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Thermodynamic investigations on derivatives of pyrimidine nucleic acid bases Joint use of calorimetric, volumetric and structural data for the description of properties of pyrimidine nucleic acid bases and their derivatives

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Abstract

The experimental enthalpies of solution $\Delta_{sol}H_m^{\infty}$, van't Hoff enthalpies of sublimation $\Delta_s^g H_m^0$ of solid compounds, partial molar volumes V_2^0, and partial molar heat capacities $C_{p,2}^0$ of aqueous solutions of pyrimidine nucleic acid bases and their derivatives, determined previously and collected here, are discussed in terms of calculated structural parameters. Relations have been established between the calorimetric and volumetric properties. Correlations have been developed to relate both the enthalpies of solvation and the partial molar heat capacities to the polar and apolar parts of the accessible molecular surface areas.

Keywords: Aqueous solutions of pyrimidine nucleic acid bases and their derivatives; Enthalpies of solution $\Delta_{sol}H_m^{\infty}$; The van't Hoff enthalpies of sublimation $\Delta_s^g H_m^0$ of solid compounds; Partial molar volumes V_2^0; Partial molar heat capacities $C_{p,2}^0$; Structural parameters

1. Introduction

The knowledge of the hydration scheme and hydration energies of nucleic acid bases is of fundamental importance for the explanation of the effect the aqueous environment exercises on base pairing and stacking interactions, and thus on spatial organization, of polynucleotide chains in aqueous solutions. It is desirable to establish the extent in which calorimetric and volumetric investigations (as well as determinations of enthalpies of solution and sublimation, partial molar volume, and heat capacity), when correlated with structural parameters, can help us describe the interactions of particular atoms and functional groups of the skeleton of the base with its liquid environment, i.e. with liquid water.

The chemical nature of the bases allows us to assume both hydrophilic and hydrophobic interactions with water to occur simultaneously. The method we have chosen is to screen functional groups to see what happens when certain polar and apolar atoms in the diketopyrimidine skeleton are withdrawn from their direct interactions with the hydration shell by being substituted with methyl or other alkyl groups. This study is concerned with pyrimidine nucleic acid bases, viz., uracil, thymine, cytosine (Fig. 1), their methylated and like alkylated derivatives including

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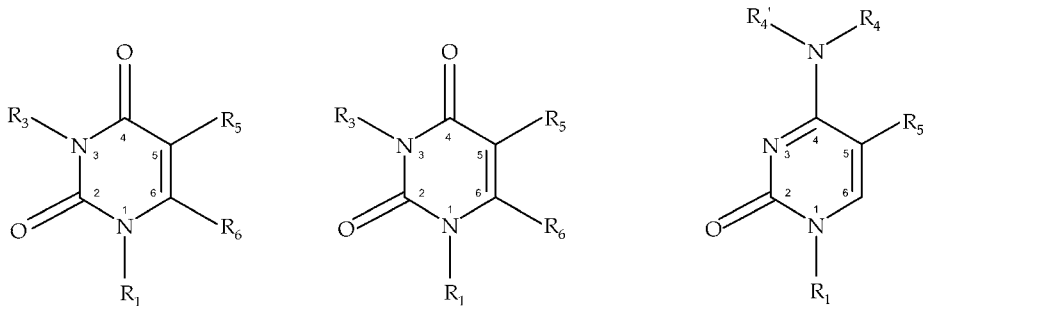

Fig. 1. Structural formulas of pyrimidine nucleic acid bases.

alkylated uracil derivatives endowed with long alkyl side chains, and cyclooligomethyleneuracils. This study involves also halouracils, aminouracils, nitrouracil, and methoxy and hydroxy derivatives of cytosine.

For these groups of compounds, the enthalpies of solution $\Delta_{sol}H_m^{\infty}$, van't Hoff enthalpies of sublimation $\Delta_s^g H_m^0$ of solid compounds, partial molar volumes V_2^0, and partial molar heat capacities $C_{p,2}^0$ have been previously determined [1–21]. These data constitute the largest thermodynamic database for pyrimidine nucleic acid bases and their derivatives. Reports published by other investigators, and the data collected in the NIST database, include the enthalpies of sublimation only for uracil, cytosine and several methylated uracil derivatives. In most cases, the $\Delta_s^g H_m^0$ data reported for a given compound by various investigators are considerably inconsistent. The literature lacks any $\Delta_{sol}H_m^{\infty}$ data on aqueous solutions of derivatives of nucleic acid bases. The enthalpies of solution of aqueous solutions of uracil and thymine have been reported by Kilday [22,34] and Gill et al. [23]. Only few data are available for partial molar volumes V_2^0 and partial molar heat capacities $C_{p,2}^0$. The V_2^0 and $C_{p,2}^0$ data for uracil, thymidine and cytosine reported by Kishore et al. [24], are well consistent with the present data (Table 1).

To interpret the solute–solvent interactions of the compounds studied, their calorimetric and volumetric data and the structural parameters have been used jointly. The relationships established here were first assumed to comprise each compound investigated. When the all-over relationships proved too difficult to determine, the scope of the correlation was dwindled to comprise selected groups only or a single group of compounds, whereupon their similarities and differences were duly pointed out. In developing these relationships particular resort was taken in the model suggested by Zielenkiewicz and Poznański [25,26] to describe the volumetric properties of the compounds studied. This model is based on the assumption that the density of the solvent present among the molecules of the hydration shell depends on the structure and polarity of the solute itself.

It should be noted that several efforts have already been undertaken to interpret the experimental data of particular groups of compounds and to establish the relations between the thermodynamic data and the structural parameters. While the work was continued, our reasoning was dilated and the methods used to define the structural parameters of the molecules investigated were modified. The parameters reported in this work were determined only after the methods used to calculate them had been made uniform.

