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Solubilities in Water of Uracil and Its Halogenated Derivatives

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The solubilities of crystalline compounds, uracil, 5-fluorouracil, 5-chlorouracil, 6-chlorouracil, 5-bromouracil, 5-iodouracil, and 5-(trifluoromethyl)uracil, in water have been determined at 25 °C by the isothermal saturation method. The molar standard Gibbs energies ($\Delta_{sol}G_m^o$) and the molar entropies of solution ($\Delta_{sol}S_m^o$) were determined on the basis of the solubilities and previously determined molar enthalpies of solution ($\Delta_{sol}H_m^o$). The thermodynamic parameters of sublimation ($\Delta_{sub}G_m^o$, $\Delta_{sub}S_m^o$) were calculated from the previously determined molar enthalpies of sublimation $\Delta_{sub}H_m^o$. The values obtained were used for calculation of the thermodynamic parameters of solvation ($\Delta_{solv}G_m^o$, $\Delta_{solv}S_m^o$). The thermodynamic functions of solvation and solution were correlated with the values of the surface-accessible areas, the partial molar volumes V_2^o, the molecular volumes V_2^M, and the parameters β of the compounds investigated.

Introduction

The determination of the thermodynamic properties of uracil and its halogenated, amino, and nitro derivatives was the subject of previous research.[1–7]

These investigations are aimed at the experimental determinations of apparent molar volumes, heat capacities, enthalpies of sublimation, solution, and solvation in aqueous and methanol solutions. Their purpose was also to study solute–solvent interactions. Derivatives of uracil deserve particular attention among all series of derivatives of nucleic pyrimidine bases. The thermodynamic properties of this group of compounds are important in view of their medical application. Uracil derivatives substituted at the 5-position constitute a class of biologically significant molecules. 5-Fluorouracil (5-FU) has been one of the most widely used chemotherapeutic agents for the treatment of common malignancies.[8]

The 5-substituted uracils with mono substitution of fluorine containing moieties at N-1 show biological activity of appreciable significance as antivirals.[9] The compounds 5-bromouracil and 5-fluorouracil have been found to be the competitive inhibitors of human thymidine phosphorylase.[10,11] 5-Substituted uracil derivatives were reported as a new class of nonsteroidal anti-inflammatory agents possessing antioxidative activity.[12]

The solubility of a drug substance is an important physicochemical parameter that has a significant role in various physical and biological processes.

In this paper are reported the solubilities in water of uracil (Figure 1) and its halogenated derivatives at 25 °C. This paper constitutes a continuation of investigations of the halogenated derivatives of uracil.[1,3,4,6]

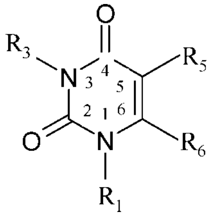

Figure 1. Structural formula of uracil $R_1 = R_3 = R_5 = R_6 = H$.

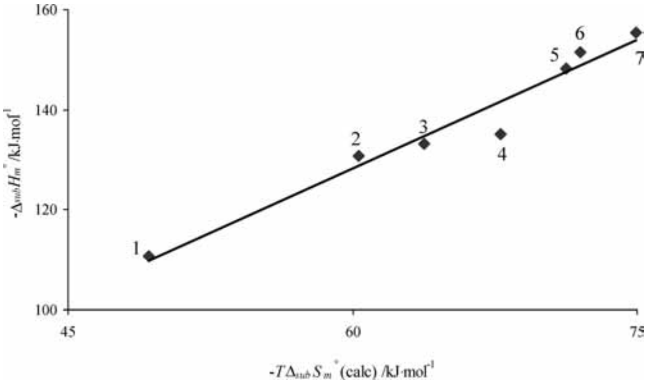

Figure 2. Dependence of the enthalpy of sublimation on the entropy term of sublimation: 1, 5-(trifluoromethyl)uracil; 2, uracil; 3, 5-fluorouracil; 4, 6-chlorouracil; 5, 5-chlorouracil; 6, 5-bromouracil; 7, 5-iodouracil.

Materials and Method

The objects of the study were seven compounds. The compounds used were obtained from specialized chemical companies.

Uracil (Lot: 21H3494, CAS: 66-22-8), 5-fluorouracil (Lot: 40H7700, CAS: 51-21-8), 5-chlorouracil (Lot: 29H1337, CAS: 1820-81-1), and 5-bromouracil (Lot: 21H3494, CAS: 51-20-7) of min. 99 % purity were purchased from the Sigma Chemical Co., Ltd.

5-(Trifluoromethyl)uracil (No. 22,327-1, CAS: 54-20-6) of 98 % purity was supplied from the Aldrich Chemicals Co., Ltd. 6-Chlorouracil (6-chloro-2,6-dihydroxypyrimidine; 4-chlorouracil) (No.1875, CAS: 427-27-3) of 98 % purity and 5-iodouracil (Lot: C7298, CAS: 696-07-1) (> 98 % purity) were purchased from Avocado Research Chemicals, Ltd.

