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Vapor Pressures, Molar Enthalpies of Sublimation, and Molar Enthalpies of Solution in Water of 5-(Trifluoromethyl)uracil

Wojciech Zielenkiewicz* and Piotr Szterner

Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

Vapor pressures, enthalpies of sublimation, enthalpies of solution at infinite dilution, and densities of the aqueous solutions of crystalline 5-(trifluoromethyl)uracil were determined. Vapor pressures and enthalpies of sublimation were measured by the Knudsen effusion method. The heats of solution in water were determined at 298.15 K over the range of concentrations of 0.495 to 0.948 mmol·kg^{-1} by using an isoperibol solution calorimeter. The molar enthalpy of hydration was calculated by subtracting the estimated molar enthalpy of sublimation and the molar enthalpy of solution. Densities of the solutions were measured with an Anton Paar DMA 60/602 digital densimeter, and the partial volume was estimated. The purity of the substance was determined using a DSC 910 DuPont differential scanning calorimeter with a Thermal Analyzer 1090. The values of the enthalpy of interaction and the enthalpy of cavity formation were calculated.

Introduction

The thermodynamic properties of pyrimidine nucleic acid bases, namely, of uracil and their alkylated, halogenated amino and nitro derivatives, were the subject of our intensive research.[1−6] A knowledge of the hydration process of nucleic acid derivatives is important for an understanding of their interaction with water. Thus, the determination of the enthalpy of hydration derived from the experimentally determined enthalpy of solution and the enthalpy of sublimation could be helpful in the designation of the nature of these interactions.

Thermodynamic data are also important in view of the medical applications. Some of the 5-substituted uracils exhibit significant pharmacological activity and have been used as antitumor, antibacterial, and antiviral drugs. For example, 5-fluorouracil has been used to treat cancer.[7] Analogues of 5-trifluoromethyl uracil have been investigated as aniviral agents. 5-Trifluoromethyl-2′-deoxyuridine (viroptic, trifluridine, trifluorothymidine, TFT) was used experimentally for the treatment of acyclovir-resistant and foscarnet-resistant herpes simplex virus HSV infection (at nasal, oral, eye),[8,9] and was used to treat epithelial keratitis caused by the herpes simplex virus. The herpes simplex virus (HSV) can cause corneal infections in humans and lead to permanent scarring, loss of vision, and blindness. Current treatment of epithelial HSV keratitis consists of using antiviral DNA analogues.[10]

The main indication for trifluridine is for primary and recurrent HSV infections of the cornea and conjunctiva.[11] It is also used in the treatment of acyclovir-resistant mucocutaneous HSV infection in patients with AIDS.[12] 5-Trifluoromethyl-2′-deoxyuridine was investigated as an anticancer agent.[13] 5-Fluorouracil, 5-fluoro-2′-deoxyuridine, and 5-trifluorothymidine are antimetabolites that are metabolized to their corresponding active forms that inhibit DNA synthesis via inhibition of thymidylate synthase (TS).[14] The action of 5-trifluoromethyl-2′-deoxyuridine on DNA synthesis was investigated in vitro assay systems with purified DNA polymerases. 5-Trifluoromethyl-2′-deoxyuridine was incorporated into the DNA of mammalian cells in culture.[15]

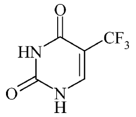

Figure 1. Structural formula of 5-(trifluoromethyl)uracil.

Experimental Section

Chemicals. 5-(Trifluoromethyl)uracil was purchased from Aldrich Chemical Co. Ltd (no. 22,327-1); the molar mass was equal to 0.18009 kg·mol^{-1}, and the mole fraction purity was better than 0.99, as determined by means of a DuPont 910 differential scanning calorimeter equipped with a 1090 Thermal Analyzer. The structural formula of this compound is given in Figure 1.