Since the compounds investigated are hydrophobic in nature, the relationships examined included $\Delta_{sol}H_m^{\infty}$, V_2^0 and $C_{p,2}^0$ versus the number of the CH_2– groups attached to the skeleton directly and of other groups thereon; and contributions were determined due to particular atoms (O, Cl, Br, I, F) and due to functional groups (–CH_2, –NH_2, –OH) in the values of $\Delta_{sol}H_m^{\infty}$, V_2^0 and $C_{p,2}^0$.

Table 1
The enthalpies of solution $\Delta_{sol}H_m^{\infty}$, van't Hoff enthalpies of sublimation $\Delta_s^g H_m^0$, partial molar volumes V_2^0 and partial molar heat capacities $C_{p,2}^0$ of pyrimidine nucleic acid bases and their derivatives *i*

No.	Compound	Abbreviated name of the compound	V_2^0 ($cm^3\,mol^{-1}$)	$C_{p,2}^0$ ($J\,K^{-1}\,mol^{-1}$)	$\Delta_{sol}H_m^{\infty}$ ($kJ\,mol^{-1}$)	$\Delta_s^g H_m^0$ ($J\,mol^{-1}$)
1	Uracil	Ura	71.86 [6]	172.0 [9], 137 [1]	29.50 [10]	130.82 [10]
2	1-Methyluracil	m^1 Ura	89.7 [4]	207.1 [4], 205.0 [1]	23.5 [2]	112.5 [2]
3	3-Methyluracil	m^3 Ura	88.7 [7]	–	–	–
4	5-Methyluracil (thymine)	m^5 Ura	88.8 [8]	220.0 [1], 232.5 [8]	24.32 [22]	124.4 [2]
5	6-Methyluracil	m^6 Ura	85.3 [14]	–	–	–
6	1,3-Dimethyluracil	$m_2^{1,3}$ Ura	109.2 [4]	286.4[4], 295.0[1]	15.7 [2]	101.7 [2]
7	3,6-Dimethyluracil	$m_2^{3,6}$ Ura	106.8 [7]	–	–	–
8	1,6-Dimethyluracil	$m_2^{1,6}$ Ura	104.9 [7]	–	21.7 [12]	91.6 [12]
9	1,5-Dimethyluracil (1-methylthymine)	$m_2^{1,5}$ Ura	106.5 [7]	–	22.20 [23]	120.1 [2]
10	5,6-Dimethyluracil	$m_2^{5,6}$ Ura	104.7 [7]	–	–	–
11	1,3,5-Trimethyluracil (1,3-dimethylthymine)	$m_3^{1,3,5}$ Ura	125.5 [7]	373.0 [1]	10.20 [2]	109.2 [2], 103.5 [13]
12	1,3,6-Trimethyluracil	$m_3^{1,3,6}$ Ura	123.8 [7]	363.9 [3], 357.2 [1]	12.34 [2]	106.7 [7]
13	1,3,5,6-Tetramethyluracil	$m_4^{1,3,5,6}$ Ura	139.6 [5]	441.9 [5]	10.23 [14]	103.9 [14]
14	1,3-Dimethyl-5-ethyluracil	$m_2^{1,3}$ e^5 Ura	140.8 [7]	473.4 [1]	8.7 [11]	110.0 [11], 98.7 [13]
15	1,3-Dimethyl-5-propyluracil	$m_2^{1,3}$ p^5 Ura	157.2 [7]	581.9 [18]	12.4 [11]	115.1 [11], 111.0 [13]
16	1,3-Dimethyl-5-izopropyluracil	$m^{1,3}$ $izop^5$ Ura	–	–	–	102.9 [13]
17	1,3-Dimethyl-5-butyluracil	$m_2^{1,3}$ b^5 Ura	173.2 [7]	643.0 [18]	16.5 [11]	98.3 [11], 106.3 [13]
18	1,3-Dimethyl-6-ethyluracil	$m_2^{1,3}$ e^6 Ura	140.3 [3]	455.2 [3]	12.79 [12]	96.1 [12]
19	1,3-Dimethyl-6-propyluracil	$m_2^{1,3}$ p^6 Ura	156.4 [3]	451.8 [3]	11.94 [12]	109.2 [12]
20	1,3-Dimethyl-6-butyluracil	$m_2^{1,3}$ b^6 Ura	172.4 [3]	634.2 [3]	14.14 [12]	90.6 [12]
21	1,6-Dimethyl-3-ethyluracil	$m_2^{1,6}$ e^3 Ura	141.4 [5]	457.3 [5]	10.15 [14]	77.1 [14]
22	1,6-Dimethyl-3-propyluracil	$m_2^{1,6}$ p^3 Ura	157.6 [5]	547.0 [5]	12.80 [14]	118.5 [14]
23	1,6-Dimethyl-3-butyluracil	$m_2^{1,6}$ b^3 Ura	173.8 [5]	627.0 [5]	10.80 [14]	91.6 [14]
24	5-Methyl-1,3-diethyluracil (1,3-diethylthymine)	m^5 $e^{1,3}$ Ura	159.6 [4]	565.1 [1], 577.8 [4]	9.6 [2]	95.0 [2]
25	1,3-Dimethyl-5,6-trimethylenouracil	$m_2^{1,3}$ $(CH_2)_3^{5,6}$ Ura	145.3 [4]	441.8 [4]	7.60 [11]	114.2 [11]
26	1,3-Dimethyl-5,6-tetramethylenouracil	$m_2^{1,3}$ $(CH_2)_4^{5,6}$ Ura	157.9 [4]	505 [4]	9.7 [11]	115.1 [11]
27	1,3-Dimethyl-5,6-pentamethylenouracil	$m_2^{1,3}$ $(CH_2)_5^{5,6}$ Ura	173.1 [4]	580 [4]	–	113.4 [11]
28	5-Fluorouracil	5F Ura	74.51 [6]	199.4 [9]	25.38 [10]	133.22 [10]
29	5-Chlorouracil	5Cl Ura	84.30 [6]	272.2 [9]	21.30 [10]	148.26 [10]
30	6-Chlorouracil	6Cl Ura	86.95 [6]	276.7 [9]	20.94 [10]	135.22 [10]
31	5-Bromouracil	5Br Ura	91.5 [6]	325.3 [9]	27.08 [10]	151.44 [10]
32	5-Iodouracil	5I Ura	100.9 [6]	258.5 [9]	28.47 [10]	155.47 [10]
33	5-Aminouracil	$5NH_2$ Ura	77.4 [6]	124.3 [9]	37.02 [15]	–
34	6-Aminouracil	$6NH_2$ Ura	77.9 [6]	136.9 [9]	18.38 [15]	–
35	6-Amino-1,3-dimethyluracil	$6NH_2$ $m_2^{1,3}$	116.12 [6]	377.8 [9]	20.18 [15]	–
36	5-Nitrouracil	$5NO_2$ Ura	85.00 [6]	190.0 [9]	35.21 [15]	–
37	5-Chloro-6-methyluracil	5Cl m^6 Ura	100.8 [15]	–	–	–
38	5-Methylene-5-chloromethyl	$5CH_2$ Cl	98.7 [15]	–	–	–
39	5-Chloro-1,3-dimethyluracil	5Cl $m_2^{1,3}$ Ura	116.1 [15]	–	–	–