The solubilities of the investigated compounds were determined at 25 °C by the isothermal saturation method for aqueous solutions. The apparatus used was presented previously.[13]

Saturated solutions were prepared in an apparatus holding 15 cm^3 glass ampoules, which could be rotated by 180°. This

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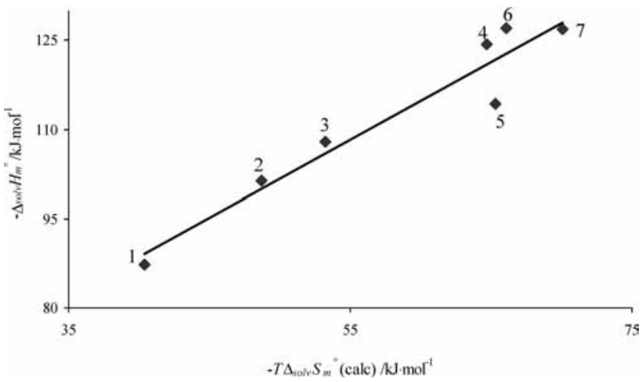

Figure 3. Dependence of the enthalpy of solvation on the entropy term of solvation: 1, 5-(trifluoromethyl)uracil; 2, uracil; 3, 5-fluorouracil; 4, 5-bromouracil; 5, 6-chlorouracil; 6, 5-iodouracil; 7, 5-chlorouracil.

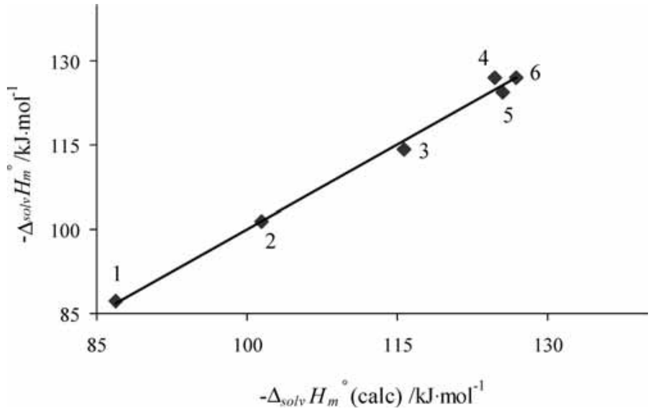

Figure 4. Estimation of $\Delta_{solv}H_m^\circ$ as a function of the nonpolar S_{np}, polar S_p, and halogen S_{halo} parts of the molecular accessible surface areas: 1, 5-(trifluoromethyl)uracil; 2, uracil; 3, 6-chlorouracil; 4, 5-chlorouracil; 5, 5-bromouracil; 6, 5-iodouracil.

equipment was immersed in a thermostat. The temperature in the thermostat was measured with a Hewlett-Packard model 2801A quartz thermometer and controlled with a PID (type 650 operated with a type 651 power unit, UNIPAN, Warsaw, Poland) temperature controller to ± 0.001 °C. The substance examined was placed in a glass ampoule and weighed. The sample mass was in the range (70 to 200) mg. The volume of added water was 6 cm^3. The sample mass was determined with the accuracy of $1 \cdot 10^{-5}$ g using the balance Mettler AT 261 Delta Range. All of the solutions were prepared using distilled and deionized water.

A glass ball was placed inside the ampoule, which was somewhat smaller in diameter than the ampule. 5-Iodouracil and 5-bromouracil solutions when prepared were shielded from access to white light. The solute and solvent were continuously mixed together for 3 days at a speed of 25 rpm. After the experiment was completed, the sample was centrifuged at 40 000 rpm for 40 min at (25 ± 0.1) °C. The supernatant liquid was collected and diluted, and its concentration was determined with a UV−vis-2401 PC Shimadzu spectrophotometer. The wavelength measurement precision was 0.1 nm. The experiments were repeated three times for each compound.

The solubilities were calculated using the Beer−Lambert law[14]

$$A = \varepsilon \cdot c \cdot l \tag{1}$$

where A is the absorbance of the sample at a given wavelength; ε is the molar absorption coefficient; c is the molar concentration of the absorbing species; and l is the length of the sample.

Table 1. Solution m Concentrations Investigated, the Values Determined for Absorbance A, the Wavenumber λ_{max} at which Absorbance A of the Samples Was Determined, and the Coefficients of Determination R^2 for $A = f$ (Concentration)

m / mmol·L^{-1}	A	m / mmol·L^{-1}	A	m / mmol·L^{-1}	A
uracil		5-fluorouracil		5-chlorouracil	
λ_{max} = 258.7 nm		λ_{max} = 265.6 nm		λ_{max} = 272.8 nm	
R^2 = 0.999		R^2 = 0.998		R^2 = 0.999	
0.025	0.0271	0.069	0.0499	0.042	0.0325
0.133	0.1252	0.091	0.0632	0.085	0.0620
0.399	0.3293	0.139	0.1039	0.127	0.0879
0.665	0.5509	0.163	0.1196	0.732	0.4284
0.798	0.6697	0.209	0.1534	1.465	0.7661
0.931	0.7742	0.244	0.1730	2.190	1.1811
1.064	0.8772	0.272	0.1895	2.930	1.5425
1.197	0.9976	0.278	0.2054	3.662	1.9330
1.331	1.0852	0.326	0.2296	4.185	2.2404
		0.348	0.2545	4.395	2.2705
		0.408	0.2861	5.232	2.7410
		0.417	0.3028		
		0.489	0.3433		
		0.556	0.4019		
		0.571	0.3955		
		0.626	0.4503		
		0.734	0.5059		
		0.776	0.5434		
		0.799	0.5549		
		0.806	0.5605		
6-chlorouracil		5-bromouracil		5-iodouracil	
λ_{max} = 265.6 nm		λ_{max} = 275.4 nm		λ_{max} = 282.6 nm	
R^2 = 0.998		R^2 = 0.999		R^2 = 0.999	
0.075	0.063	0.069	0.0512	0.037	0.0244
0.317	0.285	0.080	0.0609	0.075	0.0516
0.633	0.589	0.104	0.0835	0.108	0.0703
0.950	0.811	0.138	0.1036	0.108	0.0679
1.267	1.103	0.173	0.1312	0.113	0.0763
1.584	1.370	0.190	0.1499	0.144	0.0982
1.901	1.664	0.243	0.1781	0.151	0.0961
2.218	1.971	0.381	0.2776	0.189	0.1198
2.535	2.163	0.572	0.4152	0.226	0.1420
2.851	2.555	0.762	0.5446	0.264	0.1668
		0.953	0.6911	0.289	0.1810
		1.144	0.8189	0.340	0.2126
		1.334	0.9442	0.433	0.2716
		1.716	1.2128	0.578	0.3605
				0.723	0.4469
				0.867	0.5321
				1.012	0.6229
				1.300	0.7915
5-(trifluoromethyl)uracil					
λ_{max} = 256.4 nm					
R^2 = 0.998					
0.095	0.0874				
0.191	0.1518				
0.287	0.2199				
0.383	0.2950				
0.479	0.3668				
0.410	0.3124				
0.479	0.3428				
0.234	0.1580				
0.704	0.5227				
0.938	0.6898				
1.173	0.8675				
1.407	1.0034				
1.642	1.1530				
1.877	1.3746				

