraud Model B60 Setaram thermobalance was used for the measurements of vapor pressure (Figure 2). This apparatus consists essentially of a

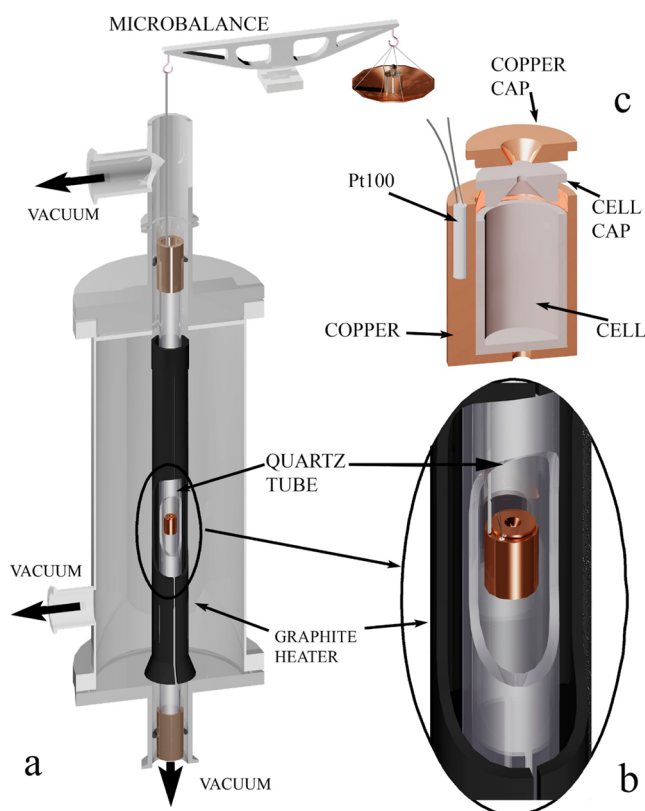


Figure 2. Scheme of the experimental apparatus used in this work.

furnace, a microbalance and a vacuum system. The heating element is a graphite heater contained in a vacuum chamber; within this resistor is placed a quartz tube that contains the measuring cell (Figure 2a). The cell is inserted into a copper cylinder with a cap (Figure 2b and c), which has the purpose of equalize the temperature of the sample and to allow an optimal temperature measurement. The copper cylinder is suspended to the arm of a microbalance with a standard measurement uncertainty of 0.01 mg. The temperature was measured via a Pt100 Platinum Resistance Thermometers, with a standard measurements uncertainty estimated to be less than 0.2 K, inserted in the copper cylinder as reported in Figure 2c. The measurement system is connected to two efficient vacuum systems, each constituted by a rotary and a diffusion pumps. The temperature control and the measurements of the mass loss are made through a data logger (HP 34970A) driven by a Labview software that permit the continuous control of the system.

2.2. Experimental Procedure. DMU (99% pure), 5-FDMU (99% pure), 5-BrDMU (99% pure), and 5-IDMU (99% pure) were supplied by Sigma Chemical Co., with the purities certified by the supplier. All substances were further purified by vacuum sublimation (Table 1).

In the experiments, we used three cells, made in pyrophyllite, with different effusion holes diameters (cell A, 3 mm; cell B, 1 mm; and cell C, 0.3 mm).

Before the measurements on the samples, some calibration runs were made for each cell to determine the constants of the

Table 1. Sample Information

sample	source	initial mole fraction purity	purification method
DMU	Sigma Chemical Co.	0.99	sublimation
5-FDMU	Sigma Chemical Co.	0.99	sublimation
5-BrDMU	Sigma Chemical Co.	0.99	sublimation
5-IDMU	Sigma Chemical Co.	0.99	sublimation

Knudsen equation.²² For the calibration, we used benzoic acid^{23,24} and cadmium²⁵ as standard substances with well-known vapor pressures.

The temperature was changed during the measurements to obtain isotherm periods to evaluate the mass loss rate at different constant temperatures. For each sample, two of the three cells mentioned above have been used in order to start measurements from the lowest possible values of temperature and pressure. For each cell, the measurements were carried out varying three times the temperature from highest to lowest value, as shown in Table 2. In this way, a change in the composition of the sample, caused by decomposition reactions, would produce a gradual variation of the vapor pressures and, therefore, three nonoverlapping data sets. In the measurements reported here, these problems have not been encountered. This also ensures that there were no significant amounts of impurities. In fact, if the sample contained volatile impurities, they would be vaporized in the early stages of the measurements. If nonvolatile impurities were present, they would increase their concentration during the vaporization of the sample. In both cases, we would have obtained descending series of vapor pressure measurements.

