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Vapor Pressures, Molar Enthalpies of Sublimation, and Molar Enthalpies of Solution in Water of Selected Amino Derivatives of Uracil and 5-Nitrouracil

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Vapor pressures and enthalpies of sublimation of crystalline 5-aminouracil, 6-aminouracil, 6-amino-1-methyluracil, 6-amino-1,3-dimethyluracil, and 5-nitrouracil were measured by the Knudsen effusion method. The heats of solution in water were determined at 298.15 K over the range of concentrations (0.828 to 1.845) mmol·kg^{-1} by using an isoperibol solution calorimeter**.** The molar enthalpies of solution at infinite dilution were evaluated. The molar enthalpy of hydration was calculated by subtracting the estimated molar enthalpy of sublimation and the molar enthalpy of solution. The contributions of the $-NH_2$, $-NO_3$, and $-CH_3$ groups to the molar enthalpies of solution, sublimation, and hydration were calculated by applying a simple additivity scheme. The molar enthalpies of hydration were correlated with the structural parameters of the compounds investigated. They were found to be linearly related to the polar and to the apolar parts of the accessible surface areas of the compound studied.

Introduction

The thermodynamic properties of derivatives of nucleic acid bases are important for many reasons. Vapor pressures are indispensable not only to calculation of the enthalpies of sublimation but also to evaluation of impending hazards of these considerably toxic compounds. Both the enthalpy of solvation evaluated from the experimentally determined enthalpy of solution, and the enthalpy of sublimation corrected for the term corresponding to the energy required to make a cavity in liquid water enable the energy of solute−solvent interactions to be evaluated.[1−15] In the case of aqueous solutions of nucleic acid bases and their derivatives, such determinations are of fundamental importance to explain base pairing and stacking interactions and thus for the spatial organization of polynucleotide chains in aqueous solutions. Thermodynamic data are also important in view of the medical applications of these compounds.

Among organic molecules, nitrogen heterocycles are well-known to take a special place as pharmaceuticals. The pyrimidine nucleus is the key feature of various drugs. The 5-substituted uracils exhibit a significant pharmacological activity and have been used as antitumor, antibacterial, and antiviral drugs. 5-Aminodiarylpyrimidine (DAPY) analogues are excellent drug candidates against wild-type HIV-1 and its single mutants.[16] Thio derivatives of 5-nitrouracil have shown antibacterial activity.[17] 5-Nitrouracil has been known to inhibit thymidine phosphorylase.[18] 5-Cinnamoyl-6-aminouracil derivatives have been investigated as anticancer agents.[19] 6-Aminouracil has been found to inhibit the uracil−DNA glycosylase[20] and the dihydropyrimidine dehydrogenase enzymes.[21] Divalent metal complexes with binegative N,N,O-tridentate uracil-derivative hydrazones derived from 6-amino-5-formyl-1,3-dimethyluracil are promising candidates for pharmacological agents.[22] The prospective clinical use of the present compounds or their analogues has prompted us to undertake thermodynamic investigations and to determine the enthalpies of sublimation and solution of halouracils and of amino and nitrogen derivatives of uracil. The results concerning halouracils have been reported elsewhere.[15] The present paper sets out to describe results of the investigations on amino derivatives of uracil and 5-nitrouracil.

Experimental Section

Materials. The compounds used for the experiments included 5-aminouracil, 6-aminouracil, 6-amino-1,3-dimethyluracil, 6-amino-1-methyluracil, and 5-nitrouracil, having the molar masses (0.127 103, 0.127 103, 0.155 157, 0.141 130, and 0.157 085) kg·mol^{-1}, respectively. Each compound exhibited a mole fraction purity of better than 0.99, as determined by means of a DuPont 910 differential scanning calorimeter equipped with a 1090 thermal analyzer.

Apparatus and Procedures. An isoperibol solution calorimeter was used to measure the heat of solution in water at 298.15 K. The calorimeter and the working procedure have been described in detail elsewhere.[15,23] The calorimeter consists of a measuring steel vessel of total volume 80 mL and normal working volume 65 mL; an external metallic shield; two thermistors nominally 150 Ω at 25 °C; a glass ampule of 1.5 mL volume; a 98 Ω calibration heater, and a stirrer. The thermistors form the arms of a Wheastone bridge, which is coupled with a Keithley nanovoltometer and an IBM PC computer. The external shield is submerged in a water thermostat bath in which the temperature is sensed by a 100 Ω resistance platinum thermometer and regulated by a PID regulator UNIPAN (Poland) type 650. The calibration heater is used to release a known amount of heat. Initiation of the solvation process takes place after lowering the stirrer and breaking of the ampule containing the substance studied. The studied heat effect was evaluated using the method of corrected temperature rise with the Regnault−Phaundler correction. The lowest heat effect detectable corresponds to 0.15 J. Initiation of the solvation process takes place

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after lowering the stirrer and breaking of the ampule containing the substance studied.