Apparaturs and Procedures. An isoperibol solution calorimeter was used to measure the heat of solution in water at 298.15 K. The calorimeter consists of the following parts: the proper calorimeter, the measuring system, and the thermostat. The proper calorimeter consists of a measuring steel vessel of total volume 80 cm^3 and normal working volume 65 cm^3, an external metallic shield, two thermistors, nominally 150 Ω, a glass ampule of 1.5-cm^3 volume, and a 98-Ω calibration heater and stirrer. The external shield is submerged in thermostated water bath (30 dm^3) in which the temperature is sensed by a 100-Ω resistance platinum thermometer and regulated by a PID regulator providing temperature constants of better than 1×10^{-3} K. The thermistors located in the calorimetric vessel form the arms of the Wheatstone bridge, which is coupled to a 181 Keithley nanovoltmeter and an IBM PC computer. The method of corrected temperature rise with the Regnault−Phaundler correction was used to evaluate the studied heat effect. The lowest detectable heat effect corresponds to 0.15 J. The calorimeter and the working procedure have been described in detail elsewhere.[4,16] The calorimeter was calibrated by determining the heat of

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* Corresponding author. E-mail: zivf@ichf.edu.pl.

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solution of potassium chloride (mass fraction 0.9999) in water.[16] Before each measurement, the calorimeter was calibrated by means of the Joule effect.

The solid vapor-pressure measurements (and the subsequent evaluation of the molar enthalpies of sublimation) were carried out by the Knudsen effusion method used in conjunction with the device and the working procedure described previously.[2,4,17] The apparatus consisted of a steel sublimation cell placed in a thermostat and connected to a high-vacuum system maintained at a pressure of 10^{-4} Pa. The duration of each sublimation experiment was 6 h, and the time of sublimation was determined with an accuracy of 1 s. The sample mass was determined with accuracy of 10^{-5} g before and after the measurement. The temperature in the thermostat was kept constant to ±0.01 K by means of a UNIPAN 650 thermoregulator. Test measurements were performed on benzoic acid of mass fraction 0.9999 obtained from the Central Office of Measures (Warsaw, Poland).[4]

The molar enthalpy of sublimation, $\Delta_s^g H_m$, was calculated at the average temperature T_m of the experimental range by the least-squares method as the slope of the straight line expressed by

$$\ln\left(\frac{p}{p^0}\right) = -\frac{A}{T_m} + B = -\frac{\Delta_s^g H_m}{RT_m} + \frac{\Delta S}{R} \qquad (1)$$

where ΔS is the entropy increment associated with the sublimation process of the studied compound at T_m and $p^0 = 10^5$ Pa.

We calculated the vapor pressure using the values of the molar mass of monomers. The existence of monomers in the gas phase was confirmed by E1 mass spectra analysis made by means of an AMD-604 (AMD GmbH, Harssted, Germany) double-focusing mass spectrometer with BE geometry (electron energy 70 eV, acceleration voltage 8 kV, source temperature 473 K).

The enthalpies of sublimation were corrected to a temperature of 298.15 K by[18]

$$\Delta_s^g H_m^0(298.15) = \Delta_s^g H_m(T_m) + (0.75 + 0.15C_p)(T_m - 298.15) \qquad (2)$$

where C_p is the heat capacity of cyclic functional groups of the solid phase at 298.15 K.[19]

The enthalpy of hydration, $\Delta_{hyd}H_m^0$, was calculated as the difference in the enthalpy of solution at infinite dilution, $\Delta_{sol}H_m^\infty$, and the enthalpy of sublimation, $\Delta_s^g H_m^0$, at a temperature of 298.15 K,

$$\Delta_{hyd}H_m^0 = \Delta_{sol}H_m^\infty - \Delta_s^g H_m^0 \qquad (3)$$

The enthalpy of hydration, $\Delta_{hyd}H_m^0$, can be used to evaluate the enthalpy of solute−solvent interactions, $\Delta_{int}H_m$, from the experimental enthalpies of solvation corrected for the term related to the energy required to make a cavity in liquid water. In this way, it becomes possible to compare the values of the enthalpy of interactions established in this semiempirical way to those estimated by quantum mechanical calculations.