The vapor pressures of the sample were obtained using the Knudsen equation

$$p = K \cdot \frac{\Delta m}{\Delta T} \sqrt{\frac{T}{M}} \quad (1)$$

where T is the sample temperature, M the molar mass of the effusing vapor, K the constant including the geometrical characteristics of the effusion holes of the cell and $\Delta m/\Delta t$ the rate of mass loss of the sample.

The standard uncertainties (u) of the calculated vapor pressures are estimated to be $u(p) = 0.05p$.

In Table 2 measured temperatures, mass loss, and isothermal time periods are reported for DMU, 5-FDMU, 5-BrDMU, and 5-IDMU. From these measured parameters, via Knudsen equation, vapor pressures were determined and reported in the same table in logarithmic form. Using the least-squares method, the logarithm of the pressure as a function of the reciprocal temperature was determined for each run. Table 3 gives the parameters of the obtained equations and the corresponding measurement temperature range. These equations represent, for the studied compounds, the integrated form of the Clausius–Clapeyron equation

$$\ln(p/p^\circ) = A - B \cdot (K/T) \quad (2)$$

where $p^\circ = 0.1$ MPa, A is a constant and $B = \Delta^\circ H^\circ(\langle T \rangle)/R$

3. RESULTS AND DISCUSSION

Figure 3 compares the DMU, 5-FDMU, 5-BrDMU, and 5-IDMU vapor pressures. In this figure, a trend is evident, that is, the vapor pressure increases when molecular weight decreases. This trend

Table 2. Knudsen Vapor Pressure Data for DMU, 5-FDMU, 5-BrDMU, and 5-IDMU^a

cell	<i>T</i>	Δt	Δm	$\ln p$	$\Delta p/p_{\text{calc}}^b$	cell	<i>T</i>	Δt	Δm	$\ln p$	$\Delta p/p_{\text{calc}}^b$
	K	s	mg	Pa			K	s	mg	Pa	
DMU						5-BrDMU					
B	337.6	2752	6.037	0.69	−1.8	A	333.2	7565	1.76	−3.64	0.9
	327.8	1950	1.618	−0.30	2.8		323.1	6780	0.45	−4.91	2.1
	318.0	2550	0.714	−1.40	1.3		313.2	17940	0.33	−6.21	6.4
	308.2	4450	0.395	−2.56	0.9		303.3	86760	0.33	−7.79	−6.6
	298.3	46749	1.186	−3.83	−2.2		293.3	291122	0.26	−9.28	−0.9
	334.9	2923	4.586	0.35	−7.5		330.0	3560	0.53	−4.08	−4.0
	324.8	2362	1.398	−0.64	0.6		320.2	9561	0.42	−5.33	−0.4
	315.0	3021	0.606	−1.74	1.7		310.3	27460	0.34	−6.61	8.0
	306.6	4761	0.355	−2.74	2.3		300.3	126330	0.33	−8.19	−0.9
	331.8	3020	3.665	0.09	−1.4		327.0	3400	0.35	−4.46	−3.5
	321.9	2421	1.079	−0.93	3.6		317.2	11302	0.33	−5.73	0.3
	312.1	3511	0.497	−2.09	1.1		307.3	48008	0.35	−7.13	−1.3
	302.2	9486	0.402	−3.31	−0.5		297.3	214055	0.36	−8.62	0.7
	293.3	30420	0.391	−4.52	−4.9	B	357.9	2020	1.02	−0.97	1.4
C	357.7	8144	11.426	2.44	−2.5		347.8	2920	0.52	−2.02	3.0
	347.8	2491	1.502	1.59	3.2		337.6	10022	0.56	−3.20	0.8
	338.0	2091	0.488	0.62	2.7		327.7	34122	0.60	−4.38	0.9
	354.7	1991	2.202	2.20	0.7		360.6	2621	1.69	−0.72	−1.9
	344.9	2390	1.070	1.28	1.4		350.6	2777	0.66	−1.74	0.1
	335.1	4290	0.711	0.28	−1.8		340.8	7041	0.55	−2.87	−2.6
	351.7	2690	2.212	1.90	−1.6		330.7	27581	0.68	−4.04	−1.4
	341.9	2900	0.956	0.97	−0.7		354.5	4021	1.41	−1.34	−0.5
	360.5	2780	5.266	2.75	2.4		344.6	3720	0.45	−2.41	0.0
							334.8	9519	0.38	−3.54	0.3
5-FDMU						5-IDMU					
A	322.9	1600	2.10	−1.76	2.1	A	362.5	1351	1.174	−2.37	1.8
	312.8	2281	0.97	−2.90	6.5		352.6	1921	0.588	−3.43	3.6
	303.0	8552	0.99	−4.22	−3.6		342.9	4212	0.422	−4.56	2.5
	288.1	52962	0.87	−6.19	2.0		333.2	10019	0.301	−5.78	0.1
	287.6	110283	1.67	−6.28	0.8		323.4	40062	0.360	−7.00	4.9
	325.7	2111	3.47	−1.53	−6.3		367.3	2802	3.797	−1.92	−3.9
	315.9	1881	1.10	−2.58	1.1		357.5	2210	1.107	−2.93	−0.9
	306.1	6391	1.16	−3.77	2.1		347.8	4310	0.737	−4.02	0.2
	296.0	15481	0.77	−5.07	4.0		338.0	10117	0.552	−5.18	0.8
	319.8	1581	1.43	−2.13	0.5		328.2	30653	0.447	−6.51	−8.5
	309.9	5070	1.41	−3.33	−0.7	B	392.1	2491	6.477	0.61	−0.7
	300.0	18360	1.46	−4.60	−2.7		382.4	2662	2.840	−0.29	−0.1
	293.2	24094	0.72	−5.59	−9.3		372.7	2101	0.893	−1.22	2.2
	290.0	65470	1.42	−5.92	1.7		362.7	3177	0.485	−2.26	2.2
B	354.8	1320	7.11	1.39	−1.8		353.5	8030	0.450	−3.28	1.7
	342.0	1371	2.29	0.20	2.1		389.2	1680	3.355	0.35	−0.6
	334.8	2670	2.20	−0.52	3.1		379.5	1540	1.254	−0.56	1.0
	325.0	5721	1.67	−1.57	2.1		369.8	2031	0.637	−1.53	1.4
	315.2	5821	0.55	−2.71	−0.7		360.0	3820	0.400	−2.64	−6.7
	351.6	2120	8.65	1.11	−0.3		386.3	3274	4.956	0.07	−1.5
	341.8	2021	3.35	0.19	2.7		376.5	2100	1.293	−0.85	1.6
	332.0	2220	1.36	−0.82	1.6		366.8	2750	0.629	−1.85	−0.1
	322.3	4921	1.05	−1.89	0.9		357.1	6930	0.566	−2.89	0.0
	348.6	2121	6.40	0.80	−2.5						
	338.8	4120	4.84	−0.16	−2.2						
	329.1	4321	1.89	−1.16	−0.9						
	319.3	7820	1.15	−2.27	−3.9						