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.[12,15,25] The apparatus consisted of a steel sublimation cell placed in a water thermostat and connected to a high-vacuum system maintained at the pressure 10^{-4} Pa. The experimental substance was placed in a Knudsen cell of height 24 mm and diameter 20 mm. The Knudsen cell was closed by a cover with a tantalum membrane containing an effusion hole. Test measurements were performed on benzoic acid of mass fraction 0.9999 obtained from the Central Office of Measures (Warsaw, Poland). The measurements of the vapor pressure of benzoic acid were made for six temperatures in the temperature interval (303.7 to 313.6) K. The value of the molar enthalpy of sublimation, (89.9 ± 0.7) kJ·mol^{-1},[12] was obtained and is in agreement with those (89.7 ± 0.5) kJ·mol^{-1} recommended by IUPAC.[24]

The vapor pressure p was evaluated by means of the equation

$$p = (\Delta m/taw)(2RT/M)^{1/2} \qquad (1)$$

where a is the surface area of the effusion hole, Δm is the mass of substance sublimed in time t, T is the experimental temperature, R is the universal gas constant, M is the molar mass of the substance, and w is the Clausing coefficient.

In eq 1, the molar mass was assumed to be that of the monomer. The existence of monomers in the gas phase was confirmed by a mass-spectrometric analysis. The Clausing coefficient, which describes the resistance to flow of the vapor stream through the effusion orifice, is given by[26]

$$w = 0.0147(L/r)^2 + 0.349(L/r) + 0.9982 \qquad (2)$$

where r is the radius of the effusion hole and L is the height of the effusion hole (thickness of the tantalum membrane). Vapor pressure measurements were carried out with a tantalum membrane of thickness 0.040 mm with an effusion hole of diameter 2.005 mm. Clausing's coefficient equals $w = 1.0121$. In most measurements, the sublimation experiment was continued for 6 h and the time of sublimation was determined to within 1 s. The sample mass was determined with an accuracy of 1×10^{-5} g before and after the measurement.

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

$$\ln(p/p°) = -A/T_m + B = -\Delta_s^g H_m/(RT_m) + \Delta S/R \qquad (3)$$

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

The enthalpies of sublimation were corrected to the temperature 298.15 K by[27]

$$\Delta_s^g H_m^\circ(298.15) = \Delta_s^g H_m(T_m) + (0.75 + 0.15C_p)(T_m - 298.15) \qquad (4)$$

where C_p is the heat capacity of cyclic functional groups of the solid phase at 298.15 K.[28]

Table 1. Experimental Vapor Pressure Data

series 1			series 2		
T/K	Δm/mg	p/Pa	T/K	Δm/mg	p/Pa
			5-Aminouracil		
433.11	3.17[b]	0.019 41	433.16	3.39	0.020 72
436.70	4.17[b]	0.025 60	438.65	5.42	0.033 33
445.07	8.67	0.053 73	440.48	6.31	0.038 90
445.97	9.20	0.057 07	442.32	7.76	0.047 94
447.76	10.72	0.066 64	444.14	8.45	0.052 31
453.10	15.95[b]	0.099 70	445.96	9.70	0.060 18
			6-Aminouracil		
478.60	2.17	0.013 94	478.61	2.14	0.01375
482.16	2.98	0.019 22	480.40	2.58	0.016 61
485.60	3.72[a]	0.024 13	483.92	3.30	0.021 32
489.24	4.86	0.031 58	485.70	3.73	0.024 15
491.02	5.43	0.035 34	487.50	4.35	0.028 21
492.65	6.40	0.041 76	491.00	5.40	0.035 15
			6-Amino-1-methyluracil		
456.84	4.74	0.028 24	458.65	5.34	0.031 88
459.55	6.37	0.038 07	462.22	7.71	0.046 21
463.15	8.36	0.050 15	464.07	9.04	0.054 29
466.10	10.60	0.063 80	466.07	10.70	0.064 40
467.87	12.45	0.075 07	468.75	13.20	0.079 67
			6-Amino-1,3-dimethyluracil		
409.00	3.43[b]	0.018 45	401.59	1.86	0.009 90
410.80	4.60	0.024 78	407.21	3.12	0.016 73
412.67	5.32[b]	0.028 74	409.99	4.29	0.023 09
416.43	6.75[b]	0.039 68	412.82	5.80	0.031 33
420.22	11.16	0.060 82	415.86	8.03	0.044 77
425.66	19.20	0.105 31	418.41	9.83	0.053 45
			5-Nitrouracil		
434.95	1.77	0.009 75	431.25	1.31	0.007 18
436.81	2.09	0.011 54	433.14	1.53	0.008 41
438.63	2.35	0.013 00	434.98	1.84	0.010 14
440.46	2.92	0.016 20	442.17	3.77[b]	0.020 96
442.27	3.56	0.019 78	445.93	5.24	0.029 24
447.76	5.97	0.033 38	453.11	10.85[b]	0.061 04

