J. Chem. Eng. Data **2005,** *50,* 1139−1143

Thermodynamic Investigation of Uracil and Its Halo Derivatives. Enthalpies of Solution and Solvation in Methanol

Wojciech Zielenkiewicz* and Piotr Szterner

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

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The enthalpy of solution of uracil, 5-fluorouracil, 5-chlorouracil, 6-chlorouracil, 5-bromouracil, 5-iodouracil, and 5-(trifluoromethyl)uracil in methanol at 298.15 K using the isoperibol solution calorimeter has been determined in the range of concentration (0.472 to 1.848) × 10^{-3}/mol·kg^{-1}. The enthalpies of solvation were determined from the experimentally obtained enthalpies of solution and the previously determined enthalpies of sublimation for aqueous and methanol solutions. The transfer enthalpies of solution $\Delta_{tr}H_m$ for water−methanol, and the enthalpy of cavity formation $\Delta_{cav}H_m$, the enthalpy of solute−solvent interaction $\Delta_{int}H_m$ were calculated. The enthalpy of solvation $\Delta_{solv}H_m$, sublimation $\Delta_s^g H_m^o$, interaction $\Delta_{int}H_m$, and transfer $\Delta_{tr}H_m$ were correlated with the values of the surface-accessible areas of the compounds investigated.

Introduction

The thermodynamic properties of uracil and its alkylated, halogenated amino and nitro derivatives in an aqueous solution have been the subject of our intensive research.[1−4] These investigations have been aimed at the experimental determinations of apparent molar volumes, heat capacities, and enthalpies of solution of aqueous solution and sublimation. Their purpose was also to study solute−solvent interactions.

Halo derivatives of uracil deserve particular attention among all series of derivatives of nucleic pyrimidine bases. The properties of this group of compounds are important in view of their medical applications. Some of the 5-substituted uracils exhibit significant pharmacological activity and have been used as antitumor, antibacterial, and antiviral drugs.[4] For example, 5-fluorouracil has been used to treat cancer.[2,5] Analogues of 5-(trifluoromethyl)uracil have been investigated as antiviral agents.[4] The compounds 5-bromouracil and 5-fluorouracil have been found to be the competitive inhibitors of human thymidine phosphorylase.[2,6] The prospects of the clinical use of the presented compounds or their analogues have induced us to undertake thermodynamic investigations.

In this work, the results of measurements of the enthalpies of solution in methanol solutions are presented. The standard molar enthalpies of solution $\Delta_{sol}H_m^\infty$ were calculated. The obtained results, combined with the data of the standard molar enthalpies of sublimation of solid compounds, $\Delta_s^g H_m^o$, and the standard molar enthalpies of solution, $\Delta_{sol}H_m^\infty$, in water[2] were used to determine the standard molar enthalpies of solvation, $\Delta_{solv}H_m^o$, and the transfer enthalpy, $\Delta_{tr}H_m^o$, of water to methanol solution. Data on the enthalpies of solvation and cavity formation, $\Delta_{cav}H_m$, obtained in a semiempirical way were used to calculate the enthalpies of solute−solvent interaction, $\Delta_{int}H_m$. The obtained values of $\Delta_{solv}H_m^o$, $\Delta_{tr}H_m^o$, $\Delta_{int}H_m$ were correlated with polar and apolar parts of molecular S^M-accessible surface areas (ASA) of the compounds studied. To distinguish the polar and apolar parts of ASA, the model of solute−solvent interaction was applied in which it was assumed that (a) for methanol, which is more active as a donor than an acceptor of protons, the solvent interacts mainly with solute oxygen and nitrogen atoms and (b) in aqueous solutions both proton acceptors and donors are involved in specific solute−solvent interactions. The correlation between the polarity of the compounds and the enthalpy of solvation was also determined. Polarity was defined as the ratio of the molecular surface area of polar groups and atoms exposed to solvent to the total molecular surface-accessible area.

Experimental Section

Uracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil (lots 21H3494, 40H7700, and 29H1337 (Sigma), respectively), 6-chlorouracil (6-chloro-2,6-dihydroxypyrimidine; 4-chlorouracil) (1875 Lancaster), 5-iodouracil (lot C7298 Avocado), and 5-(trifluoromethyl)uracil (22, 327-1 Aldrich) (purity >0.99) were used in the experiments as received. CAS numbers for these compounds are the following: [66-22-8], [51-21-8], [1820-81-1], [51-20-7], [427-27-3], [696-07-1], and [54-20-6], respectively. Structural formulas of the compounds studied are presented in Figure 1.