^aStandard uncertainties *u* are *u*(*T*) = 0.2 K, *u*(*m*) = 0.01 mg, and *u*(*p*) = 0.05 p. ^b $\Delta p/p_{\text{calc}} = (p - p_{\text{calc}})/p_{\text{calc}}$, where *p*_{calc} are calculated using the Clausius–Clapeyron equations reported in Table 3.

is the same that we have with the halogen bond strength, so suggesting that the halogen bond might also affect the vapor pressure.

From the slope of the Clausius–Clapeyron equations (*B* in eq 2) reported in Table 3, the standard molar sublimation enthalpy $\Delta_{\text{sub}}^{\circ}H^{\circ}(\langle T \rangle)$, referred to the mean temperature of

Table 3. Temperature Dependence of the Vapour Pressures of DMU, 5-FDMU, 5-BrDMU, and 5-IDMU

compound	cell	ΔT	no of points	$\log(p/\text{kPa})=A-B/(T/\text{K})$					
		K		A^a		B^a			
DMU	B	293.3–337.6	14	35.00	\pm	0.20	11578	\pm	65
	C	335.1–360.5	9	34.71	\pm	0.32	11532	\pm	111
5-FDMU	A	287.6–325.7	14	34.86	\pm	0.28	11831	\pm	86
	B	315.2–354.8	13	34.13	\pm	0.18	11608	\pm	60
5-BrDMU	A	293.3–333.2	13	37.66	\pm	0.29	13761	\pm	90
	B	327.7–360.6	11	36.07	\pm	0.16	13260	\pm	57
5-IDMU	A	323.4–367.3	10	36.15	\pm	0.33	13970	\pm	113
	B	353.5–392.1	13	36.43	\pm	0.21	14040	\pm	80

^aThe associated uncertainties are standard uncertainties of the fitted parameters.