[a] Measurements were made at 12 h. [b] Measurement were made at 24 h.

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

series	$-A$	B	T/K	$\Delta_s^g H_m$/kJ·mol^{-1}
		5-Aminouracil		
1	16 312 ± 203	33.7 ± 0.4	433.1−453.1	135.6 ± 1.7
2	16 282 ± 556	33.7 ± 1.2	433.1−446.0	135.3 ± 4.6
		6-Aminouracil		
1	17 753 ± 478	32.8 ± 1.0	478.6−492.6	147.6 ± 4.0
2	17 620 ± 543	32.5 ± 1.1	478.6−491.0	146.5 ± 4.5
		6-Amino-1-methyluracil		
1	18 302 ± 446	36.5 ± 0.9	456.8−469.6	152.1 ± 3.7
2	18 822 ± 592	37.6 ± 1.2	458.6−470.5	156.5 ± 4.9
		6-Amino-1,3-dimethyluracil		
1	17 611 ± 555	39.1 ± 1.3	409.0−425.6	146.4 ± 4.6
2	17 361 ± 494	38.6 ± 1.2	401.6−418.4	144.3 ± 4.1
		5-Nitrouracil		
1	19 142 ± 252	39.4 ± 0.6	431.2−453.1	159.1 ± 2.1
2	18 955 ± 593	38.9 ± 1.3	434.9−447.7	157.6 ± 4.9

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

$$\Delta_{hyd}H_m^\circ = \Delta_{sol}H_m^\infty - \Delta_s^g H_m^\circ \qquad (5)$$

Similarly as before,[29−31] the resulting $\Delta_{hyd}H_m^\circ$ values were correlated with nonpolar, S_{np}, and polar, S_p, parts of

Table 3. Enthalpies of Solution of Uracil Derivatives

m/mmol·kg^{-1}	$\Delta_{sol}H_m$/kJ·mol^{-1}	m/mmol·kg^{-1}	$\Delta_{sol}H_m$/kJ·mol^{-1}
5-aminouracil		6-aminouracil	
0.828	37.66	1.033	18.25
0.875	36.72	1.112	18.35
1.028	37.37	1.222	18.36
1.210	36.68	1.277	18.82
1.281	37.15	1.440	18.53
1.553	36.55	1.845	18.00
6-amino-1-methyluracil		6-amino-1,3-dimethyluracil	
0.856	27.29	0.901	20.63
0.984	26.83	0.924	20.74
1.091	27.64	0.983	20.20
1.255	26.46	1.108	19.79
1.341	26.59	1.134	19.86
1.415	27.01	1.134	19.84
5-nitrouracil			
0.935	35.39		
0.960	34.29		
0.990	35.30		
0.991	35.06		
1.069	35.67		
1.355	35.55		