The molar absorption coefficients ε for derivatives of uracils were obtained before the solubility determination. The UV spectra were recorded in the range (200 to 400) nm for the determination of the molar absorption coefficients for solutions

Table 2. Molar Absorption Coefficient ε, the Solubilities C_w, and the Molar Fraction of the Investigated Substances in Saturated Solution X_2

compound	pH range	$\varepsilon \cdot 10^3$ $\mathrm{L \cdot mol^{-1} \cdot cm^{-1}}$	C_w $\mathrm{mmol \cdot L^{-1}}$	X_2
uracil	6.0 to 6.3	8.161 ± 0.06	41.25 ± 0.10	0.000743
5-fluorouracil	6.3 to 7.0	6.912 ± 0.06	138.22 ± 0.36	0.002484
5-chlorouracil	5.8 to 6.5	5.203 ± 0.04	17.12 ± 0.64	0.000308
6-chlorouracil	4.0 to 4.5	8.782 ± 0.12	33.50 ± 0.23	0.000603
5-bromouracil	6.0 to 6.5	7.047 ± 0.03	19.08 ± 0.60	0.000272
5-iodouracil	5.8 to 6.5	6.079 ± 0.02	20.72 ± 0.50	0.000373
5-(trifluoromethyl) uracil	5.2 to 6.3	7.126 ± 0.08	149.21 ± 0.54	0.002682

of known concentration. For each investigated substance 9 to 20 measurements were made.

The standard Gibbs energies of the dissolution process $\Delta_{\mathrm{sol}}G^{\mathrm{o}}_{\mathrm{m}}$ were calculated using the following equation[15]

$$\Delta_{\mathrm{sol}}G^{\mathrm{o}}_{\mathrm{m}} = -RT \ln X_2 \tag{2}$$

where X_2 is the molar fraction of the investigated substance in the saturated solution.

The standard entropies of solution $\Delta_{\mathrm{sol}}S^{\mathrm{o}}_{\mathrm{m}}$ were obtained from the well-known equation

$$\Delta_{\mathrm{sol}}G^{\mathrm{o}}_{\mathrm{m}} = \Delta_{\mathrm{sol}}H^{\mathrm{o}}_{\mathrm{m}} - T\Delta_{\mathrm{sol}}S^{\mathrm{o}}_{\mathrm{m}} \tag{3}$$

where $\Delta_{\mathrm{sol}}H^{\mathrm{o}}_{\mathrm{m}}$ is the molar enthalpy of solution (as determined before).[1,3]

The enthalpies of solution $\Delta_{\mathrm{sol}}H^{\mathrm{o}}_{\mathrm{m}}$ in water at 298.15 K were determined experimentally using an isoperibol solution calorimeter. The calorimeter and the working procedure have been described in detail elsewhere.[1,16]

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.[1,17]

The standard entropies $\Delta_{\mathrm{sub}}S^{\mathrm{o}}_{\mathrm{m}}$ and standard Gibbs energies $\Delta_{\mathrm{sub}}G^{\mathrm{o}}_{\mathrm{m}}$ of sublimation were calculated on the basis of early determined enthalpies of sublimation $\Delta_{\mathrm{sub}}H^{\mathrm{o}}_{\mathrm{m}}$[1,3] using the following relationships[15]

$$\Delta_{\mathrm{sub}}S^{\mathrm{o}}_{\mathrm{m}} = \frac{(\Delta_{\mathrm{sub}}H^{\mathrm{o}}_{\mathrm{m}} - \Delta_{\mathrm{sub}}G^{\mathrm{o}}_{\mathrm{m}})}{T} \tag{4}$$

$$\Delta_{\mathrm{sub}}G^{\mathrm{o}}_{\mathrm{m}} = -RT \ln\left(\frac{p^{298.15}}{p_0}\right) \tag{5}$$

where $T = 298.15$ K; $p^{298.15}$ is vapor pressure[1,3] at 298.15 K; and $P_{\mathrm{o}} = 1.013 \cdot 10^5$ Pa.