The enthalpies of solution in methanol at 298.15 K were determined experimentally using a homemade isoperibol solution calorimeter. The calorimeter and the working procedure have been described in detail elsewhere.[2,7]

The calorimeter consists of the following parts: the proper calorimeter, the measuring system, and the thermostat. The proper calorimeter consists of the measuring steel vessel of total volume 80 cm^3 and normal working volume 65 cm^3; the external metallic shield; the two thermistors, nominally 150 Ω; the glass ampule of 1.5 cm^3 volume; and the 98 Ω calibration heater and stirrer. The external shield is submerged in a thermostated water bath (30 L) in which the temperature is sensed by 100 Ω platinum resistance thermometer and regulated by PID regulator providing a temperature constant of better than 1 × 10^{-3} K. The thermistors located in the calorimetric vessel form the arms of Wheatstone bridge, which is coupled to a Keithley 181 nanovoltmeter and an IBM PC.

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

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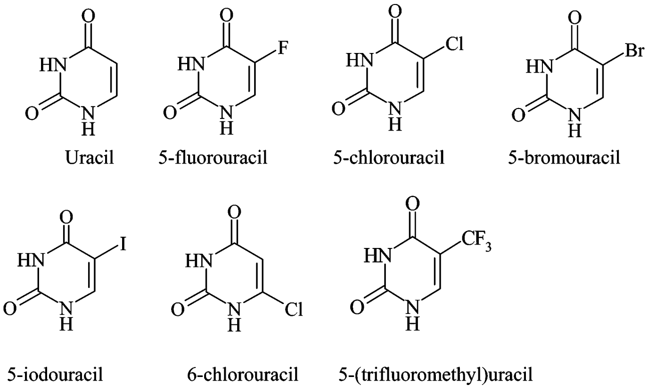

Figure 1. Structural formulas of derivatives of uracil.

Table 1. Enthalpies of Solution of Uracil and Halo Derivatives of Uracil

$m \times 10^{-3}$ mol·kg^{-1}	$\Delta_{sol}H_m$ kJ·mol^{-1}	$m \times 10^{-3}$ mol·kg^{-1}	$\Delta_{sol}H_m$ kJ·mol^{-1}
Uracil		5-Fluorouracil	
0.848	14.95	0.844	14.48
0.858	15.06	0.963	14.40
1.050	13.99	1.039	14.28
1.090	13.99	1.260	14.34
1.223	13.67	1.578	14.33
1.317	13.69	1.848	14.53
5-Chlorouracil		6-Chlorouracil	
0.652	8.85	0.624	16.84
0.899	9.62	0.862	16.98
0.901	9.58	0.948	17.27
0.954	9.31	1.116	16.90
0.982	8.83	1.609	17.90
1.245	8.85	1.680	17.38
5-Bromouracil		5-Iodouracil	
0.472	14.77	0.481	18.30
0.548	14.01	0.487	18.22
0.563	15.61	0.551	17.65
1.020	15.00	0.618	18.27
1.023	15.10	0.626	18.02
1.250	14.56	0.769	17.58
5-(Trifluoromethyl)uracil			
0.648	16.01		
0.687	16.52		
0.724	15.70		
0.760	15.08		
0.813	15.01		
0.845	15.80		

The method of corrected temperature rise with the Regnault-Phaundler correction was used to evaluate the studied heat effect. The calorimeter was calibrated by determining the enthalpy of solution of potassium chloride (mass fraction 0.9999) in water.[7] Before each measurement, the calorimeter was calibrated by means of the Joule effect.

To determine the enthalpy of solution, we used methanol of purity (mass fraction 0.998) obtained from the Riedel-de Haën company.