Table 4. Standard Enthalpy of Solution, Enthalpy of Sublimation, and Enthalpy of Hydration of Uracil Derivatives (298.15 K)

compound	$\Delta_{sol}H^{\infty}_m$ kJ·mol^{-1}	$\Delta^g_sH^\circ_m$ kJ·mol^{-1}	$-\Delta_{hyd}H^\circ_m$ kJ·mol^{-1}
uracil	29.50 ± 0.12[15]	130.82[15]	101.31[15]
5-aminouracil	37.02 ± 0.18	138.05	101.03
6-aminouracil	18.38 ± 0.24	150.40	132.02
6-amino-1-methyluracil	26.97 ± 0.18	158.22	131.25
6-amino-1,3-dimethyluracil	20.18 ± 0.17	148.72	128.54
5-nitrouracil	35.21 ± 0.20	161.41	126.20

the accessible molecule surface areas, S_M, of the compounds studied, according to the relation

$$\Delta_{hyd}H^\circ_m = aS_{np} + bS_p + c \tag{6}$$

The contributions of the $-CH_3$ and $-NH_2$ groups to the enthalpy of hydration were evaluated by applying the general simple additivity scheme[32]

$$X = X_0 + \sum_i n_i Z_i \tag{7}$$

where X_0 is a constant, Z_i is the additive value for the i-th group; and n_i is the number of i-th groups. Values of X_0 and Z_i were estimated by the least-squares linear regression method.

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 a time of (6, 12, or 24) h in two series (1 and 2) of measurements made over similar ranges of temperature. Since the substances examined have low vapor pressures at ambient temperature, the vapor pressure measurements were carried out at relatively high temperatures [(409 to 492.6) K]. A few measurements were also realized by a (12 or 24) h period of time. They are marked in Table 1, after recalculation for the period 6 h, by *a* or *b*, respectively. However, any difference in the amount of mass sublimed per unit of time was not observed.

The coefficients A and B adjusted to eq 3 are listed in Table 2 together with the molar enthalpies of sublimation evaluated therefrom and the range of experimental temperatures. The coefficients A and B evaluated for the two series of vapor pressure measurements are seen to differ only very slightly from each other, and hence, the $\Delta^g_sH_m$ values are well consistent within the range of experimental error ±(1.7 to 4.9) kJ·mol^{-1}.

Evaluated from coefficient B (eq 3), average entropy increments associated with the sublimation process correspond to (3.93, 4.05, 4.45, 4.67, and 4.71) kJ·K^{-1}·mol^{-1} for 6-aminouracil, 5-aminouracil, 6-amino-1-methyluracil, 6-amino-1,3-dimethyluracil, and 5-nitrouracil, respectively.

The molar enthalpies of solution, $\Delta_{sol}H_m$, are listed in Table 3 for uracil, for the selected amino derivatives of uracil, and for 5-nitrouracil. Over the range of concentrations examined, (0.828 to 1.845) mmol·kg^{-1}, the heat of solution is seen to be unrelated to the concentration, within the limits of experimental uncertainty. The enthalpies of solution at infinite dilution, $\Delta_{sol}H^{\infty}_m$, given in Table 4, were calculated as the mean values of all the relevant experimental data (Table 3). Table 4 gives also the mean value of the enthalpies of sublimation evaluated in series 1 and 2 (Table 2) corrected to 298.15 K according to eq 4 and the molar enthalpy of hydration, $\Delta_{hyd}H^\circ_m$, at 298.15 K.

Yanson et al.'s value reported for 5-aminouracil, $\Delta^g_sH_m$ = (145.6 ± 2.9) kJ·mol^{-1},[33] is higher by 7.55 kJ·mol^{-1} than the present value.

Analysis of the data listed in Table 4 allows us to deduce several very interesting conclusions:

(a) The molar enthalpies of solution, $\Delta_{sol}H^{\infty}_m$, of 5-amino- and 6-aminouracils are seen to be considerably different; the former is twice as high as the latter. On the other hand, the molar enthalpies of sublimation, $\Delta^g_sH^\circ_m$, are only slightly different, the former being lower (by 8.2%) than the latter.

(b) The molar enthalpies of solution, $\Delta_{sol}H_m$, of 5-aminouracil and 5-nitrouracil are nearly identical, whereas their enthalpies of sublimation, $\Delta^g_sH^\circ_m$, are considerably different.