The Gibbs energy of the sublimation process at 298.15 K of the investigated compounds can be separated into the relative fractions of both the enthalpic and the entropic terms by the following parameters[15]

$$\varsigma_{H_{\mathrm{sub}}} = \frac{\Delta_{\mathrm{sub}}H^{\mathrm{o}}_{\mathrm{m}}}{\Delta_{\mathrm{sub}}H^{\mathrm{o}}_{\mathrm{m}} + T \cdot \Delta_{\mathrm{sub}}S^{\mathrm{o}}_{\mathrm{m}}} \cdot 100\ \% \tag{6}$$

$$\varsigma_{TS_{\mathrm{sub}}} = \frac{T \cdot \Delta_{\mathrm{sub}}S^{\mathrm{o}}_{\mathrm{m}}}{\Delta_{\mathrm{sub}}H^{\mathrm{o}}_{\mathrm{m}} + T\Delta_{\mathrm{sub}}S^{\mathrm{o}}_{\mathrm{m}}} \cdot 100\ \% \tag{7}$$

The thermodynamic parameters of solvation $\Delta_{\mathrm{solv}}H^{\mathrm{o}}_{\mathrm{m}}$, $\Delta_{\mathrm{solv}}G^{\mathrm{o}}_{\mathrm{m}}$, and $\Delta_{\mathrm{solv}}S^{\mathrm{o}}_{\mathrm{m}}$ of the compounds studied were calculated using the following equation

$$\Delta_{\mathrm{solv}}Y^{\mathrm{o}}_{\mathrm{m}} = \Delta_{\mathrm{sol}}Y^{\infty}_{\mathrm{m}} - \Delta_{\mathrm{sub}}Y^{\mathrm{o}}_{\mathrm{m}} \tag{8}$$

where Y is one of the respective thermodynamic functions G, H, S.

On the basis of the experimental data of sublimation and solution, the major driving force of the solvation process can be estimated. The respective Gibbs energy was split into the relative fractions of enthalpy and entropy[15]

$$\varsigma_{H_{\mathrm{solv}}} = \frac{\Delta_{\mathrm{solv}}H^{\mathrm{o}}_{\mathrm{m}}}{\Delta_{\mathrm{solv}}H^{\mathrm{o}}_{\mathrm{m}} + T \cdot \Delta_{\mathrm{solv}}S^{\mathrm{o}}_{\mathrm{m}}} \cdot 100\ \% \tag{9}$$

$$\varsigma_{TS_{\mathrm{solv}}} = \frac{T \cdot \Delta_{\mathrm{solv}}S^{\mathrm{o}}_{\mathrm{m}}}{\Delta_{\mathrm{solv}}H^{\mathrm{o}}_{\mathrm{m}} + T\Delta_{\mathrm{solv}}S^{\mathrm{o}}_{\mathrm{m}}} \cdot 100\ \% \tag{10}$$

The obtained values of the thermodynamic functions, the standard Gibbs energies ΔG, the enthalpies ΔH, and the entropies ΔS, of solvation and solution for halogenated derivatives of uracil were correlated with nonpolar S_{np}, polar S_{p}, and halogen S_{halo} parts of molecular accessible surface areas S^{M} of the compounds studied, by the relationship

$$\Delta Y = aS_{\mathrm{np}} + bS_{\mathrm{p}} + cS_{\mathrm{halo}} + d \tag{11}$$

where Y is one of the respective thermodynamic functions G, H, S of solvation and solution and a, b, c, and d are constants.

The similar relationships between the enthalpies of solvation of methyl derivatives of cytosine, uracil, and surfaces S_{np} and S_{p} were presented in refs 18 and 19.

To distinguish the polar and apolar parts of S^{M}, the model of solute−solvent interaction was applied, in which the existence of specific and nonspecific solute−solvent interactions was established. For this purpose, it was assumed that in aqueous solutions both acceptors and donors of protons are involved in specific solute−solvent interactions. It was also assumed that water interacts mainly with oxygen, nitrogen, and polar hydrogen of the investigated substance.

The accessible molecular surface area of polar atoms S_{p} for aqueous solutions is expressed as[18]

$$S_{\mathrm{p}} = S_{\mathrm{O}} + S_{\mathrm{N}} + S_{\mathrm{H(O,N)}} \tag{12}$$

The structural parameters, the molecular volumes V_2^{M}, solvent accessible molecular surface area S^{M}, and its atomic partitions S_{O}, S_{N}, $S_{\mathrm{H(O,N)}}$, and S_{halo}, were calculated[4,19] by the GEPOL Version 12.1 algorithm[20] using structures obtained by molecular mechanics.

The obtained values of thermodynamic functions G, H, and S of solvation for halogen derivatives of uracil were correlated with the volumetric data by use of the parameters β, the partial molar volumes V_2^{o}, and molecular volumes V_2^{M}, by the relationship

$$\Delta Y = aZ + b \tag{13}$$

where Y is one of the respective thermodynamic functions G, H, S, and Z is one of the respective parameters β, V_2^{o}, V_2^{M}.

Parameter β was defined as the difference between the partial molar volume and the molecular volume[18,19]

$$\beta = V_2^{\mathrm{o}} - V_2^{\mathrm{M}} \tag{14}$$

Results and Discussion

Solubility in Water. The solution concentrations investigated and the values of absorbance (A) determined for uracil and its halogen derivatives are presented in Table 1.