The enthalpy of interaction $\Delta_{int}H_m$ was evaluated in a semiempirical way according to the relation

$$\Delta_{hyd}H_m^0 = \Delta_{cav}H_m - \Delta_{int}H_m \qquad (4)$$

where $\Delta_{cav}H_m$ is the enthalpy of cavity formation, which corresponds to the hypothetical process of creation inside the solvent of an empty cavity that can fit the solute molecule; $\Delta_{int}H_m$ is the enthalpy of solute−solvent interaction.

Table 1. Experimental Vapor Pressure Data[a]

series 1			series 2		
T/K	Δm/mg	P/Pa	T/K	Δm/mg	p/Pa
5-(trifluoromethyl)uracil					
373.02	2.50	0.01187	373.02	2.45	0.01168
378.75	4.19	0.02012	374.94	2.88	0.01376
382.54	5.97	0.02882	380.67	5.02	0.02417
386.35	8.21	0.03983	384.45	6.92	0.03348
390.15	11.46	0.05586	388.25	9.48	0.04610
392.01	13.10	0.06401	392.01	13.20	0.06450

[a] T − temperature of measurement, Δm − mass of the sublimated substance, p − vapor pressure.

The enthalpies of cavity formation were determined by the Sinanoglu method[20−22] according to the relation

$$\Delta_{cav}H_m = K_1^e S\gamma\left\{1 - \frac{\partial \ln \gamma_1}{\partial \ln T} + \frac{2}{3}\alpha_1 T\right\} \qquad (5)$$

where S is the surface-accessible area, $\gamma = {}^{N}/_{V}$ is the surface tension (N is Avogardo's number, V is the molar volume of the liquid), α_1 is the coefficient of thermal expansion, T is the temperature, and K_1^e is the constant adjusting the planar surface energy.

The constant K_1^e can be calculated from the following empirical equation:

$$K_1^e = 1 + \left(\frac{V_1}{V_2}\right)^{2/3}[K_1^e(1) - 1] \qquad (6)$$

where $K_1^e(1)$ is the factor for pure solvent and V_1 and V_2 are van der Waals volumes of the solvent and solute molecules, respectively.

For estimation, we used the following parameters of water: $K_1^e(1) = 1.277$, $\gamma = 72$ dyn·cm^{-1}, and $\alpha_1 = 0.257 \times 10^{-3}$ K^{-1}.

The solvent-accessible molecular surface area S^M and their atomic partitions S_O, S_N, $S_{H(O,N)}$, and S_{halo} were calculated with the GEPOL version 12.1 algorithm using structures obtained from molecular mechanics.[23] The following atomic radii consistent with the Tripos force field were used: 1.45 Å (N), 1.52 Å (C), 1.36 Å (O), and 1.08 Å (H) and the water radius was taken as 1.4 Å. For 5-(trifluoromethyl)uracil S^M, S_O, S_N, $S_{H(O,N)}$, and S_{halo} are following: 104.1, 23.5, 8.8, 12.6, and 33.8 Å^2.

The densities of the solutions relative to the density of pure water were measured with an Anton Paar DMA 60/602 digital densimeter. Temperature stability achieved with a Hetoterm model C8-7 thermostat was better than ±0.01 °C. The calibration constant of the densimeter was determined daily by using the known densities of water and dry air. Under these conditions, the uncertainties were 5×10^{-6} g·cm^{-3}. The apparent molar volumes were calculated from experimental densities by the usual procedure.[6] All of the solutions were prepared by weight using degassed and deionized water.

Results and Discussion

The vapor pressures p measured at temperatures T are given in Table 1 together with the masses Δm of the substance that sublimed in 6 h in two series (1 and 2) of measurements made over similar ranges of temperature.