Table 5. Contributions Z_i for CH_2(N), CH_2(C), and NH_2(C) to $\Delta_m H_{sol}$, $\Delta_m H_{sub}$, and $\Delta_m H_{hydl}$

	X_0	$Z_{NH_2(C)}$	$Z_{CH_2(N)}$	$Z_{CH_2(C)}$	r^2
	$\Delta_m H_{sol}$/kJ·mol^{-1}				
methylated derivative of uracil	29.7 ± 1.3		−6.9 ± 0.88	−3.0 ± 1.1	0.940
methylated derivative and amino derivative of uracil (6-aminouracil excluded)	30.1 ± 1.2	5.3 ± 1.4	−7.4 ± 0.7	−2.8 ± 1.0	0.961
	$\Delta_m H_{sub}$/kJ·mol^{-1}				
methylated derivative of uracil	127.9 ± 2.4	-	−12.34 ± 1.6	1.2 ± 2	0.914
methylated derivative and amino derivative of uracil (5-aminouracil excluded)	124.8 ± 3.9	36.1 ± 4.8	−8.5 ± 2.34	0.0036 ± 3.4	0.962
	$\Delta_m H_{hyd}$/kJ·mol^{-1}				
methylated derivative of uracil	98.2 ± 1.9		−5.4 ± 1.3	4.2 ± 1.6	0.760
methylated derivative and amino derivative of uracil (5-aminouracil excluded)	97.1 ± 2.3	37.2 ± 2.8	−3.8 ± 1.4	3.9 ± 2.0	0.964

(c) Substitution of the hydrogen atom at the N(1) position in the diketopyrimidine ring with a methyl group has resulted in a considerably higher heat of solution, whereas screening of the N(1) and the N(3) nitrogen atoms in the diketopyrimidine ring of 6-aminouracil has only slightly affected the enthalpy of solution of this substance in water.

(d) For 6-aminouracil, 6-amino-1-methyluracil, and 6-amino-1,3-dimethyluracil, the molar enthalpies of hydration are seen to be close to each other.

(e) The molar enthalpy of hydration of 5-aminouracil is considerably different from the values for the 6-amino derivatives of uracil; on the other hand, the molar enthalpies of hydration of 5-aminouracil and uracil are very much alike.

This work is now intended to explain the reasons underlying the above-mentioned differences in the enthalpy values.

The present data proved to be sufficient to evaluate the contributions of the $-NH_2$ group to the values of the solution, sublimation, and hydration enthalpies. For this purpose, a simple additivity scheme was used as expressed by eq 7. Calculations were performed by taking the $\Delta_{sol}H_m^{\infty}$, $\Delta_s^g H_m^{\circ}$, and $\Delta_{hyd}H_m^{\circ}$ values listed in Table 4 and supplemented with our earlier data reported elsewhere[8,15,34] on the methylated derivatives of uracil, viz., 1-methyluracil, 5-methyluracil, 1,3-dimethyluracil, 1,5-dimethyluracil, 1,6-dimethyluracil, 1,3,5-trimethyluracil, and 1,3,5,6-tetramethyluracil. The group contribution data included $Z_{NH_2(C)}$, $Z_{CH_2(N)}$, and $Z_{CH_2(C)}$, and these are listed in Table 5. Deviations from the linear pattern made us abandon the functional group contributions to the $\Delta_{sol}H_m^{\infty}$ value for 6-aminouracil and to the $\Delta_{sub}H_m^{\circ}$ and $\Delta_{hyd}H_m^{\circ}$ values for 5-aminouracil. Table 5 lists the results of the calculations performed for the aminouracils together with the methyluracils and those performed for the methyluracils only. The values of $Z_{CH_2(C)}$ and $Z_{CH_2(N)}$ evaluated in each case are only slightly different from each other. The contribution due to the $-NH_2$ group to the enthalpy of hydration is fairly consistent with that reported by Cabani[32] (-33.21 kJ·mol^{-1}). The contribution due to the $-NO_2$ group to the enthalpy of hydration, $\Delta_{hyd}H_m^{\circ}$, evaluated as the difference of these enthalpies for 5-nitrouacil and uracil, is 24.89 kJ·mol^{-1} and differs from that reported by Cabani[32] (19.47 kJ·mol^{-1}).

For the compounds investigated and complemented by the methylated derivatives of uracil, similarly as in the case of alkylated uracils and cytosines,[13,36] a linear correlation was found to relate the enthalpies of hydration to polar S_p and apolar S_{np} parts of the accessible molecular surface areas, determined according to eq 7

$$\Delta_{hyd}H_m^{\circ} = 2.16(\pm 0.33)S_p + 0.76(\pm 0.19)S_{np} - 33.37(\pm 25.94) \quad (r^2 = 0.880) \quad (8)$$

Again, 5-aminouracil was omitted in the calculations because of deviations from the linear pattern. The values of S_p and S_{np} were taken from ref 35.

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