Table 3. Molar Standard Thermodynamic Parameters of Sublimation, the Enthalpies $\Delta_{sub}H^{o}_{m}$,[1,3] the Gibbs Energies $\Delta_{sub}G^{o}_{m}$, and the Entropies $\Delta_{sub}S^{o}_{m}$, of the Investigated Compounds and the Relative Parameters of the Enthalpic $\varsigma_{H_{sub}}$ and the Entropic Terms $\varsigma_{TS_{sub}}$ of Sublimation

compound	$\Delta_{solv}H^{o}_{m}$ kJ·mol^{-1}	$\Delta_{solv}G^{o}_{m}$ kJ·mol^{-1}	$T\Delta_{solv}S^{o}_{m}$ kJ·mol^{-1}	$\Delta_{sub}S^{o}_{m}$ J·mol^{-1}·K^{-1}	$\varsigma_{H_{sub}}$ %	$\varsigma_{TS_{sub}}$ %
uracil	130.82 ± 4.45	70.51	60.31	202.28	68.4	31.6
5-fluorouracil	133.22 ± 2.74	69.46	63.76	213.85	67.6	32.4
5-chlorouracil	148.26 ± 2.50	77.00	71.26	239.00	67.5	32.5
6-chlorouracil	135.22 ± 3.30	67.40	67.82	227.46	66.6	33.4
5-bromouracil	151.44 ± 4.27	79.41	72.03	241.57	67.8	32.2
5-iodouracil	155.47 ± 2.74	80.51	74.96	251.42	67.5	32.5
5-(trifluoromethyl)uracil	110.77 ± 0.86	61.50	49.27	165.25	69.2	30.8

Table 4. Thermodynamic Functions of Uracil and Its Halo Derivatives: The Molar Standard Enthalpies, Gibbs Energies and the Standard Entropies of Solution and Solvation, $\Delta_{sol}H^{o}_{m}$, $\Delta_{sol}G^{o}_{m}$, $\Delta_{sol}S^{o}_{m}$, $\Delta_{solv}H^{o}_{m}$, $\Delta_{solv}G^{o}_{m}$, and $\Delta_{solv}S^{o}_{m}$ and the Relative Parameters of the Enthalpic $\varsigma_{H_{solv}}$ and the Entropic Terms $\varsigma_{TS_{solv}}$ of Solvation

compound	$\Delta_{sol}H^{\infty}_{m}$ kJ·mol^{-1}	$\Delta_{sol}G_{m}$ kJ·mol^{-1}	$T\Delta_{sol}S^{\infty}_{m}$ kJ·mol^{-1}	$\Delta_{sol}S^{\infty}_{m}$ J·mol^{-1}	$-\Delta_{solv}H^{o}_{m}$ kJ·mol^{-1}	$\Delta_{solv}G^{o}_{m}$ kJ·mol^{-1}	$-\Delta_{solv}S^{o}_{m}$ kJ·mol^{-1}	$-\Delta_{solv}S^{o}_{m}$ J·mol^{-1}·K^{-1}	$\varsigma_{H_{solv}}$ %	$\varsigma_{TS_{solv}}$ %
uracil	29.50 ± 0.12	17.86	11.64	39.04	101.31 ± 4.45	52.65	48.66	163.24	67.5	32.5
5-fluorouracil	25.38 ± 0.37	14.90	10.48	35.26	107.84 ± 2.76	54.56	53.28	178.59	66.9	33.1
5-chlorouracil	21.30 ± 0.06	20.10	1.20	4.06	126.96 ± 2.50	56.90	70.06	234.94	64.4	35.6
6-chlorouracil	20.94 ± 0.23	18.40	2.54	8.50	114.28 ± 3.31	49.00	65.28	218.96	63.6	36.4
5-bromouracil	27.08 ± 0.24	19.77	7.31	24.51	124.36 ± 4.30	59.64	64.72	217.06	65.7	34.3
5-iodouracil	28.47 ± 0.43	19.56	8.91	29.86	127.00 ± 2.80	60.95	66.05	221.56	65.8	34.2
5-(trifluoromethyl)uracil	23.54 ± 0.10	14.67	8.87	29.72	87.23 ± 0.90	46.83	40.40	135.53	68.3	31.7

Table 5. Determined Contributions of Groups to the Value of the Enthalpy $\Delta_{solv}H^{o}_{m,contr}$, the Gibbs Energy $\Delta_{solv}G^{o}_{m,contr}$, the Entropy of Solvation $\Delta_{solv}S^{o}_{m,contr}$ in Water (Equation 15), and the Contributions to the Value of the Enthalpy Solvation $\Delta_{solv}H^{o}_{m,contr}$ Obtained by Cabani[32] for Aliphatic Compounds

substituent	$\Delta_{solv}H^{o}_{m,contr}$ kJ·mol^{-1}	$\Delta_{solv}G^{o}_{m,contr}$ kJ·mol^{-1}	$\Delta_{solv}S^{o}_{m,contr}$ J·mol^{-1}·K^{-1}	contributions of groups in the value of the enthalpy of solvation according to Cabani[32] kJ·mol^{-1}
F	–6.53	–1.91	–15.35	–1.87
Cl(5)	–25.65	–4.25	–71.70	–6.90
Cl(6)	–12.97	3.65	–55.72	–
Br	–23.05	–6.99	–53.82	–9.27
I	–25.69	–8.30	–58.32	–9.64
CF_3	14.08	5.82	27.71	–10.17

The absorption coefficients ε were determined from the concentration dependences of absorbance at given wavelength λ_{max}. The resulting data and correlation coefficients of determination R^2 for $A = f$ (concentration) are also presented in Table 1.

The molar absorption coefficients ε, the solubilities C_w, and the molar fraction of the investigated substance in saturated solution X_2 are given in Table 2.