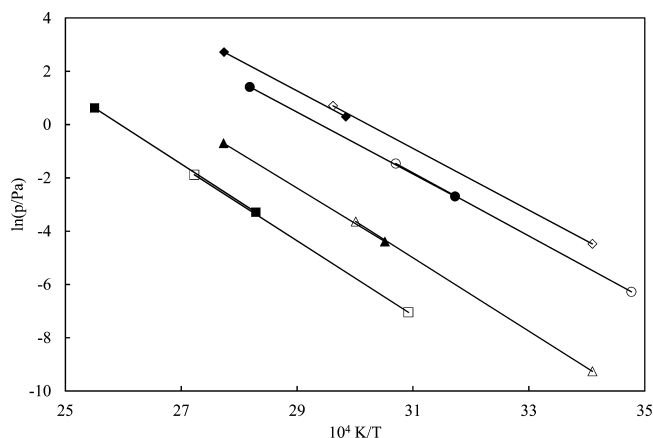


Figure 3. Vapor pressures for DMU: \diamond , cell B; \blacklozenge , cell C. Vapor pressures for 5-FDMU: \circ , cell A; \bullet , cell B. Vapor pressures for 5-BrDMU: Δ , cell A; \blacktriangle , cell B. Vapor pressures for 5-IDMU: \square , cell A; \blacksquare , cell B.

experimental range ($\langle T \rangle$), were obtained by the product of B and $R = 8.314472 \text{ J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$. Table 4 report the calculated $\Delta_c^\circ H^\circ(\langle T \rangle)$ together to the $\Delta_c^\circ S(\langle T \rangle, p(\langle T \rangle))$, derived by the ratio between $\Delta_c^\circ H^\circ(\langle T \rangle)$ and $\langle T \rangle$.

For all the compounds standard molar enthalpies of sublimation at 298 K, $\Delta_c^\circ H^\circ(298 \text{ K})$, have been determined from the experimental $\Delta_c^\circ H^\circ(\langle T \rangle)$ using the molar heat capacity differences of both solid and gaseous phases:

$$\Delta_c^\circ H^\circ(298 \text{ K}) = \Delta_c^\circ H^\circ(\langle T \rangle) + \Delta_c^\circ C_p^\circ \cdot (298 \text{ K} - \langle T \rangle) \quad (3)$$

where for DMU, 5-BrDMU, and 5-IDMU

$$\Delta_c^\circ C_p^\circ / (\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}) = -[0.75 + 0.15 \cdot C_p^\circ(\text{cr})_{\text{std}}(298 \text{ K})] \quad (4)$$

is derived by Acree and Chickos on the bases of statistical results and $C_p^\circ(\text{cr})_{\text{std}}(298 \text{ K})$ estimated using a group additivity approach.²⁶ The used $C_p^\circ(\text{cr})$ (298 K) are reported in Table 4 for all compounds.

For 5-FDMU was followed a little different method, Amaral et al.²⁷ have rearranged eq 4²⁶ in the following way:

$$\Delta_c^\circ C_p^\circ / (\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}) = -[0.9 + 0.176 \cdot C_p^\circ(\text{g})(298 \text{ K})] \quad (5)$$

where $C_p^\circ(\text{g})(298 \text{ K}) = 163.67 \text{ J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$ was derived from statistical thermodynamics.²⁷

A similar way was followed to obtain the standard molar sublimation entropy at 298 K

$$\begin{aligned} \Delta_c^\circ S^\circ(298 \text{ K}, p^\circ) &= \Delta_c^\circ S(\langle T \rangle, p(\langle T \rangle)) \\ &+ \Delta_c^\circ C_p^\circ \cdot \ln(298 \text{ K} / \langle T \rangle) \\ &- R \cdot \ln(p^\circ / p(\langle T \rangle)) \end{aligned} \quad (6)$$

where $p^\circ = 0.1 \text{ MPa}$ and $p(\langle T \rangle)$ is the vapor pressure at mean temperature of experimental range.