Table 1 (*Continued*)

No.	Compound	Abbreviated name of the compound	V_2^0 ($cm^3\,mol^{-1}$)	$C^0_{p,2}$ ($J\,K^{-1}\,mol^{-1}$)	$\Delta_{sol}H^\infty_m$ ($kJ\,mol^{-1}$)	$\Delta^g_s H^0_m$ ($J\,mol^{-1}$)
40	Cytosine	Cyt	73.7 [19]	168.5 [19]	22.81 [16]	151.7 [16]
41	1-Methylcytosine	m^1 Cyt	91.91 [17]	232.3 [17]	18.28 [16]	141.2 [16]
42	1-Methyl-N^4 hydroxycytosine	$m^{1}{}_{N^4}$ OH Cyt	97.72 [17]	289.3 [17]	19.37 [16]	126.7 [16][a]
43	1,5-Dimethylcytosine	$m_2^{1,5}$ Cyt	107.46 [17]	318.4 [17]	13.64 [16]	132.8 [16]
44	1,N^4-Dimethylcytosine	$m_2{}^{1,N^4}$ Cyt	109.29 [17]	325.1 [17]	8.48 [16]	122.2 [16]
45	1,5-Dimethyl-N^4 hydroxycytosine	$m_2^{1,5}$ N^4 OH Cyt	113.72 [17]	380.6 [17]	13.90 [16]	115.2 [16]
46	1-Methyl-N^4-methoxycytosine	$m^{1}{}_{N^4}$ Om Cyt	119.92 [17]	390.2 [17]	12.61 [16]	106.4 [16]
47	1,N^4,N^4-trimethylcytosine	$m_3{}^{1,N^4,N^4}$ Cyt	125.76 [17]	379.3 [17]	–	110.9 [16]
48	1,5,N^4-trimethylcytosine	$m_3{}^{1,5,N^4}$ Cyt	126.50 [18]	406.3 [18]	2.43 [16]	108.0 [16]
49	1,5-Dimethyl-N^4-methoxycytosine	$m_2^{1,5}$ N^4 Om Cyt	135.08 [17]	480.8 [17]	9.30 [16]	95.6 [16]
50	1,N^4-dimethyl-5-ethylcytosine	$m_2{}^{1,N^4}$ e^5 Cyt	142.4 [18]	515.0 [18]	2.78 [16]	
51	1,N^4-dimethyl-5-propylcytosine	$m_2{}^{1,N^4}$ p^5 Cyt	156.7 [18]	587.9 [18]		
52	1,N^4-dimethyl-5-butylcytosine	$m_2{}^{1,N^4}$ b^5 Cyt	172.0 [18]	688 [18]		

[a] Verkin et al. [43].

2. Methods

The experimental enthalpies of solution $\Delta_{sol}H^\infty_m$, van't Hoff enthalpies of sublimation $\Delta^g_s H^0_m$, partial molar volumes V_2^0, and partial molar heat capacities $C^0_{p,2}$, which form the basis of the present considerations, are collected in Table 1.

The structural parameters evaluated in this work are presented in Table 2. The geometrical parameters were evaluated with the aid of the SYBYL [27] program of the Tripos package by using the Tripos forcefield and Pulmann's atomic charges [28]. In order to mimic solvent screening in the absence of explicit solvent molecules, electrostatic interactions were scaled by setting a distance-dependent dielectric permeability $\varepsilon = 4^*r$ (r, radius).

Molecular volumes V_2^M, molecular surface areas S^M, and their atomic partitions: $S_{H(N,O)}$, S_O, S_N, were calculated with the aid of the GEPOL Version 12.1 algorithm [29]. The following atomic radii consistent with the Tripos forcefield were used: 1.45 Å (N), 1.52 Å (C), 1.36 Å (O), 1.08 Å (H); for water, the solvent radius was 1.4 Å. In the aqueous solutions, both proton acceptors and donors were assumed to be involved in the specific solute–solvent interactions. With this assumption in view, the accessible surface area was divided into two regions: polar and apolar (subscripts p and np, respectively). The molecular surface area of polar atoms S_p was expressed as:

$$S_p = S_N + S_O + S_{H(N,O)} \quad (1)$$

The resulting data were used to determine the polarity P of the compounds, defined as the ratio of the molecular surface area of the polar groups and atoms exposed to the solvent to the total molecular surface area S^M.