For uracil, the molar absorption coefficient $\varepsilon = 8161.0 \pm 58$ (L·mol^{-1}·cm^{-1}) determined at 258.7 nm is in good agreement with that reported by Fasman[21] of 8200 (L·mol^{-1}·cm^{-1}) at 258.3 nm, whereas Du et al.[22] reported that ε for uracil is equal to 8103 (L·mol^{-1}·cm^{-1}) at 258.0 nm. Shugar et al.[23] obtained the value $\varepsilon = 8200$ L·mol^{-1}·cm^{-1} at 259.5 nm in the pH range 4.4 to 7.2. The same value ($\varepsilon = 8200$ L·mol^{-1}·cm^{-1} at pH = 7) was obtained by Ploeser et al.[24] All these values are within the range of uncertainty measured for uracil. None of the previous values are given with an uncertainty.

The values of the solubilities determined for 5-fluorouracil, (138.22 ± 0.3) mmol·L^{-1}, and 5-(trifluoromethyl)uracil, (149.21 ± 0.5) mmol·L^{-1}, differ from the values obtained for the other compounds. The other compounds are characterized by smaller solubility.

The values obtained for the solubility of 5-chlorouracil, 5-bromouracil, and 5-iodouracil are similar: (17.1 ± 0.6, 19.1 ± 0.6, and 20.7 ± 0.5) mmol·L^{-1}. A considerable difference in solubility between 5-chlorouracil and 6-chlorouracil is visible: (17.1 ± 0.6 and 33.5 ± 0.2) mmol·L^{-1}.

The structures of the investigated compounds obtained using X-ray crystallography[25–28] allow the accurate determination of the vital differences in the structure of the various compounds and the influence of the structure on solubility.

The molecule of uracil creates two hydrogen bonds[25] and has stability from layer interaction, and a change in substituents disturbs the network of the hydrogen bond, which causes a change in the crystal lattice.

Noticeable is the difference between uracil and 5-fluorouracil, which better characterizes solubility. The structure of 5-fluorouracil has been presented previously.[26] The fluorine atoms are situated close to each other. These atoms carry negative charges and interact, repulsively destabilizing the crystal lattice. For these reasons, 5-fluorouracil dissolves better than uracil. 5-(Trifluoromethyl)uracil which has three fluorine atoms dissolves significantly better than both uracil and 5-halogenated derivatives. The difference in solubility between 5-fluorouracil and 5-(trifluoromethyl)uracil is not much (10.99 mmol·L^{-1}).

In the case of 5-substituted halogen uracils, the ability to dissolve increases with a decrease in molecular size. 5-Chlorouracil, 5-bromouracil, and 5-iodouracil are less soluble than uracil. Between 5-chlorouracil[27] and 5-bromouracil,[27] the difference in solubility is small and similar to their properties. Similarly, the difference between 5-iodouracil[28] and 5-bromouracil[27] is small.

Thermodynamics of Sublimation. Table 3 lists the determined thermodynamic parameters of sublimation, the enthalpies $\Delta_{sub}H^{o}_{m}$, the standard Gibbs energies $\Delta_{sub}G^{o}_{m}$, and the entropies $\Delta_{sub}S^{o}_{m}$, of the investigated compounds. These values were calculated using eqs 4 and 5. The molar enthalpies of sublimation were determined before[1,3] and compared with the literature data in ref 1.

To find the main driving force of the sublimation process, the relative parameters of the enthalpic and entropic terms were calculated on the basis of eqs 6 and 7. The results obtained are presented in Table 3. The main driving force of the sublimation

Table 6. Parameters *a*, *b*, *c*, and *d* and the Coefficients of Determination R^2 for Water Obtained for Relationship (11) between the Determined Enthalpies of Solvation and the Nonpolar S_{np}, Polar S_p, and Halogen S_{halo} Parts of the Molecular Accessible Surface Areas S^M

compound	a/kJ·Å^{-2}	b/kJ·Å^{-2}	c/kJ·Å^{-2}	d/kJ	R^2
	$-\Delta_{solv}H^o_m$				
uracil and its halogenated derivatives (5-fluorouracil is excluded)	-1.0 ± 0.5	38.6 ± 2.3	2.1 ± 0.2	-1690 ± 116	0.994
	$-\Delta_{solv}G^o_m$				
uracil and its halogenated derivatives (6-chlorouracil is excluded)	0.8 ± 0.2	13.0 ± 1.0	1.1 ± 0.1	-593.5 ± 52.7	0.990
	$-\Delta_{solv}S^o_m$				
uracil and its halogenated derivatives (5-chlorouracil and 6-chlorouracil are excluded)	0.0051 ± 0.0025	0.079 ± 0.014	6.9 ± 1.3	-3.8 ± 0.7	0.980
	$-\Delta_{sol}H^o_m$				
uracil and its halogenated derivatives (6-chlorouracil and 5-chlorouracil are excluded)	0.90 ± 0.07	4.2 ± 0.4	0.44 ± 0.04	-201.2 ± 20.4	0.995
	$-\Delta_{sol}G^o_m$				
uracil and its halogenated derivatives (5-fluorouracil is excluded)	0.08 ± 0.06	5.0 ± 0.3	0.24 ± 0.03	-216.1 ± 13.5	0.994

Table 7. Parameters *a* and *b* and the Coefficients of Determination R^2 for Water Obtained for the Relationship $Y = a\beta + b$ (Equation 13) between the Determined Thermodynamic Functions of Solvation and Parameter β

compound	A	b	R^2
$-\Delta_{solv}H^o_m$			
uracil and its halogenated derivatives (5-(trifluoromethyl)uracil, 5-chlorouracil are excluded)	2.1 ± 0.4	47.0 ± 13.0	0.903
$-\Delta_{solv}G^o_m$			
uracil and its halogenated derivatives (5-(trifluoromethyl)uracil, 6-chlorouracil are excluded)	0.71 ± 0.09	35 ± 3	0.956
$-\Delta_{solv}S^o_m$			
uracil and its halogenated derivatives (5-(trifluoromethyl)uracil, 5-chlorouracil are excluded)	5.3 ± 1.0	31.4 ± 33.8	0.900

