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Sublimation Thermodynamic Parameters for 5-Fluorouracil and Its 1-Methyl and 1,3-Dimethyl Derivatives from Vapor Pressure Measurements

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The vapor pressures for 5-fluorouracil, 1-methyl-5-fluorouracil, and 1,3-dimethyl-5-fluorouracil were measured by a torsion method. The following linear equations, representative of the temperature dependence in the covered temperature ranges, were selected: 5-fluorouracil, $\log(p/\text{kPa}) = (15.18 \pm 0.20) - (7860 \pm 100)\text{K}/T$, (421−483) K; 1-methyl-5-fluorouracil, $\log(p/\text{kPa}) = (12.64 \pm 0.20) - (6083 \pm 100)\text{K}/T$, (381−423) K; 1,3-dimethyl-5-fluorouracil, $\log(p/\text{kPa}) = (15.16 \pm 0.40) - (6286 \pm 200)\text{K}/T$, (338−473) K. From these equations the standard sublimation enthalpies and entropies, $\Delta_{\text{sub}}H°$ (298 K) = 154 ± 5, 116 ± 2, and 119 ± 4 kJ·mol^{-1} and $\Delta_{\text{sub}}S°$ (298 K) = 259 ± 8, 203 ± 4, and 252 ± 8 $\text{J·K}^{-1}\text{·mol}^{-1}$, respectively, for 5-fluorouracil, 1-methyl-5-fluorouracil, and 1,3-dimethyl-5-fluorouracil were determined. The vaporization behavior for these compounds was compared with that for uracil and corresponding methyl derivatives.

Introduction

In the course of the our investigation of the relationships between molecular structure and molecular environment in the context of the engineering of crystal structures of nucleobases,[1] we extended our analysis to the thermodynamic study on the sublimation of uracil and several of its methyl derivatives.[2] In that study a weak trend of the standard sublimation enthalpies and a difference of the volatility of these compounds were observed. This different sublimation behavior was justified by their crystal structures, in which the intermolecular hydrogen bonds play an important role and provide a measure of the strength of the intermolecular forces.[3]

As we wish to investigate if and how the vaporization behavior of these compounds changes when the hydrogen in the 5-position in uracil is replaced by fluorine, we decided to study the sublimation process of 5-fluorouracil (5-FU), 1-methyl-5-fluorouracil (1-m-5-FU), and 1,3-dimethyl-5-fluorouracil (1,3-dm-5-FU). No thermodynamic data associated with the sublimation of these compounds are available in the literature. For uracil and its derivatives and also for 5-FU and its derivatives, the vapor pressures were measured by a torsion method and, from the temperature dependence of their values, the sublimation enthalpy and entropy of these compounds were calculated.

Experimental Section

Materials. 5-FU (99% pure) and 1,3-dm-5-FU (98% pure) were supplied by Sigma Chemical Co., with the purities certified by the supplier. 1-m-5-FU was prepared following a procedure described by Stolarsky et al.[4] Crystallization of the product from aqueous methanol gave suitable crystals for X-ray analysis. The structure of the obtained compound has been determined in this way.