To describe the volumetric properties, a parameter α called the relative density of the solvation shell, was used. It was calculated as

$$\alpha = \frac{V_2^0 - V_2^M}{V_{1,solv}} \quad (2)$$

where V_2^0 is the partial molar volume, V_2^M is the molecular volume, and $V_{1,solv}$ is the volume of the solvation shell. The volume of the solvation shell $V_{1,solv}$ was assumed to be equal to the volume determined by rolling a sphere having a diameter equal to the solvent molecule diameter over the solute surface.

The β parameter

$$\beta = \alpha V_{1,solv} \quad (3)$$

which, in fact, is equal to $V_2^0 - V_2^M$ and represents a measure of overall solute–solvent interactions, and is unrelated to the parameterization of the solvation shell, was introduced into the present considerations.

Table 2
Molecular volumes, V_2^M, volume of solvation shell $V_{1,solv}$, accessible molecular surface areas, S^M, and their atomic partitions: $S_{H(N,O)}$, S_O, S_N, relative density of solvation shell α, polarities P, and parameter β

No.	Compound	Volume ($cm^3\,mol^{-1}$)		Surface (Å^2)							P	α	β
		V_2^M	$V_{1,solv}$	S_O	S_N	$S_{H(N,O)}$	S_{halo}	S_p	S_{np}	S^M			
1	Ura	45.2	417.3	26.0	8.3	12.3	0.0	46.7	37.7	84.3	0.45	−0.064	26.7
2	m^1 Ura	54.9	462.1	24.9	6.2	5.7	0.0	36.8	60.1	96.9	0.30	−0.075	34.8
3	m^3 Ura	54.7	461.0	23.4	6.3	6.5	0.0	36.2	61.0	97.2	0.30	−0.074	34.0
4	m^5 Ura	54.6	465.5	24.7	8.3	12.4	0.0	45.3	50.6	95.9	0.37	−0.073	34.1
5	m^6 Ura	55.0	468.2	26.1	8.0	11.3	0.0	45.4	50.2	95.6	0.37	−0.065	30.3
6	$m_2^{1,3}$ Ura	64.2	507.8	22.2	4.2	0.0	0.0	26.3	83.4	109.7	0.19	−0.089	45.0
7	$m_2^{3,6}$ Ura	64.1	513.3	23.3	5.9	5.5	0.0	34.7	73.8	108.5	0.25	−0.083	42.7
8	$m_2^{1,6}$ Ura	64.3	503.3	24.7	6.4	5.7	0.0	36.8	72.1	108.9	0.26	−0.081	40.6
9	$m_2^{1,5}$ Ura	64.2	514.6	23.6	6.2	5.7	0.0	35.5	73.0	108.5	0.25	−0.082	42.3
10	$m_2^{5,6}$ Ura	64.0	507.3	24.0	7.8	11.0	0.0	42.8	63.9	106.7	0.31	−0.080	40.7
11	$m_3^{1,3,5}$ Ura	73.6	556.7	20.6	4.1	0.0	0.0	24.6	96.9	121.6	0.16	−0.093	51.9
12	$m_3^{1,3,6}$ Ura	72.4	539.3	23.3	4.2	0.0	0.0	27.5	94.8	122.2	0.18	−0.095	51.4
13	$m_4^{1,3,5,6}$ Ura	83.0	588.3	19.4	4.3	0.0	0.0	23.8	107.6	131.3	0.14	−0.096	56.6
14	$m_2^{1,3}$ e5 Ura	83.2	606.8	20.3	4.2	0.0	0.0	24.4	109.2	133.6	0.14	−0.095	57.6
15	$m_2^{1,3}$ p5 Ura	93.6	637.7	18.7	4.1	0.0	0.0	22.8	119.5	142.3	0.12	−0.100	63.6
16	$m^{1,3}$ izop5 Ura	–	–	–	–	–	0.0	–	–	–	–	–	–
17	$m_2^{1,3}$ b^5 Ura	103.1	688.9	19.0	4.0	0.0	0.0	22.9	132.6	155.5	0.11	−0.102	70.1
18	$m_2^{1,3}$ e^6 Ura	82.9	595.2	21.8	4.4	0.0	0.0	26.2	107.2	133.3	0.15	−0.097	57.4
19	$m_2^{1,3}$ p^6 Ura	92.4	648.6	21.7	4.4	0.0	0.0	26.2	119.1	145.3	0.13	−0.099	64.0
20	$m_2^{1,3}$ b^6 Ura	102.2	702.6	21.7	4.5	0.0	0.0	26.1	132.1	158.3	0.12	−0.100	70.2
21	$m_2^{1,6}$ e^3 Ura	82.3	599.7	19.9	4.5	0.0	0.0	24.4	108.5	132.9	0.14	−0.099	59.1
22	$m_2^{1,6}$ p^3 Ura	93.1	627.8	19.5	3.7	0.0	0.0	23.2	118.8	142.0	0.12	−0.103	64.5
23	$m_2^{1,6}$ b^3 Ura	103.1	677.6	19.1	3.6	0.0	0.0	22.7	130.7	153.3	0.11	−0.104	70.7
24	m^5 $e^{1,3}$ Ura	92.0	651.6	18.2	4.2	0.0	0.0	22.4	123.0	145.3	0.12	−0.104	67.6
25	$m_2^{1,3}$ $(CH_2)_3{}^{5,6}$ Ura	87.0	607.2	21.0	4.4	0.0	0.0	25.4	108.0	133.4	0.14	−0.096	58.3
26	$m_2^{1,3}(CH_2)_4^{5,6}$ Ura	95.7	635.2	20.8	4.1	0.0	0.0	24.9	117.9	142.8	0.13	−0.098	62.2
27	$m_2^{1,3}(CH_2)_5^{5,6}$ Ura	105.9	655.8	19.6	4.2	0.0	0.0	23.8	125.2	149.0	0.12	−0.103	67.2
28	5F Ura	47.4	426.5	25.8	8.3	12.3	11.6	46.4	27.4	85.4	0.42	−0.063	26.8
29	5Cl Ura	53.7	457.7	25.2	8.3	12.3	22.1	45.8	25.9	93.8	0.38	−0.067	30.6
30	6Cl Ura	53.7	459.7	26.0	8.0	11.3	23.3	45.4	26.0	94.6	0.38	−0.074	34.0
31	5 Br Ura	56.8	469.3	24.9	8.3	12.3	28.5	45.5	25.8	99.8	0.36	−0.074	34.7
32	5J Ura	63.5	494.8	24.2	8.3	12.3	39.1	44.8	24.0	107.9	0.33	−0.076	37.4
33	5 NH_2 Ura	53.2	462.1	25.3	17.0	24.5	0.0	66.8	26.3	93.1	0.56	−0.052	24.2
34	6NH_2 Ura	52.7	456.7	26.1	16.4	23.9	0.0	66.4	26.4	92.8	0.55	−0.055	25.2
35	6NH_2 $m_2^{1,3}$	72.6	542.3	21.6	12.3	11.1	0.0	45.1	71.8	116.9	0.29	−0.080	43.5
36	5NO_2 Ura	56.5	471.7	46.7	11.5	12.0	0.0	70.3	24.2	94.4	0.56	−0.060	28.5
37	5Cl m^6 Ura	63.2	499.5	25.2	7.9	11.2	20.3	44.3	39.9	104.5	0.32	−0.075	37.7
38	5CH_2 Cl	62.8	506.3	26.1	7.9	11.3	22.5	45.3	37.9	105.7	0.33	−0.071	35.9
39	5Cl $m_2^{1,3}$ Ura	72.4	550.3	20.6	4.1	0.0	22.0	24.6	71.8	118.4	0.16	−0.079	43.7
40	Cyt	47.6	435.6	14.1	20.5	19.7	0.0	54.3	36.2	90.5	0.49	−0.060	26.1
41	m^1 Cyt	57.1	482.2	13.1	18.2	13.0	0.0	44.3	59.4	103.7	0.34	−0.072	34.8