The values of the enthalpy of solvation $\Delta_{solv}H_m^o$ for aqueous and methanol solutions were calculated as the difference between the standard molar enthalpy of solution at infinite dilution $\Delta_{sol}H_m^\infty$ and the enthalpy of sublimation $\Delta_s^g H_m^o$:

$$\Delta_{solv}H_m^o = \Delta_{sol}H_m^\infty - \Delta_s^g H_m^o \qquad (1)$$

The enthalpies of sublimation of crystalline compounds were determined by the Knudsen effusion method and were described earlier.[4] The values obtained experimentally were corrected to a temperature of 298.15 K [4] according to the relationship given by Chickos.[8] The enthalpy of solvation $\Delta_{solv}H_m^o$ was used to evaluate the enthalpy of interaction $\Delta_{int}H_m$ according to eq 2

$$\Delta_{solv}H_m^o = \Delta_{cav}H_m - \Delta_{int}H_m \qquad (2)$$

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

The enthalpy of cavity formation was calculated by the Sinanoglu method[9−11] using eq 3

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

where S^M is the molecular surface-accessible area, γ is the surface tension coefficient, 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 was calculated according to the Sinanoglu theory[9−11] from the following empirical equation

$$K_1^e = 1 + \left(\frac{V_1}{V_2}\right)^{2/3} [K_1^e(1) - 1] \qquad (4)$$

where $K_1^e(1)$ is the factor for pure solvent and V_1 and V_2 are the van der Waals volumes of the solvent and solute molecules, respectively. To estimate the enthalpy of cavity formation, we used the following parameters for water: $K_1^e(1) = 1.277$, $\gamma = 72 \times 10^{-3}$ N·m^{-1}, $\alpha_1 = 0.257 \times 10^{-3}$ K^{-1}.

The transfer molar enthalpies of solution $\Delta_{tr}H_m$ to water (L_1) and to methanol (L_2) were evaluated according to the equation

$$\Delta_{tr}H_m(L_1 \rightarrow L_2) = \Delta_{solv}H_m(L_2) - \Delta_{solv}H_m(L_1) = \Delta_{sol}H_m^\infty(L_2) - \Delta_{sol}H_m(L_1) \qquad (5)$$

The solvent-accessible molecular surface area S^M and its 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.[12] The following atomic radii consistent with the Tripos force field were used: 1.45 Å (N), 1.52 Å (C), 1.36 Å (O), 1.08 Å (H), 1.30 Å (F), 1.80 Å (Br), 1.65 Å (Cl), and 2.05 Å (I); the water radius was assumed to be 1.4 Å, and the methanol radius was assumed to be 1.86 Å. In the estimation of S^M of uracil, we assumed the existence of one form—the most stable tautomeric form. It is known that uracil occurs in several tautomeric forms.[13,14] The experimental examination of uracil by UV[15], NMR,[16] Raman, and IR spectra[17,18] suggests that the 4,4-dioxo dilactam tautomer is the stable and predominant form in the gas phase, in solution, and even in the solid state. Quantum-chemical calculations of thermodynamic properties for tautomers of uracil confirm the stability of this form (the 4,4-dioxo dilactam tautomer).[13,14]

The obtained values $\Delta_s^g H_m^o$, $\Delta_{solv}H_m^o$, and $\Delta_{int}H_m$ were correlated with nonpolar S_{np} and polar S_p parts of the accessible molecular surface areas, S^M, of the compounds studied, according to the concept of Spolar and Freire,[19,20] by the relation

$$\Delta H = aS_{np} + bS_p + c \qquad (6)$$

Because fluorine participates in hydrogen bonding,[21] its

Table 2. Enthalpy of Sublimation, Molar Enthalpies of Transfer for Water−Methanol, ($\Delta_{tr}H_m$), Standard Enthalpy of Solution in Water and Methanol, and Enthalpy of Solvation of Uracil and Halo Derivatives of Uracil (T = 298.15 K)

			water[2,4]		methanol	
compound	$\Delta_s^g H_m^o$	$-\Delta_{tr}H_m^o$	$\Delta_{sol}H_m^\infty$	$-\Delta_{solv}H_m^o$	$\Delta_{sol}H_m^\infty$	$-\Delta_{solv}H_m^o$
			kJ·mol^{-1}			
uracil	130.82 ± 1.40	15.30 ± 0.27	29.50 ± 0.12	101.31±1.40	14.22 ± 0.25	116.60 ± 1.22
5-fluorouracil	133.22 ± 2.11	10.98 ± 0.37	25.38 ± 0.37	107.84 ± 2.14	14.40 ± 0.03	118.82 ± 2.11
5-chlorouracil	148.26 ± 2.42	12.13±0.27	21.30 ± 0.06	126.96 ± 2.42	9.17 ± 0.27	139.09 ± 2.43
6-chlorouracil	135.22 ± 1.97	3.74 ± 0.28	20.94 ± 0.23	114.28 ± 1.98	17.20 ± 0.16	118.02 ± 1.97
5-bromouracil	151.44 ± 2.50	12.24 ± 0.32	27.08 ± 0.24	124.36 ± 2.5	14.84 ± 0.22	136.60 ± 2.51
5-iodouracil	155.47 ± 2.39	10.47 ± 0.50	28.47 ± 0.43	126.99 ± 2.43	18.01 ± 0.26	137.46 ± 2.40
5-(trifluoromethyl)uracil	110.77 ± 2.12	7.84 ± 0.25	23.54 ± 0.10	87.23 ± 2.12	15.70 ± 0.23	95.07 ± 2.13