Table 1. Torsion Vapor Pressure Data for 5-FU, 1-m-5-FU, and 1,3-dm-5-FU

run 1		run 2		run 3	
T/K	$-\log(p/\text{kPa})$	T/K	$-\log(p/\text{kPa})$	T/K	$-\log(p/\text{kPa})$
		5-FU			
443.5	2.59	431.0	3.11	421.0	3.39
448.0	2.41	432.5	2.97	431.0	3.05
453.5	2.25	437.0	2.83	440.5	2.69
458.0	1.98	442.0	2.64	447.0	2.35
464.5	1.72	447.5	2.43	453.5	2.05
471.0	1.53	455.5	2.01	457.0	1.93
475.0	1.39	462.0	1.83	463.5	1.74
483.0	1.21	468.0	1.60	468.5	1.52
		477.5	1.37	475.5	1.30
		1-m-5-FU			
381.0	3.39	392.0	2.87	387.0	3.07
386.0	3.13	394.5	2.73	392.0	2.87
388.5	3.05	398.0	2.62	394.0	2.77
394.5	2.86	401.0	2.51	397.5	2.64
398.0	2.71	404.0	2.41	401.0	2.51
402.0	2.58	406.5	2.31	403.0	2.43
406.0	2.40	409.5	2.21	404.5	2.37
411.5	2.19	413.0	2.09	409.0	2.22
416.0	1.98	416.5	1.96	412.0	2.12
		420.0	1.82	414.5	2.04
		421.5	1.75		
		423.0	1.69		
		1,3-dm-5-FU			
340.0	3.24	342.0	3.09	338.0	3.31
343.5	3.05	345.5	2.88	345.5	2.91
349.0	2.77	347.0	2.81	351.0	2.66
352.5	2.63	349.0	2.71	354.0	2.50
356.0	2.40	353.5	2.52	358.5	2.28
360.0	2.20	356.0	2.37	362.5	2.03
364.5	1.96	361.0	2.13	367.5	1.85
				373.0	1.60

Apparatus and Procedures. The vapor pressures of these compounds were measured by a torsion method.[5] The torsion assembly was described in detail in our previous work.[6] A conventional pyrophyllite cell, with effusion holes of 1.0 mm in diameter, was used in this study. The torsion assembly was suspended from an arm of a vacuum balance (Chann 1000) in order to measure the mass loss rate of the sample during the pressure measurements. In this way,

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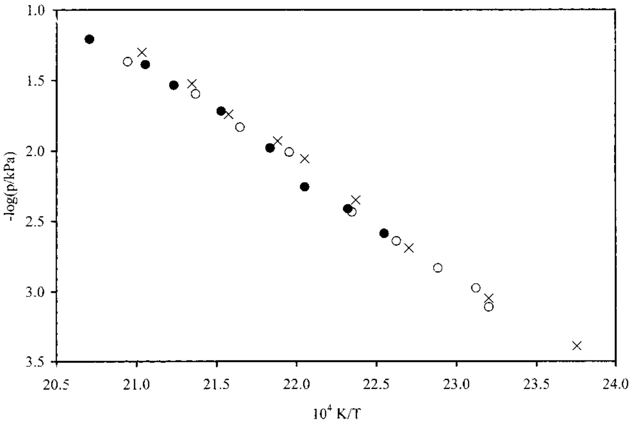

Figure 1. Vapor pressures for 5-FU: ●, run A; ○, run B; ×, run C.

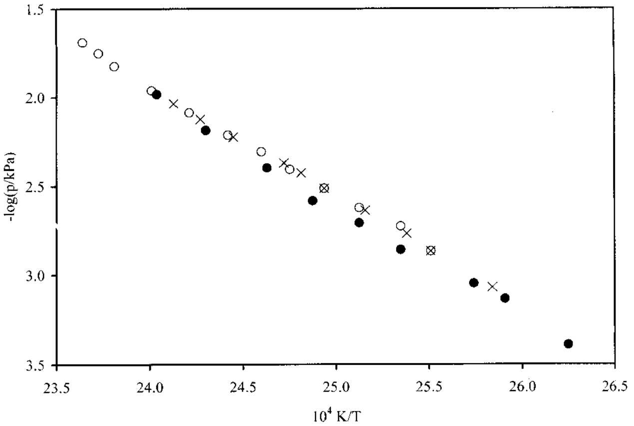

Figure 2. Vapor pressures for 1-m-5-FU: ●, run A; ○, run B; ×, run C.