Table 2 (*Continued*)

No.	Compound	Volume ($cm^3\,mol^{-1}$)		Surface (Å^2)							P	α	β
		V_2^M	$V_{1,solv}$	S_O	S_N	$S_{H(N,O)}$	S_{halo}	S_p	S_{np}	S^M			
42	m^1 N^4 OH Cyt	61.8	511.9	22.3	14.9	13.5	0.0	50.6	59.2	109.8	0.36	−0.070	36.0
43	$m_2^{1,5}$ Cyt	66.7	523.0	13.1	17.9	11.8	0.0	42.8	70.9	113.7	0.29	−0.078	40.7
44	$m_2{}^{1,N^4}$ Cyt	66.3	530.4	13.2	14.5	5.9	0.0	33.6	82.6	116.2	0.23	−0.081	43.0
45	$m_2^{1,5}$ N^4 OH Cyt	71.3	552.9	22.3	14.3	12.2	0.0	48.8	70.6	119.4	0.31	−0.077	42.5
46	m^1 N^4 Om Cyt	71.0	571.1	19.2	14.2	5.1	0.0	38.6	87.2	125.8	0.24	−0.086	48.9
47	$m_3{}^{1,5N^4,N^4}$ Cyt	75.4	579.6	13.2	10.9	0.0	0.0	24.0	105.1	129.1	0.15	−0.087	50.4
48	$m_3{}^{1,5N^4}$ Cyt	76.0	577.3	12.7	12.7	10.8	0.0	36.2	90.9	127.2	0.22	−0.087	50.5
49	$m_2^{1,5}$ N^4 Om Cyt	80.4	613.0	19.3	13.5	3.8	0.0	36.6	98.3	135.0	0.21	−0.089	54.7
50	$m_2{}^{1,N^4}$ e^5 Cyt	86.1	626.9	12.8	12.6	4.0	0.0	29.3	109.5	138.7	0.16	−0.090	56.3
51	$m_2{}^{1,N^4}$ p^5 Cyt	95.8	675.1	12.8	12.4	10.4	0.0	35.5	115.4	151.0	0.18	−0.090	60.9
52	$m_2{}^{1,N^4}$ b^5 Cyt	105.7	715.7	12.7	12.2	9.4	0.0	34.3	126.6	160.9	0.16	−0.093	66.3