For each compound a pair of sublimation enthalpy and entropy at 298 K was determined corresponding to two different temperature range experiments. From these values, we have determined the average standard enthalpy and entropy of

Table 4. Molar Sublimation Enthalpy and Entropy of DMU, 5-FDMU, 5-BrDMU, and 5-IDMU

compound	cell	$\langle T \rangle$	$p(\langle T \rangle)$	$\Delta_c^\circ H^\circ(\langle T \rangle)^a$	$\Delta_c^\circ S(\langle T \rangle, p(\langle T \rangle))^a$	$C_p^\circ(\text{cr})(298 \text{ K})^b$	$\Delta_c^\circ H^\circ(298 \text{ K})^d$	$\Delta_c^\circ S^\circ(298 \text{ K})^d$
		K	Pa	$\text{kJ}\cdot\text{mol}^{-1}$	$\text{J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$	$\text{J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$	$\text{kJ}\cdot\text{mol}^{-1}$	$\text{J}\cdot\text{K}^{-1}\cdot\text{mol}^{-1}$
DMU	B	316.6	0.2081	96.3 ± 0.5	304.1 ± 1.7	194.4	96.8	197.1
	C	348.0	4.8166	95.9 ± 0.9	275.5 ± 2.7	194.4	97.4	197.5
5-FDMU	A	305.1	0.0056	98.4 ± 0.7	322.4 ± 2.3	$C_p^\circ(\text{g})=163.67^c$	98.6	184.3
		335.0	0.4535	96.5 ± 0.5	288.1 ± 1.5	$C_p^\circ(\text{g})=163.67^c$	97.6	189.3
	B						98.1 ± 1.4	186.8 ± 4.6
5-BrDMU	A	313.5	0.0015	114.4 ± 0.7	365.0 ± 2.4	226.8	114.9	217.0
	B	344.3	0.0670	110.3 ± 0.5	320.2 ± 1.4	226.8	111.9	207.0
5-IDMU	A						113.4 ± 1.4	212.0 ± 4.8
		345.3	0.0135	116.2 ± 0.9	336.4 ± 2.7	222.3	117.8	209.9
	B	373.0	0.2980	116.7 ± 0.7	313.0 ± 1.8	222.3	119.3	214.8
							118.5 ± 1.8	212.3 ± 5.4

^aThe uncertainties are standard uncertainties. ^bDetermined in according with Acree and Chickos's²⁴ procedure. ^cReported by Amaral et al.²⁷ ^dThe associated uncertainties are expanded uncertainties (0.95 level of confidence).

Table 5. Comparison of the Temperature Dependence of the Sublimation Enthalpies for DMU and 5-FDMU

compound	ref	method	$\langle T \rangle$	$\Delta H^\circ(\langle T \rangle)$	$\Delta_g^\circ H^\circ(298 \text{ K})$
			K	$\text{kJ}\cdot\text{mol}^{-1}$	$\text{kJ}\cdot\text{mol}^{-1}$
DMU	Clark et al. ³⁰	spectroscopic	357	92 ^a	106 ^c
	Nowak et al. ³¹	spectroscopic	426	46 \pm 4.2 ^a	66 ^c
	Murata et al. ²⁸	calorimetric	298	96.4 \pm 1.4 ^b	96.0 ^c
	Teplitskii et al. ³²	quartz resonator	338	101.7 \pm 2.1 ^b	103 ^c
	Imamura et al. ²⁹	calorimetric	298	96.9 ^b	96.9
	Brunetti et al. ¹⁷	torsion-effusion	338	115.8 \pm 3.0 ^b	117 ^c
	This work	Knudsen-effusion			97.1 \pm 1.8
55-FDMU	Amaral et al. ²⁷	Knudsen	328.16	95.9 \pm 0.6 ^b	96.8 \pm 0.6
	Brunetti et al. ¹⁸	torsion-effusion	355	119 \pm 4 ^b	120.7 ^c
	this work	Knudsen-effusion			98.1 \pm 1.4

^aVaporization enthalpy. ^bSublimation enthalpy. ^cCalculated from the $\Delta H^\circ(\langle T \rangle)$ reported by the author and the $\Delta_g^\circ C_p^\circ$ contribute as proposed by Acree and Chickos.²⁴ To correct the evaporation enthalpy of DMU was used also the $\Delta_c^\circ H(398 \text{ K}) = 14.6 \text{ kJ}\cdot\text{mol}^{-1}$ reported by Sakiyama and Imamura.³³

sublimation at 298 K, reported in Table 4. The uncertainties associated with these values are the expanded uncertainties (0.95 level of confidence) derived from the greater standard uncertainties associated with the $\Delta_g^\circ H^\circ(\langle T \rangle)$ or $\Delta_g^\circ S^\circ(\langle T \rangle, p(\langle T \rangle))$ used to determine $\Delta_g^\circ H^\circ(298 \text{ K})$ and $\Delta_g^\circ C_p^\circ(298 \text{ K}, p^\circ)$, respectively. Because the adjustment of the enthalpy and entropy of sublimation, involving $\Delta_g^\circ C_p^\circ$, from the average temperature to 298 K is small, it was not considered an increase in uncertainty due to the estimation of $\Delta_g^\circ C_p^\circ$.