atomic surface was assumed to be hydrophilic, whereas the surfaces of other halo atoms were considered to be hydrophobic. The accessible molecular surface area of polar atoms S_p for aqueous solutions is expressed as

$$S_p = S_O + S_N + S_{H(O,N)} + S_F \tag{7}$$

whereas for methanol solutions it was calculated as

$$S_p = S_O + S_N + S_F \tag{8}$$

Methanol, which is more active as a donor than as an acceptor of protons, interacts mainly with solute oxygen, nitrogen,[22,23] and fluorine atoms.

Polarity P was determined by eq 9:

$$P = \frac{S_p}{S^M} \tag{9}$$

Results and Discussion

The values of the enthalpies of solution $\Delta_{sol}H_m$ of uracil and halo derivatives of uracil in methanol at concentrations m are presented in Table 1. Within the experimental uncertainty in the examined range of concentrations (0.472 to 1.848) × 10^{-3}/mol·kg^{-1}, no concentration dependence of the enthalpy of solution was observed. The values of standard molar enthalpies of solution at infinite dilution $\Delta_{sol}H_m^\infty$ given in Table 2 have been calculated on the basis of the average value calculated from all of the experimental data points for the enthalpies of solution. The obtained value $\Delta_{sol}H_m^\infty$ = (14.22 ± 0.25) kJ·mol^{-1} for uracil is consistent with those given by Żółkiewski et al.,[24] (14.34 ± 0.20) kJ·mol^{-1}.

For uracil and its halogenated derivatives, the enthalpy of solution decreases in the following order: 5-iodouracil < 6-chlorouracil < 5-(trifluoromethyl)uracil < 5-bromouracil < 5-fluorouracil < uracil < 5-chlorouracil. The same Table presents values of the enthalpies of sublimation,[2,4] solvation in aqueous and methanol solutions, and transfer of water−methanol solution.

It can be seen from the data collected in Table 2 that the smallest differences in the values of solvation enthalpy are between uracil and 5-fluorouracil. This is probably connected with the size of hydrogen and fluorine molecules and their donor−acceptor properties. For 5-chlorouracil, 5-bromouracil, and 5-iodouracil, the solvation enthalpies are lower by approximately 20 kJ·mol^{-1} than $\Delta_{solv}H_m^o$, the value obtained for uracil.

The contributions of atoms F, Cl(5), Cl(6), Br, I, and CF_3 to the values of the enthalpies of solvation, calculated as the difference between the $\Delta_{solv}H_m^o$ values of halo derivatives of uracil and uracil, are equal to (−6.53, −25.65, −12.91, −23.05, −25.68, and −14.08) kJ·mol^{-1}, respectively. These increased values differ considerably from those obtained by Cabani et al.[25] for aliphatic compounds that correspond to (1.87, −6.90, −9.27, −9.64, and −10.17) kJ·mol^{-1} for atoms F, Cl, Br, I, and CF_3, respectively.[25]

Table 3. Enthalpies of Cavity Formation $\Delta_{cav}H_m$ and Enthalpies of Solute−Solvent Interaction in the Solvent Used

	water		methanol	
	$\Delta_{cav}H_m$	$-\Delta_{int}H_m$	$\Delta_{cav}H_m$	$-\Delta_{int}H_m$
solute	kJ·mol^{-1}	kJ·mol^{-1}	kJ·mol^{-1}	kJ·mol^{-1}
uracil	53.96	155.27	20.22	136.82
5-fluorouracil	55.72	163.56	20.72	139.54
5-chlorouracil	61.71	188.67	22.60	161.69
6-chlorouracil	61.67	175.95	22.56	140.58
5-bromouracil	64.14	188.5	23.32	159.92
5-(trifluoromethyl)uracil	67.82	155.05	24.49	119.56

In the investigated systems of uracil derivatives, there is strong electron coupling between a substituent and the π-electron system of the pyrimidine ring, which is well seen[26] in the changes in both the UV spectra and values of the pK of dissociation of protons H3 and H1. It should also be pointed out that in the case of halo derivatives (5-chlorouracil and 6-chlorouracil) a vital difference was observed between the obtained values 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. Thus, there are differences in the values of the enthalpy of solvation for 5-chlorouracil and 6-chlorouracil. In water and methanol, they are as follows: −12.68 and −21.07 kJ·mol^{-1}.