3. Results and discussion

The data in Table 1, viz., V_2^0 and $C_{p,2}^0$, are seen (Fig. 2a and b) to be linearly related to the number of the –CH_2 groups attached to the skeleton directly and to other functional groups. For alkylated uracils, the incremental value of V_2^0 per CH_2 group is $17.06 \pm 0.17\,cm^3\,mol^{-1}$ (regression coefficient $r^2 = 0.998$), whereas for alkylated cytosines the value is $16.37 \pm 0.27\,cm^3\,mol^{-1}$ ($r^2 = 0.998$). In the calculations, the data for cyclooligomethyleneuracils were omitted. For this group of compounds, the incremental value of V_2^0 per CH_2 group is $13.9 \pm 0.75\,cm^3\,mol^{-1}$ ($r^2 = 0.997$). The constraint imposed on the CH_2 motion by cyclization, has affected the results of the correlation obtained [4]. This observation agrees well with the effects observed in cycloalkanes and in other cyclic compounds [30]. For alkylated uracils, the incremental value of $C_{p,2}^0$ is $82.9 \pm 2.5\,JK^{-1}\,mol^{-1}$ ($r^2 = 0.987$), whereas for the derivatives of cytosine, the value is $88.0 \pm 3.4\,JK^{-1}\,mol^{-1}$ ($r^2 = 0.987$). These values of the increments are similar to those reported for other series of hydrophobic compounds, viz., homologous series of hydrocarbons [31], aliphatic amines [32] and various hydrocarbon derivatives carrying polar groups [33]. For these compounds, the increment of partial molar volume for –CH_2 is $16\,cm^3\,mol^{-1}$, whereas the increment of partial molar heat capacity is closer to $84\,JK^{-1}\,mol^{-1}$. The resulting partial molar heat capacities are considerably higher than the heat capacities determined for the solid compounds: partial molar heat capacity $C_{p,2}^0$ for uracil is $172.0\,JK^{-1}\,mol^{-1}$, for solid uracil $C_{p,solid} = 120.5\,JK^{-1}\,mol^{-1}$ [34]; for thymine $C_{p,2}^0$ is $220.0\,JK^{-1}\,mol^{-1}$, for solid thymine $C_{p,solid} = 150 \pm 6.9\,JK^{-1}\,mol^{-1}$ [37]. The data thus reflect the hydrophobic properties of the compounds studied.

The relation $\Delta_{solv}H_m = f(n_{CH_2})$ was also examined (Fig. 2c). As can be seen from Fig. 2c, only the methylated uracils and cytosines produce the linear course of the function $\Delta_{solv}H_m = f(n_{CH_2})$. The uracil derivatives carrying long alkyl side chains, viz., compounds of the series 1,3-dimethyl-5-alkyluracils, 1,6-dimethyl-3-alkyluracils and 1,3-dimethyl-6-alkyluracils, cyclooligomethyleneuracils, aminouracils, and 1,3-dimethyluracil, reveal considerable deviations of the function from the linear course. The reason is the erratic changes which afflict the values of the enthalpy of solvation, $\Delta_{solv}H_m$ [21], viz., the higher values of the enthalpy increment correspond to the odd numbers of –CH_2 groups added, whereas the lower values correspond to those endowed with the even n_{CH_2} number. The crystal structure of the solid compounds is the factor responsible for this phenomenon as is evident from a comparison of the sublimation enthalpies and packing energies for