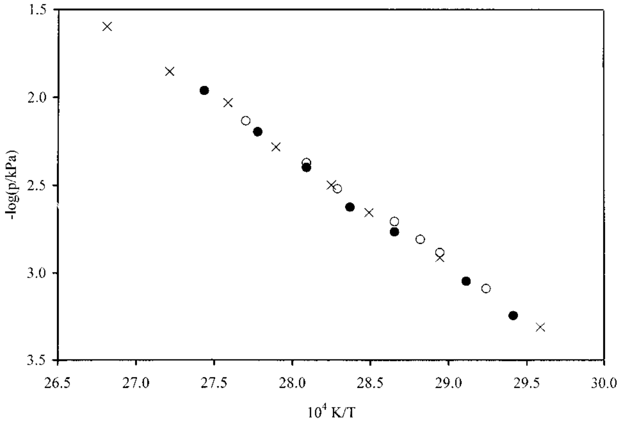

Figure 3. Vapor pressures for 1,3-dm-5-FU: ●, run A; ○, run B; ×, run C.

at some temperatures, in addition to the vapor pressures, the vapor molecular weight was calculated by the well-known Knudsen equation.[7]

Both the torsion constant of the cell that is needed to convert the torsion angles to pressure values and the Knudsen constant that is needed to convert the mass loss rate of the sample in the vapor molecular weight were determined in the customary way by vaporizing a pure standard having a well-known vapor pressure.[8] In this work cadmium[8] was used. The values of these constants were checked in experiments carried out before and after the vaporization runs of each compound. The values so obtained ranged ~±5% of their average. The uncertainty of the torsion constant value and that of the experimental torsion angles produce a displacement of the final log p no larger than ~±0.03. The uncertainty associated with the temperature measurements was estimated to be ±1 K. Second-law sublimation enthalpy values for cadmium were obtained from the slopes of log α vs $1/T$ (where α is the torsion angle). Good agreement of these enthalpies (at the experimental middle temperatures) with those selected by Hultgren et al.[8] was taken as a check of the reliability of the method.

Table 2. Temperature Dependence of the Vapor Pressures for 5-FU, 1-m-5-FU, and 1,3-dm-5-FU

compound	run	ΔT/K	no. of points	$\log(p/\mathrm{kPa}) = A - B/(T/\mathrm{K})$ A^a	B^a
5-FU	1	443.5−483.0	8	15.02 ± 0.65	7805 ± 299
	2	431.0−477.5	9	15.16 ± 0.49	7859 ± 221
	3	421.0−475.5	9	15.34 ± 0.40	7909 ± 180
1-m-5-FU	1	381.0−416.0	9	12.74 ± 0.37	6143 ± 147
	2	392.0−423.0	12	12.72 ± 0.22	6106 ± 88
	3	387.0−414.0	10	12.45 ± 0.17	6002 ± 67
1,3-dm-5-FU	1	340.0−364.5	7	15.71 ± 0.38	6446 ± 132
	2	342.0−361.0	7	14.73 ± 0.32	6088 ± 112
	3	338.0−373.0	8	15.05 ± 0.26	6209 ± 91

[a] The errors are standard deviations.

Table 3. Selected Temperature Dependence of the Vapor Pressures and Sublimation Enthalpies and Entropies for Uracil, 5-FU, and Their Derivatives

compound	$\log(p/\mathrm{kPa}) = A - B/T$ A	B	T K	$\Delta H°(\mathrm{T})$ kJ·mol⁻¹	$\Delta S°(\mathrm{T})$ kJ·mol⁻¹
uracil	12.29 ± 0.15	6634 ± 100	439	127 ± 2	196 ± 3
5-FU	15.18 ± 0.20	7860 ± 100	452	150 ± 2	252 ± 4
1-methyluracil	13.75 ± 0.15	6357 ± 150	386	122 ± 3	224 ± 3
1-m--FU	12.64 ± 0.20	6083 ± 100	402	116 ± 2	203 ± 4
1,3-dimethyluracil	15.10 ± 0.10	6049 ± 100	338	116 ± 2	250 ± 2
1,3-dm-5-FU	15.16 ± 0.40	6246 ± 200	356	119 ± 4	252 ± 8

The vapor pressures of 5-FU, 1-m-5-FU, and 1,3-dm-5-FU are reported in Table 1 and in Figures 1−3. For each sublimation run a linear regression of the logarithm of the pressures as a function of the reciprocal temperature was carried out by a least-squares method. Table 2 gives the parameters of the equations and the valid temperature ranges. From these fits, the following equations were selected by weighting the slope and intercept of each equation proportionally to the number of points:

5-FU

$$\log(p/\mathrm{kPa}) = 15.18 \pm 0.20 - (7860 \pm 100)\mathrm{K}/T \qquad (421-483)\ \mathrm{K} \quad (1)$$

1-m-5-FU

$$\log(p/\mathrm{kPa}) = 12.64 \pm 0.20 - (6083 \pm 100)\mathrm{K}/T \qquad (381-423)\ \mathrm{K} \quad (2)$$

1,3-dm-5-FU

$$\log(p/\mathrm{kPa}) = 15.16 \pm 0.40 - (6246 \pm 200)\mathrm{K}/T \qquad (338-373)\ \mathrm{K} \quad (3)$$

The associated uncertainties are given.

Discussion

The selected eqs 1−3 for vapor pressures of 5-FU, 1-m-5-FU, and 1,3-dm-5-FU are compared in Table 3 and Figure 4 with those previously determined for uracil and its derivatives. This comparison shows that, in the covered

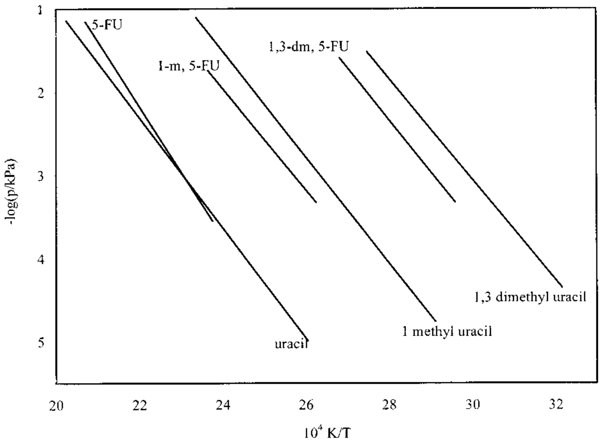

Figure 4. Comparison of the temperature dependence of the vapor pressures for uracil, 5-fluorouracil, and their derivatives.

temperature ranges, the vaporization behavior for uracil and 5-FU and for their corresponding methyl derivatives are comparable even though the vapor pressures for the methyl derivatives of 5-FU are slightly lower than those of uracil.

The vapor molecular weight of all these compounds calculated by the Knudsen method shows that their vaporizations are practically congruent so that, from the slopes and intercepts of eqs 1−3, their second-law sublimation enthalpies and entropies, referred to the mean temperature of the covered ranges, could be calculated. These values are reported in Table 3. Whereas the sublimation enthalpies and entropies of methyl derivatives are comparable, for 5-FU their values are higher than those obtained for uracil. This finding is not surprising because methyl derivatives of uracil and 5-FU form similar three-dimensional patterns of intermolecular hydrogen bonds in the solid state, whereas 5-FU in the crystal exhibits a higher degree of association than uracil.[9,10] It is also interesting to note that $\Delta_{sub}S°$ (439 K) = 196 $J{\cdot}K^{-1}{\cdot}mol^{-1}$ for uracil agrees fairly well with the value of 186 $J{\cdot}K^{-1}{\cdot}mol^{-1}$ obtained as a difference of absolute entropies for gaseous uracil (derived from a spectroscopic study) and for solid uracil (derived from calorimetric measurements), both reported by Bardi et al.[11]

In the absence of C_p values, it is not possible to calculate standard enthalpy and entropy values at the usual reference temperature of 298 K. Values listed in Table 3 for 1-m-5-FU and 1,3-dm-5-FU are those based on measurements in a temperature range close to 298 K. For 5-FU values derived from measurements around 450 K were corrected by increments of 4 $kJ{\cdot}mol^{-1}$ and 7 $J{\cdot}K^{-1}{\cdot}mol^{-1}$, on the basis of results reported for uracil by Bardi et al.[11] The final associated uncertainties overestimated, considering that the experiments were carried out in comparatively small temperature ranges and taking into account both the uncertainties in temperature and in low torsion angle measurements and the corrections of the thermodynamic data.

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