In literature, there are works that report enthalpies of sublimation for DMU^{17,28–32} and 5-FDMU,^{18,27} as shown in Table 5 together with our average values at 298 K. Only two authors have reported these enthalpies at 298 K.^{28,29} In the other cases, we have calculated the values at 298 by the method described above for our values. For DMU, Clark et al.³⁰ and Novak et al.³¹ have carried out measurements at high temperature with spectroscopic methods and reported values of vaporization enthalpies at average temperature of the measurement range ($\Delta_f^\circ H^\circ(\langle T \rangle)$). We have used the following relationships to determine the enthalpies of sublimation at melting point:

$$\begin{aligned} \Delta_f^\circ H^\circ(T_{\text{fus}})/(\text{kJ}\cdot\text{mol}^{-1}) \\ = \Delta_f^\circ H^\circ(\langle T \rangle) + \Delta_f^\circ C_p^\circ(T_{\text{fus}} - \langle T \rangle) \end{aligned} \quad (7)$$

$$\Delta_c^\circ H^\circ(T_{\text{fus}})/(\text{kJ}\cdot\text{mol}^{-1}) = \Delta_c^\circ H^\circ(T_{\text{fus}}) + \Delta_f^\circ H^\circ(T_{\text{fus}}) \quad (8)$$

where $\Delta_f^\circ C_p^\circ/(\text{J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}) = -[10.58 + 0.26\cdot C_p(l)_{\text{estd}}(298.15 \text{ K})]$, $C_p(l)_{\text{estd}}(298.15 \text{ K}) = 295 \text{ J}\cdot\text{mol}^{-1}\cdot\text{K}^{-1}$ as reported by Acree and Chickos,²⁶ $T_{\text{fus}} = 398 \text{ K}$ and $\Delta_c^\circ H(398 \text{ K}) = 14.6 \text{ kJ}\cdot\text{mol}^{-1}$.³³

Equations 3 and 4 have allowed to determine the $\Delta_g^\circ H^\circ(298 \text{ K})$.

The values in Table 5 are discordant and difficult to compare. For both substances, the higher sublimation enthalpies are those determined by us in previous works^{17,18} by the torsion-effusion method and are different from those reported in this work. These discrepancies are evident also in Figures 4 and 5, which compare the relative percent differences $\Delta p/p_{\text{calc}} = (p - p_{\text{calc}})/p_{\text{calc}} \cdot 100$ between the experimental vapor pressures (p) and the vapor pressures calculated with the corresponding equation reported in Table 3 (p_{calc}) for present and previous works.^{17,18,27} The error bars reported in Figures 4 and 5 are combined standard uncertainties of $\Delta p/p_{\text{calc}}$ obtained combining uncertainties of the experimental vapor pressures reported by the authors and the uncertainties on p_{calc} derived from standard uncertainties on the

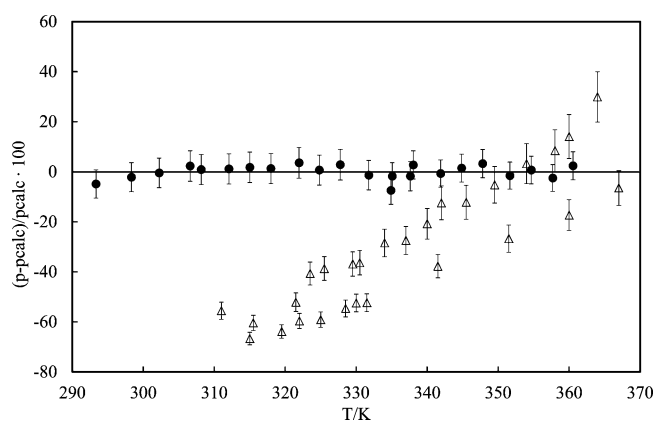


Figure 4. Relative percent differences of the experimental vapor pressures (p) from those calculated (p_{calc}) with the corresponding equation reported in Table 3 for DMU: ●, this work; Δ, Brunetti et al.¹⁷ The error bars represent the combined standard uncertainties calculated from the uncertainties of the experimental vapor pressures reported by the authors and the uncertainties on p_{calc} derived from standard uncertainties on the fitted $\ln(p_{\text{calc}}/\text{Pa})$.