The obtained values of the transfer enthalpy of solution, $\Delta_{tr}H_m^o$, water → methanol are negative. This results from the strong donor properties of methanol.[22,23] The lowest of these values was obtained for uracil, −15.30 kJ·mol^{-1}. This indicates its highly hydrophobic properties. The value of $\Delta_{tr}H_m^o$ = −3.74 kJ·mol^{-1} determined for 6-chlorouracil is lower than the values determined for other halouracils and significantly differs from them. A considerable difference in the values of $\Delta_{tr}H_m^o$ between 5-(trifluoromethyl)uracil and 5-fluorouracil (−3.14 kJ·mol^{-1}) is connected with the proton-accepting property of fluorine,[21,26] which is a strong donor.[27]

The values calculated from the values of the enthalpy of cavity formation and of the enthalpy of interaction are presented in Table 3. These data suggest that interaction enthalpies for halo derivatives of uracil are approximately 20 kJ·mol^{-1} lower in methanol than in water. And the largest difference can be observed in the case of 5-(trifluoromethyl)uracil (i.e., 35.5 kJ·mol^{-1}).

Molecular surface areas, atomic partitions, and polarities of the compound studied in water and methanol are presented in Table 4.

The results of correlations of the values of $\Delta_s^g H_m^o$, $\Delta_{sol} H_m^\infty$, and $\Delta_{int}H_m$ with polar and nonpolar parts of surface-accessible areas are given in Table 5 and presented in

Table 4. Molecular Surface Areas, Atomic Partitions, and Polarity of the Compound Studied in Water and Methanol

		surface/Å^2							
compound	solvent	S_O	S_N	$S_{H(N,O)}$	S_{halo}	S_p	S_{np}	S^M	P
uracil	water	26.1	8.8	12.5	0.0	47.4	37.5	84.9	0.56
	methanol	25.4	8.1	12.0	0.0	33.5	47.8	81.3	0.41
5-fluorouracil	water	26.0	8.8	12.5	11.21	58.5	27.4	85.8	0.68
	methanol	25.0	8.1	12.0	10.5	43.6	37.8	81.4	0.53
5-chlorouracil	water	25.2	8.8	12.5	22.8	46.5	49.4	96.0	0.48
	methanol	24.4	8.1	12.0	22.1	32.5	59.1	91.6	0.35
6-chlorouracil	water	26.1	8.5	11.6	23.5	46.2	49.13	95.4	0.48
	methanol	25.4	7.8	10.9	24.0	33.2	58.6	91.8	0.36
5-bromouracil	water	24.9	8.8	12.5	28.6	46.2	54.8	101.0	0.45
	methanol	24.1	8.1	12.0	27.8	32.2	63.2	95.4	0.34
5-iodouracil	water	24.3	8.8	12.5	39.7	45.6	64.2	109.9	0.41
	methanol	23.4	8.1	12.0	38.4	31.5	73	104.5	0.30
5-(trifluoromethyl)uracil	water	24.3	8.8	12.5	33.8	78.7	25.4	104.1	0.75
	methanol	23.4	8.1	12.0	31.4	62.9	34.4	97.3	0.64

Table 5. Parameters *a*, *b*, and *c* and Coefficient of Correlation R^2 for Water and Methanol Obtained for the Relationship $\Delta H = aS_{np} + bS_p + c$ and Equation 10