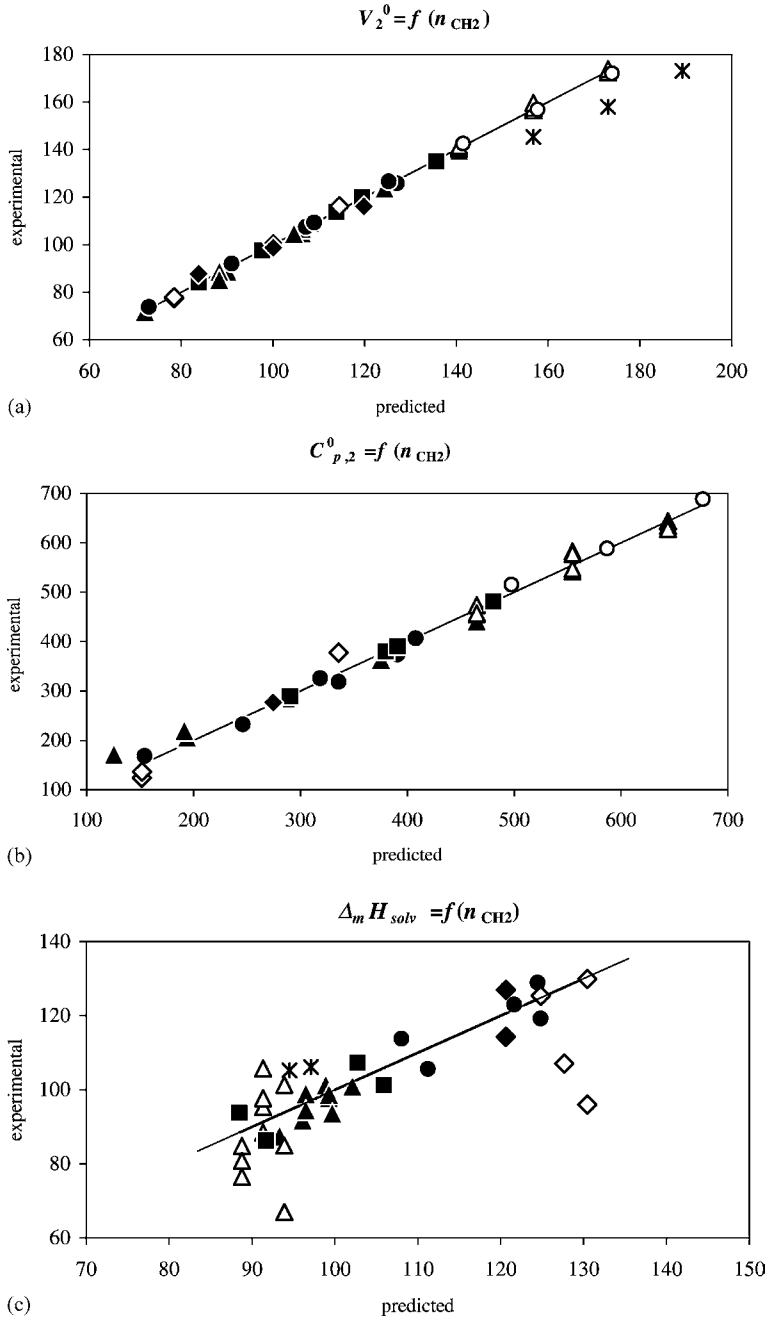

Fig. 2. (a) Partial molar volumes; (b) partial molar heat capacities and (c) enthalpies of solvation of aqueous solutions of derivatives of uracil and cytosine plotted against the number of alkyl carbons ((▲) methylated uracils; (△) derivatives of uracil with long alkyl side chains; (◇) cyclooligomethyleneuracils; (◆) halouracils; (□) amino derivatives of uracil; (✶) nitrouracil; (●) methyl, (■) hydroxy and methoxy derivatives of cytosine). The symbols used in this Figure have identical meanings in the remaining Figures.

1,3-dimethyluracil-5-alkyluracils [21]. Deviations from the linear course of the function $\Delta_{solv}H_m = f(n_{CH_2})$, similarly as those observed in the course of the $V_2^0 = f(n_{CH_2})$ function, occur in the case of cyclooligomethyleneuracils. This is caused by the more compact structure of these compounds as compared with that of other alkylated derivatives of uracil. The constraint imposed on the CH_2 motion by cyclization has affected the results of the correlation. Practically, in each correlation presented in this study, the property data of aminouracils and nitrouracil deviate from those of the other compounds investigated.

The $\Delta_{solv}H_m$, V_2^0, and $C_{p,2}^0$ data were also analyzed in terms of the general additivity scheme [35]. The calculations were made according to the general formula

$$X = X_0 + \sum_i n_i Z_i \quad (4)$$

where X_0 is a constant; Z_i is the additive value for group i, and n_i is the number of type i groups. Values X_0 and Z_i were estimated by using the multiple linear regression routine based on least squares. For cytosine derivatives, five types of contributions were distinguished: $Z_{CH_2(N)}$, $Z_{CH_2(C)}$, $Z_{CH_2(N^4)}$, $Z_{CH_2(O)}$, and Z_O. They correspond to the substitution of hydrogen on C, N and O (in OH on N^4) atoms with a CH_3 group and to the replacement of hydrogen on the N^4 atom by an OH group. For uracil derivatives, the four types of contributions distinguished are $Z_{CH_2(N)}$, $Z_{CH_2(C)}$, $Z_{NH_2(C)}$, and $Z_{Cl(C)}$. The resulting Z_i data are presented in Tables 3 and 4. The calculations were carried out by taking into account: (a) jointly the derivatives of uracil and cytosine; (b) the derivatives of uracil; and (c) the derivatives of cytosine. Additionally, the amount of the data used to determine a given correlation was reduced by excluding those derivatives of uracil whose data worsened considerably the reliability of the correlation as characterized by the regression coefficient r^2.

Undoubtedly, the contributions $Z_{CH_2(O)}$, Z_O, $Z_{NH_2(C)}$, and $Z_{Cl(C)}$ presented in Tables 3 and 4 enrich our knowledge about the contributions of various functional groups and atoms attached to the pyrimidine skeleton and to other groups thereon. They also allow to draw several conclusions concerning the solute–solvent interactions involved. Inspection of the data obtained allows to see that the values of $\Delta_{solv}H_m$, V_2^0, and $C_{p,2}^0$ depend not only on the number of the CH_2 groups attached, but also on the position of substitution. The data listed in Table 3 indicate clearly that such changes do occur in the enthalpy of solvation, both in the derivatives of cytosine and uracil. The specificity of substitution of hydrogen with a CH_3 group on the N^4 or C(5) atom of the cytosine skeleton is evident. Most interestingly, the substitution at the *N*-ring nitrogen atom on the uracil skeleton brings about a reduction of $\Delta_{solv}H_m$ with a mean increment of $-3.8\,kJ\,mol^{-1}$; substitution of the hydrogen atom on the C(5) or C(6) ring carbon atom produces an opposite effect, viz., an increase in $\Delta_{solv}H_m$ by an average of $3.0\,kJ\,mol^{-1}$. This means that there exists a difference in the methyl substitution at the "polar" and the "apolar" atoms of the uracil skeleton. This fact clearly indicates that methyl groups can be used as the thermochemical probes of energy of water binding around the skeleton of uracil, thymine and cytosine. Furthermore, the present results of thermochemical investigations can be used to evaluate the enthalpy $\Delta_{int}H_m$ of solute–solvent interactions from the experimental enthalpies of solvation corrected by 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 semi-empirical way with those evaluated by quantum-mechanical calculations. However, the $\Delta_{int}H_m$ numerical values depend strongly on the type of method adopted to calculate the enthalpy required to make a cavity in liquid water. Results of the calculations carried out by using the Scale Particle Theory and by the Sinagoglu method have been considerably inconsistent [36,37]. Among other things, each of these methods makes use of what is known as the molecular surface area of the molecule studied. In the present work, this quantity has been adopted as the basis for further considerations. Looking for a qualitative explanation of the $\Delta_{solv}H_m$-values obtained for methylated uracils and cytosines, a relationship was assumed to hold true between the calorimetric quantities ($\Delta_{solv}H_m$, $C_{p,2}^0$) and the polar and the apolar parts of the accessible surface areas. The function $\Delta_{solv}H_m = f(S_p, S_{np})$ was assumed to take on the following form:

$$\Delta_{solv}H_m = aS_p + bS_{np} + c \quad (5)$$

where *a*, *b*, *c*, are constants. The following correlations were obtained.