Table 8. Parameters *a* and *b* and the Coefficients of Determination R^2 for Water Obtained for the Relationship $Y = aV^o_2 + b$ (Equation 13) between the Determined Thermodynamic Functions of Solvation and the Partial Molar Volumes V^o_2

compound	A	b	R^2
$-\Delta_{solv}H^o_m$			
uracil and its halogenated derivatives (5-(trifluoromethyl)uracil, 5-chlorouracil are excluded)	41.0 ± 11.6	0.9 ± 0.1	0.932
$-\Delta_{solv}G^o_m$			
uracil and its halogenated derivatives (5-(trifluoromethyl)uracil, 6-chlorouracil are excluded)	0.30 ± 0.03	33.1 ± 2.6	0.966

Table 9. Parameters *a* and *b* and the Coefficients of Determination R^2 for Water Obtained for the Relationship $Y = aV^M_2 + b$ (Equation 13) between the Determined Thermodynamic Functions of Solvation and the Molecular Volumes V^M_2

compound	A	b	R^2
$-\Delta_{solv}H^o_m$			
uracil and its halogenated derivatives (5-(trifluoromethyl)uracil, 5-chlorouracil are excluded)	1.4 ± 0.2	38.5 ± 12.0	0.932
$-\Delta_{solv}G^o_m$			
uracil and its halogenated derivatives (5-(trifluoromethyl)uracil, 6-chlorouracil are excluded)	0.46 ± 0.05	32.3 ± 3.0	0.960

process for all the investigated compounds is the enthalpy. The sublimation is enthalpy-driven with a fraction of (66.6 to 69.2) %.

A correlation between the enthalpic and the entropic terms of the Gibbs energy is observed for the sublimation process. As follows from Figure 2, the compensation effect is observed for all seven investigated substances.

Thermodynamics of Solvation. In Table 4 are presented the molar standard enthalpies, Gibbs energies, and the standard entropies of solution and solvation, $\Delta_{sol}H^o_m$, $\Delta_{sol}G^o_m$, $\Delta_{sol}S^o_m$, $\Delta_{solv}H^o_m$, $\Delta_{solv}G^o_m$, and $\Delta_{solv}S^o_m$, in water of the uracil and its halogenated derivatives. The thermodynamic parameters of solution and solvation were calculated from eqs 2, 3, and 8. The molar enthalpies of solution were determined before[1,3] and compared with the literature data in ref 1.

In Table 4, the relative parameters of the enthalpic $\varsigma_{H_{solv}}$ and entropic terms $\varsigma_{TS_{solv}}$ of solvation are also presented. The parameters were calculated on the basis of eqs 9 and 10.

The properties of 6-chlorouracil differ from the properties of the 5-halouracil compounds. Its dissociation is greater than the 5-halogenated derivatives of uracil.[29]

The values of the enthalpy of solvation and solubility of 6-chlorouracil are clearly different than 5-chlorouracil. In addition, the enthalpies of solvation determined for 5-chlorouracil, 5-bromouracil, and 5-iodouracil are considerably different than the values determined for 5-fluorouracil and 5-(trifluoromethyl)uracil. This is connected with the creation of a hydrogen bond and with the proton-accepting property of fluorine.[30,31]

In the investigated systems of uracil derivatives, there is strong electron coupling between a substituent and the π-electron system of the pyrimidine ring as is well seen in the 5 and 6 substituted derivatives. In the case of 5-chlorouracil and 6-chlorouracil, a vital difference of 12.68 kJ·mol^{-1} was observed between the obtained values of the enthalpy of solvation. This demonstrates explicitly that the enthalpy of solvation is very dependent on the place of substitution electron coupling in the systems of the investigated derivatives of uracil.

It follows from Table 4 that the process of solvation is enthalpy driven. For the substances investigated, the enthalpy fraction of the solvation is (63.6 to 68.3) %.

We can observe that the entropic term of the solubility process is lower than the enthalpic term. This fact confirms that the solubility process for the investigated substances is enthalpy controlled. An enthalpy−entropy compensation effect of solvation in water for the investigated compounds is observed and is evident in Figure 3.

On the basis of the values obtained for the enthalpies, the Gibbs energies and the entropies of solvation in water, the contributions of the following substituents were determined: F, Cl(5), Cl(6), Br, I, and CF_3. The contributions $\Delta_{\mathrm{solv}}Y^{\mathrm{o}}_{\mathrm{m,contr}}$ of substituents were calculated on the basies of the difference between the thermodynamic quantities of solvation of halo derivatives of uracil and uracil

$$\Delta_{\mathrm{solv}}Y^{\mathrm{o}}_{\mathrm{m,contr}} = \Delta_{\mathrm{solv}}Y^{\mathrm{o}}_{\mathrm{m}}(1) - \Delta_{\mathrm{solv}}Y^{\mathrm{o}}_{\mathrm{m}}(2) \qquad (15)$$

where Y is one of the respective thermodynamic functions (G, H, S) of solvation of a suitable halogenated derivative of uracil (1) and uracil (2).

The contributions determined are presented in Table 5. Also in this table are the contributions of groups obtained by Cabani[32] for aliphatic compounds. The contributions of groups were calculated on the basis of additivity scheme groups using the least-squares linear regression.