Table 2 lists the values of the A and B coefficients of eq 1, the values of the enthalpy of sublimation $\Delta_s^g H_m$, and the

Table 2. Vapor Pressure of Equation 1, Coefficients *A* and *B*, Enthalpies of Sublimation $\Delta_s^g H_m$, and Ranges of Experimental Temperature *T*

series	$-A$	B	T/K	$\Delta_s^g H_m$/kJ·mol^{-1}
		5-(trifluoromethyl)uracil		
1	13050 ± 100	30.5 ± 0.2	373.02−392.01	108.5 ± 0.8
2	13088 ± 116	30.6 ± 0.3	373.02−392.01	108.8 ± 0.9

Table 3. Enthalpies of Solution of 5-(Trifluoromethyl)uracil

m/mmol·kg^{-1}	$\Delta_{sol}H_m$/kJ·mol^{-1}
5-trifluoromethyluracil	
0.495	23.82
0.578	23.33
0.725	23.76
0.746	23.30
0.822	23.33
0.948	23.72

Table 4. Standard Enthalpy of Solution at Infinite Dilution, Enthalpy of Sublimation, and Enthalpy of Hydration of 5-(Trifluoromethyl)uracil (298.15 K)

compound	$\Delta_{sol}H_m^\infty$/kJ·mol^{-1}	$\Delta_s^g H_m^0$/ kJ·mol^{-1}	$-\Delta_{hyd}H_m^0$/ kJ·mol^{-1}
5-trifluoro-methyluracil	23.54 ± 0.10	110.77 ± 0.85	87.23 ± 0.85

Table 5. Apparent Molar Volumes V_ϕ of Aqueous Solutions of 5-(Trifluoromethyl)uracil at 25 °C

m/mol·kg^{-1}	d/g·cm^{-3}	V_ϕ/cm^3·mol^{-1}
	5-(trifluoromethyl)uracil	
0.010336	0.997880	98.48
0.010923	0.997938	97.94
0.011011	0.997946	97.87
0.011218	0.997960	97.58
0.011866	0.998017	97.80
0.012922	0.998089	98.43

range of temperatures T at which the measurements were carried out. A and B coefficients and values of $\Delta_s^g H_m$ with the standard deviation of the mean were calculated by the least-squares method.

Evaluated from coefficient B (eq 1), the average entropy increment associated with the sublimation process is 3.67 J·K^{-1}·mol^{-1}. The values of the enthalpies of solution $\Delta_{sol}H_m$ of 5-(trifluoromethyl)uracil in concentrations m are collected in Table 3. Within the experimental uncertainty in the experimental range of concentrations (0.495 to 0.948) mM, no concentration dependence of the enthalpy of solution was observed.

The enthalpies of solution at infinite dilution, $\Delta_{sol}H_m^\infty$, given in Table 4 were calculated as the mean values of all of the relevant experimental data (Table 3). Table 4 also gives the mean value of the enthalpies of sublimation evaluated in series 1 and 2 (Table 2) corrected to 298.15 K and the molar enthalpy of hydration $\Delta_{hyd}H_m^0$ at 298.15 K.

The apparent molar volumes are collected in Table 5, where m is molality, d is the density of solution, and V_ϕ is the apparent molar volume. The partial molar volume of 5-trifluoromethyluracil (98.01 cm^3·mol^{-1}) was calculated as the average of all apparent molar volumes. The obtained results were compared with previously determined thermodynamic values for uracil and halo derivatives of uracil.[3,4]

The relation ln $p = f(^1/_T)$ is presented graphically in Figure 2, whereas the differences between the value of the standard enthalpy of solution Δ^∞, the enthalpy of sublimation $\Delta_s^g H_m^0$, the enthalpy of hydration $\Delta_{hyd}H_m^0$, and the partial molar volume V_2^0 of 5-(trifluoromethyl)uracil $(CF_3)^5$Ura, 5-fluorouracil, uracil, and 5-methyluracil[1−3] are given in Table 6.