solvent	a/kJ·Å^{-2}	b/kJ·Å^{-2}	c/kJ	R^2
		$\Delta_{solv}H^o_m$		
water	0.61 ± 0.39	−0.48 ± 0.47	111.91 ± 40.10	0.827
methanol	0.50 ± 0.37	−0.76 ± 0.45	127.20 ± 35.78	0.880
		$\Delta_{int}H_m$		
water	1.41 ± 0.69	0.29 ± 0.64	99.21 ± 59.39	0.800
methanol	0.96 ± 0.62	−0.37 ± 0.60	112.30 ± 52.76	0.870
		$\Delta_s^g H^o_m$		
water	0.60 ± 0.29	−0.58 ± 0.34	143.75 ± 29.29	0.911
methanol	0.64 ± 0.31	−0.58 ± 0.38	127.57 ± 29.60	0.914
		$\Delta_{tr}H_m$		
water	0.57 ± 1.36	8.60 ± 1.27	−48.5 ± 26.6	0.983
methanol	0.93 ± 1.46	9.60 ± 1.37		
water	2.65 ± 1.07	7.42 ± 1.60		0.926
methanol	3.18 ± 1.14	8.49 ± 1.81		

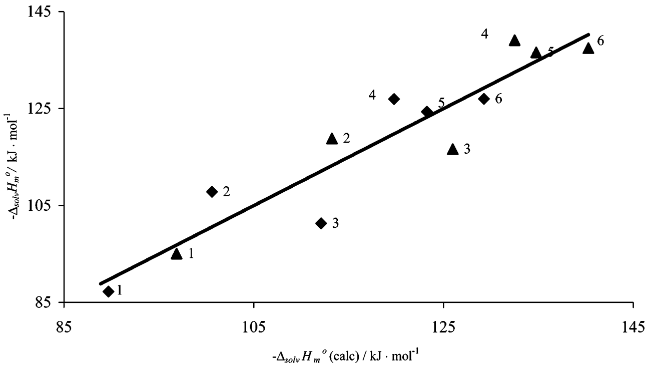

Figure 2. Estimation of the $\Delta_{solv}H^o_m$ as a function of S_{np} and S_p obtained for ◆, water and ▲, methanol solutions; 1, 5-(trifluoromethyl)uracil; 2, 5-fluorouracil; 3, uracil; 4, 5-chlorouracil; 5, 5-bromouracil; 6, 5-iodouracil.

Figures 2 and 3. As can be seen in all of the discussed cases, the obtained correlations are linear. 6-Chlorouracil was excluded from the calculations because including its enthalpy value was worsening the correlation significantly. It was found that the polarity also correlates linearly with the enthalpy of solvation in methanol solution

$$\Delta_{solv}H^o_m/\text{kJ·mol}^{-1} = 176.5(\pm 10.5) - 122.7(\pm 23.7)P \quad (r = 0.870) \quad (10)$$

whereas for water solution it was found that

$$\Delta_{solv}H^o_m/\text{kJ·mol}^{-1} = 173.2(\pm 14.9) - 109.4(\pm 26.2)P \quad (r = 0.813) \quad (11)$$

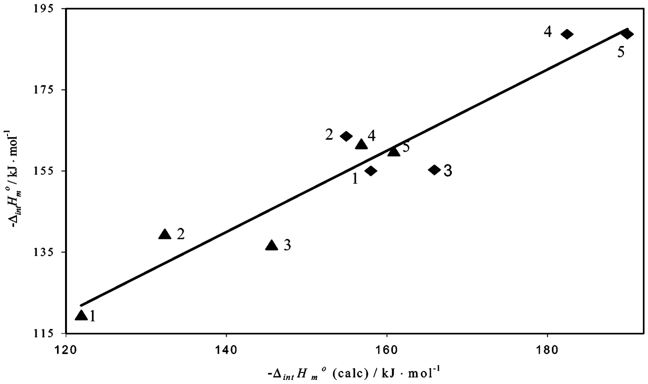

Figure 3. Estimation of $\Delta_{int}H^o_m$ as function of S_{np} and S_p obtained for ◆, water and ▲, methanol solutions: 1, 5-(trifluoromethyl)uracil; 2, 5-fluorouracil, 3, uracil; 4, 5-chlorouracil; 5, 5-bromouracil.

In both estimations, 6-chlorouracil was omitted because of its deviations from the linear pattern.

The properties of 6-chlorouracil differ from the properties of 5-halo-uracil. Its dehydrogenation (creation of the (M−H$^-$) anion) is more intense in comparison to that of 5-chlorouracil.The thermodynamics for abstraction from both N sites is more favorable in 6-chlorouracil, in particular from the N3 position.[28]

Acknowledgment

We thank Dr. A. Zielenkiewicz and Dr. J. Poznañski for their helpful assistance and fruitful discussions.

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Received for review September 24, 2004. Accepted May 4, 2005.

JE049656O