Comparison with the data of Cabani shows some vital differences between the values determined for aromatic and aliphatic compounds.

In the investigated systems of uracil derivatives, there is strong electron coupling between a substituent and the π-electron system of the pyrimidine ring

In the case of halo derivatives, a vital difference was observed between the determined values of contributions of groups to the value of the enthalpy of solvation than for aliphatic compounds. In the case 5-chlorouracil and 6-chlorouracil, a difference of –12.68 kJ·mol^{-1} was observed between the obtained values of the contribution of chlorine atom in positions (5) and (6) to the value of the enthalpy of solvation. This explicitly demonstrates that the enthalpy of solvation is very dependent on the place of substitution of electron coupling in the systems of halo derivatives.

The structural parameters, molecular surface areas S^{M}, atomic partitions, S_{O}, S_{N}, $S_{\mathrm{H(O,N)}}$, S_{halo}, nonpolar S_{np}, polar S_{p}, and halogen S_{halo} parts of the molecular accessible surface areas and the parameter β, and the molecular volumes V_2^{M} of the compound studied in water were taken from refs 4 and 19. The results of correlations of the values of $\Delta_{\mathrm{solv}}H^{\mathrm{o}}_{\mathrm{m}}$, $\Delta_{\mathrm{solv}}G^{\mathrm{o}}_{\mathrm{m}}$, $\Delta_{\mathrm{solv}}S^{\mathrm{o}}_{\mathrm{m}}$, $\Delta_{\mathrm{sol}}H^{\mathrm{o}}_{\mathrm{m}}$, and $\Delta_{\mathrm{sol}}G^{\mathrm{o}}_{\mathrm{m}}$ for halogenated derivatives of uracil with the nonpolar S_{np}, polar S_{p}, and halogen S_{halo} parts of the molecular accessible surface areas are given in Table 6. The correlations obtained are presented in Figures 4, 5, and 6. As can be seen in all cases, the correlations obtained are linear. The coefficients of determination obtained were 0.900 to 0.995.

The results of the correlations of the thermodynamic functions of solvation with the parameter β and molecular volumes V_2^{M} of the compound studied in water are presented in Tables 7 to 9.

A similar relationship has been found between the enthalpies of solvation and parameters β for cytosine and its methyl, methoxy, and hydroxyl derivatives.[18] Zielenkiewicz et al.[33] also demonstrated that the Gibbs free energy of water reorganization around small alkanes is proportional to the parameter β.

The results given in Table 9 indicate that the enthalpy of solvation correlates with the parameter β, being a measure of the solute induced solvent reorganization. The parameter β represents the total effect of the solute-induced solvent reorganization resulting from solute−solvent interactions. This parameter can be assumed to be proportional to the Gibbs energy of the solute-induced reorganization of the hydrating water structure.

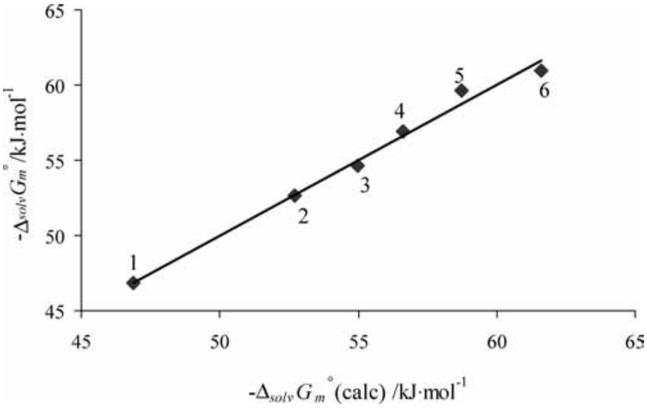

Figure 5. Estimation of $\Delta_{\mathrm{solv}}G^{\mathrm{o}}_{\mathrm{m}}$ as a function of the nonpolar S_{np}, polar S_{p}, and halogen S_{halo} parts of the molecular accessible surface areas: 1, 5-(trifluoromethyl)uracil; 2, uracil; 3, 5-fluorouracil; 4, 5-chlorouracil; 5, 5-bromouracil; 6, 5-iodouracil.

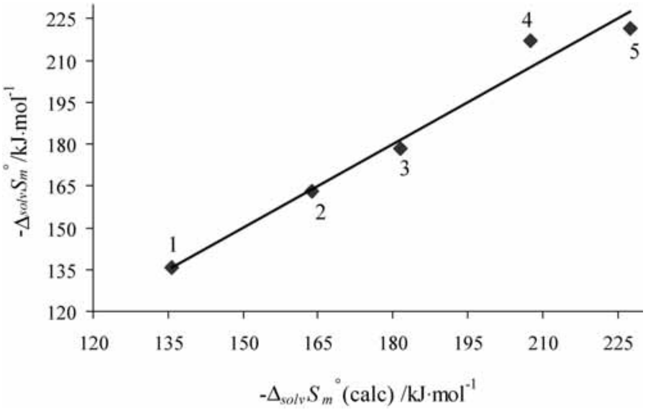

Figure 6. Estimation of $\Delta_{\mathrm{solv}}S^{\mathrm{o}}_{\mathrm{m}}$ as a function of the nonpolar S_{np}, polar S_{p}, and halogen S_{halo} parts of the molecular accessible surface areas: 1, 5-(trifluoromethyl)uracil; 2, uracil; 3, 5-fluorouracil; 4, 5-bromouracil; 5, 5-iodouracil.

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