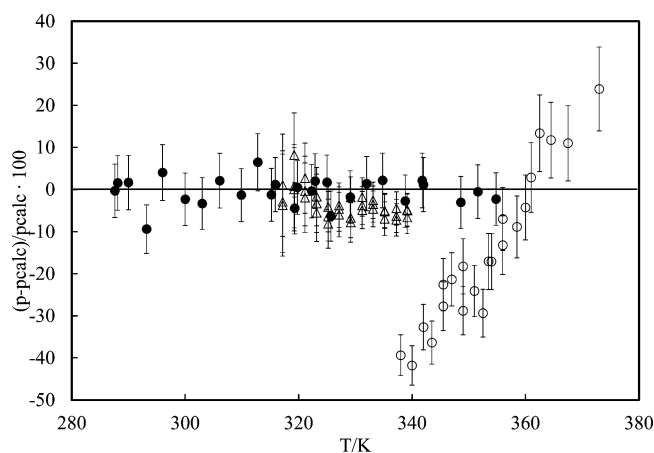


Figure 5. Relative percent differences of the experimental vapor pressures (p) from those calculated (p_{calc}) with the corresponding equation reported in Table 3 for 5-FDMU: ●, this work; Δ, Amaral et al.;²⁷ ○, Brunetti et al.¹⁸ The error bars represent the combined standard uncertainties calculated from the uncertainties of the experimental vapor pressures reported by the authors and the uncertainties on p_{calc} derived from standard uncertainties on the fitted $\ln(p_{\text{calc}}/\text{Pa})$.

fitted $\ln(p_{\text{calc}}/\text{Pa})$ reported in Table 3. Both Figures 4 and 5 show an evident temperature trend in the old data. This may indicate the presence of a systematic error in the previous measurements. Unfortunately, we do not have a clear explanation for this problem; however, it might have been caused by the lack of purification of the samples in the previous experiments or by a problem with temperature measurements. Indeed, in the torsion apparatus, the temperature was measured by a thermocouple placed near, but not in contact with, the measurement cell. This may have produced errors in temperature measurements. In the Knudsen apparatus, this problem is removed as the temperature is measured by a PT00 in contact with the cell.

Regarding the 5-FDMU, as shown in Figures 5 and 6, our new measurements are in very good agreement with those of Amaral et al.²⁷ for the value of enthalpy of sublimation as well as for the values of the vapor pressure.

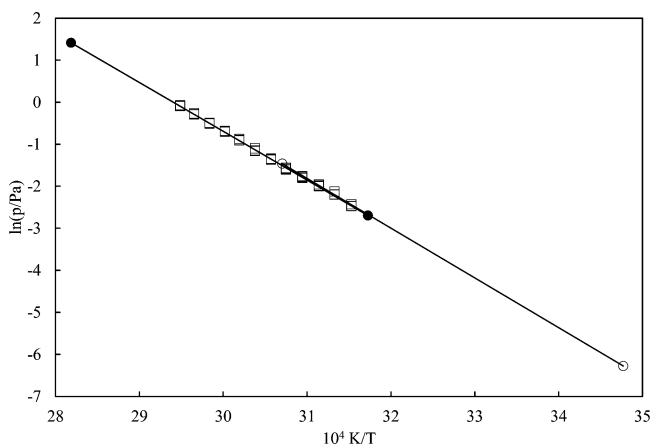


Figure 6. Comparison of the temperature dependence of the vapor pressures for 5-FDMU: \square , Amaral et al.;²⁷ \circ , cell A in this work; \bullet , cell B in this work.

The ability of all 5-XDMUs but 5-FDMU to act as XB donor is now suggested from a comparison of the differences in sublimation enthalpies, $\Delta(\Delta_f H^\circ(298\text{ K}))$, between uracil (U) and its 5-haloderivatives (5-XUs), and between DMU and 5-XDMUs (Table 6).

Table 6. Comparison of $\Delta(\Delta_f H^\circ(298\text{ K}))$ in $\text{kJ}\cdot\text{mol}^{-1}$ for 5-XU and for 5-XDMU in This Work

X	5-XU ^a	5-XDMU ^{b,c}
F	1.7 ± 1.2^{27}	1.0 ± 1.4
Cl	17.5 ± 2.4^{34}	
Br	20.6 ± 2.5^{34}	16.3 ± 1.4
I	24.7 ± 2.4^{34}	21.4 ± 1.8

^aDifferences in sublimation enthalpies ($\Delta_f H^\circ$) between uracil and its 5-haloderivatives. ^bDifferences in sublimation enthalpies ($\Delta_f H^\circ$) between 1,3-dimethyluracil and its 5-haloderivatives. ^cThe associated uncertainties are expanded uncertainties (0.95 level of confidence).