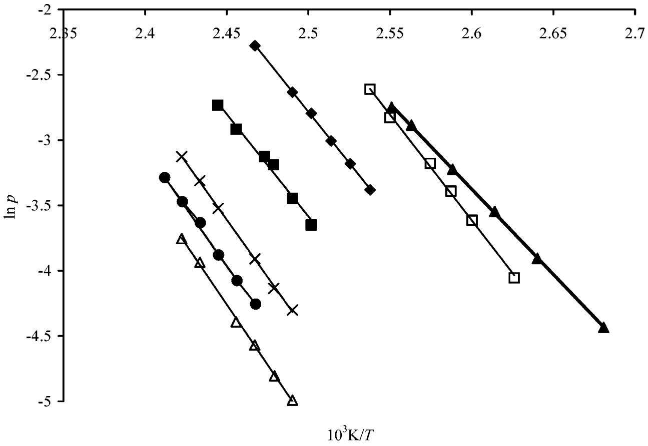

Figure 2. Dependence of ln p on $^1/_T$ for 5-(trifluoromethyl)uracil and uracil and halo derivatives of uracil: △, 5-iodoracil; ●, 5-bromouracil; □, 6-chlorouracil; ×, 5-chlorouracil; ◆, 5-fluorouracil; ■, uracil; and ▲, 5-(trifluoromethyl)uracil.

Table 6. Differences between the Values of the Standard Enthalpy of Solution, the Enthalpy of Sublimation, the Enthalpy of Hydration, and Partial Molar Volumes of 5-(Trifluoromethyl)uracil $(CF_3)^5$Ura, Uracil, 5-Fluorouracil, and 5-Methyluracil

difference between	$\delta\Delta_{sol}H_m^\infty$ kJ·mol^{-1}	$\delta\Delta_s^g H_m^0$ kJ·mol^{-1}	$\delta\Delta_{hyd}H_m^0$ kJ·mol^{-1}	δV_2^0 cm^3·mol^{-1}
$(CF_3)^5$Ura and uracil	−5.96	−20.05	14.08	26.15
5-fluorouracil and uracil	−4.12	2.4	−6.53	2.65
$(CF_3)^5$Ura and 5-methyluracil	−0.78	−13.63	12.87	

In conclusion, hydrogen atom substitution in uracil by a fluorine atom contributes to the values of $\Delta_{sol}H_m^\infty$, $\Delta_s^g H_m^0$, $\Delta_{hyd}H_m^0$, and V_2^0 (−4.12 kJ·mol^{-1}, 2.4 kJ·mol^{-1}, 6.53 kJ·mol^{-1}, and 2.65 cm^3·mol^{-1}, respectively), whereas the introduction of the CF_3 group at the 5 position of uracil results in values for $\Delta_{sol}H_m^\infty$, $\Delta_s^g H_m^0$, $\Delta_{hyd}H_m^0$, and V_2^0 of −5.96 kJ·mol^{-1}, −20.05 kJ·mol^{-1}, 14.08 kJ·mol^{-1}, and 26.15 cm^3·mol^{-1}, respectively.

Obtained values for 5-(trifluoromethyl)uracil differ significantly from those previously obtained for 5-fluorouracil.

Substitution of the hydrogen atoms of the diketopirymidine ring of the uracil molecule by group CF_3 in the uracil molecule gives a change in the enthalpy of hydration of 14.08 kJ·mol^{-1}. This change is greater than the value (10.17 kJ·mol^{-1}) resulting from a calculation of the atoms' contribution according to the simple additivity scheme given for aliphatic compounds by Cabani et al.[21] However, substitution of the hydrogen atoms of uracil by one atom of F gives increments of the enthalpy of hydration of −6.53 kJ·mol^{-1}.[4] These increments are about 3 times greater as a result of the calculation of the atoms' contribution, according to Cabani et al.[21]

To calculate the value of the enthalpy of interaction $\Delta_{int}H_m$(eq 4), the determination of the value of the enthalpy of cavity formation $\Delta_{cav}H_m$ was required. Calculations were performed according to the Sinanoglu method (eqs 5 and 6). For 5-(trifluoromethyl)uracil, $\Delta_{cav}H_m$ and $\Delta_{int}H_m$ for aqueous solutions have values of 67.82 kJ·mol^{-1} and 155.05 kJ·mol^{-1}, respectively. The obtained values directly characterizing solute−solvent interactions can also be used to verify the calculation in a quantum mechanical way.

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