$\Delta_f H^\circ$ can be referred, as already mentioned, to the strength in crystal cohesion, a function of the intermolecular interactions, which are revealed by the X-ray structure. Within possible intermolecular interactions, hydrogen bonds are characterized by specific geometric and energetic properties and contribute considerably to the packing energy. [It should be noted, however, that the crystal cohesion of an organic compound is a complex

function of intermolecular forces driving the spatial disposition of molecules, and the crystal lattice energy, which can be experimentally determined from sublimation enthalpy measurements, is conditional on three terms: van der Waals, electrostatic and HB.³⁵] Therefore, in the case of the 5-XUs, the increasing differences in $\Delta_f H^\circ$ between 5-FU, 5-ClU, 5-BrU, 5-IU, and U can be explained, as a first approximation, by the different role exerted by the N–H \cdots O intermolecular hydrogen bonds and C–H \cdots O contacts in the crystals.

5-FU has two polymorphic forms, I and the less stable II. In the triclinic form I, obtained upon slow evaporation of hot water solution,³⁶ the crystal structure is close to that of the parent U,³⁷ as each molecule is surrounded by five neighboring molecules through N–H \cdots O and C–H \cdots O intermolecular hydrogen bonds. Form II is monoclinic and was obtained after three months by slow evaporation at room temperature of a saturated solution in dry nitromethane.³⁸ In the solid, each molecule forms two hydrogen-bonded dimers with adjacent molecules to give ribbons which run nearly parallel to one another to form rippled layers. A stronger association is present in the isostructural 5-BrU and 5-ClU, where the crystal structures exhibit planar sheets of nonpolar antiparallel symmetric ribbons through N–H \cdots O hydrogen bonds.³⁹ In 5-IU adjacent molecules are N–H \cdots O hydrogen-bonded to form sets of planar ribbons. The set of ribbons run approximately perpendicular to each other and are joined by additional strong N–H \cdots O hydrogen bonds.¹¹ Noticeably, the water solubility of 5-XUs decreases in the order $F \gg Cl > Br > I$.⁴⁰ No XB intermolecular interactions have been observed in the crystal structures of pure 5-XUs, but recently the XRD analysis of three solvated 5-IUs with potential XB acceptors (*N,N*-dimethylformamide, *N*-methylformamide, and formamide), together with quantum chemical calculations performed at high level of sophistication, revealed that the 5-IU unit can form moderate XBs, which compete with HBs in the overall structure organization.⁴¹

In a similar way, the differences in $\Delta_f H^\circ$ reported between 5-XDMUs and DMU (Table 6), which decrease in the order 5-IDMU > 5-BrDMU > 5-FDMU and follow the sequence in polarizability of the halogen substituents, could be referred to the existence of XB in the crystals.

As indicated above, DMU and 5-XDMUs cannot form in the crystal strong intermolecular hydrogen bonds. DMU molecules are associated in the crystal in planar centrosymmetric dimers via C–H \cdots O contacts.¹⁹ Adjacent 5-FDMU molecules form sheets through C–H \cdots O interactions,²⁰ but no XBs have been observed in the structure. Interestingly, in 5-ClDMU, which also forms centrosymmetric dimers via C–H \cdots O contacts, very weak XB (Cl \cdots O = 3.26 Å, ~ 0.98 times the sum of van der Waals radii) connects the Cl atom to the C=O oxygen atom of adjacent molecules and contributes to stabilize the structure.²¹ Concerning 5-BrDMU and 5-IDMU, although no X-ray crystal structures have appeared so far in the literature, it seems possible to foresee the existence of halogen bonds in crystals containing these units, as their $\Delta_f H^\circ$ reflect the potential of these nucleobases as a XB donor of medium strength.

4. CONCLUSIONS

In the present study, we have redetermined the molar enthalpies of sublimation of DMU and 5-FDMU, due to suspicions on the accuracy of previously reported values,¹⁸ and determined the sublimation enthalpies of 5-BrDMU and 5-IDMU. These results suggest the possibility that 5-BrDMU and 5-IDMU, but not 5-FDMU, act as XB donors in the crystal. On this base, we believe

that a better understanding of the XB intermolecular interactions associated with molecular recognition of 5-XDMUs can be obtained by quantum chemical calculation together with accurate X-ray diffraction analysis of 5-BrDMU and 5-IDMU, and their cocrystals or solvate structures with suitable systems having electron donors. Indeed, this approach is under way in this laboratory.

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Notes

The authors declare no competing financial interest.

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