Table 3
Contributions Z_i for CH_2(N), $\{CH_2(C)\}'$, $\{CH_2(C)\}''$, $CH_2(N^4)$, NH_2(C), Cl(C), CH_2(O) and O substitution to $\Delta_{solv}H_m$

	Ura	Cyt	$Z_{CH_2(N)}$	$Z_{\{CH_2(C)\}'}$	$Z_{\{CH_2(C)\}''}$	$Z_{CH_2(N4)}$	$Z_{NH_2(C)}$	$Z_{Cl(C)}$	$Z_{CH_2(O)}$	Z_0	r^2
$\Delta_m H_{solv}$ (kJ mol^{-1})											
U + C 1, 2, 4, 6, 8, 9, 11–15, 17–20, 22–26, 29, 30, 34, 35, 40–52	98.9 ± 4.2	124.5 ± 4.6	−2.8 ± 2.6	3.2 ± 2.7	−2.6 ± 1.6	−13.6 ± 6.7	31.6 ± 6.1	21.7 ± 6.7	−14.3 ± 7.3	−18.9 ± 6.7	0.810
U + C 1, 2, 4, 6, 9, 11, 12, 29, 30, 34, 35, 40–46, 48–50	101.0 ± 2.7	126.2 ± 2.9	−3.5 ± 1.7	−0.7 ± 2.0	–	−12.7 ± 4.3	30.2 ± 3.9	19.7 ± 4.2	−14.3 ± 4.6	−18.1 ± 4.3	0.932
U 1, 2, 4, 6, 8, 9, 11–15, 17–20, 22–26, 29, 30, 34, 35	96.1 ± 4.4	–	−3.3 ± 2.6	7.1 ± 3.2	−2.9 ± 1.6	–	34.9 ± 6.2	24.5 ± 6.7	–	–	0.787
U 1, 2, 4, 6, 9, 11, 12, 29, 30, 34, 35	98.5 ± 2.7	–	−3.8 ± 1.6	3.0 ± 2.4	–	–	33.0 ± 3.8	22.1 ± 4.1	–	–	0.939
C 40–47, 49–52	–	128.9 ± 1.4	−4.7 ± 1.8	−6.4 ± 1.0	–	−11.4 ± 1.4	–	–	−14.3 ± 1.4	−16.7 ± 1.4	0.996

Table 4
Contributions Z_i for $CH_2(N)$, $CH_2(C)$, $CH_2(N^4)$, $NH_2(C)$, Cl(C), $CH_2(O)$ and O substitution to V_2^0 and $C_{p,2}^0$

	Ura	Cyt	$Z_{CH_2(N)}$	$Z_{CH_2(C)}$	$Z_{CH_2(N4)}$	$Z_{NH_2(C)}$	$Z_{CL(C)}$	$Z_{CH_2(O)}$	Z_0	r^2
V_2^0 ($cm^3\,mol^{-1}$)										
U + C 1–15, 17–24, 29, 30, 33–35, 40–52	72.1 ± 0.5	73.0 ± 0.7	18.0 ± 0.3	16.2 ± 0.2	–	6.4 ± 1.0	11.7 ± 0.8	21.8 ± 1.4	6.6 ± 1.1	0.998
U 1–15, 17–24, 29, 30–35, 40	71.6 ± 0.6	–	18.1 ± 0.4	16.4 ± 0.3	–	6.8 ± 1.1	12.1 ± 0.9	–	–	0.998
U_{alk} 1–15, 17–24	71.2 ± 0.5	–	18.5 ± 0.3	16.3 ± 0.2	–	–	–	–	–	0.999
C 40–52	–	74.2 ± 0.7	17.5 ± 0.4	15.9 ± 0.2	–	–	–	21.8 ± 0.9	6.0 ± 0.7	0.999
$C_{p,2}^0$ ($JK^{-1}\,mol^{-1}$)										
U + C 1, 2, 4, 6, 11–15, 17–23, 29, 30, 33, 35, 40–52	125.4 ± 12.1	162.5 ± 12.0	81.9 ± 6.9	88.4 ± 3.2	74.8 ± 11.2	33.0 ± 15.1	149.1 ± 19.0	100.6 ± 20.8	46.3 ± 18.6	0.987
U 1, 2, 4, 6, 11–15, 17–23, 29, 30, 33	127.2 ± 14.2	–	85.8 ± 8.3	84.3 ± 4.8	–	28.6 ± 17.6	147.3 ± 21.9	–		0.984
C 40–52	–	168.3 ± 10.7	66.2 ± 13.0	94.5 ± 2.6	75.8 ± 6.3	–	–	100.6 ± 10.7	53.2 ± 10.3	0.997

For methylated uracils (compounds Nos. 1, 2, 4, 6, 8, 9, 12, 13):

$$\Delta_{\mathrm{solv}}H_m = 1.51(\pm0.23)S_{\mathrm{p}} + 0.42(\pm0.09)S_{\mathrm{np}} + 24(\pm31), \quad r^2 = 0.932 \tag{6}$$

provided the value of $\Delta_{\mathrm{solv}}H_{\mathrm{m}}$ for 1, 3, 5 m^3 Ura is omitted.

For cytosine and their derivatives:

$$H_{\mathrm{solv}}H_{\mathrm{m}} = -2.19(\pm0.83)S_{\mathrm{p}} - 1.33(\pm0.26)S_{\mathrm{np}} + 299(\pm55), \quad r^2 = 0.923 \tag{7}$$

The observed and the calculated (from Eqs. (6) and (7)) $\Delta_{\mathrm{solv}}H_{\mathrm{m}}$-values are intercompared graphically in Fig. 3. This plot shows evidently that inferring on hydrophilic and hydrophobic interactions with water with the aid of the method in which certain polar and apolar atoms of the diketopyrimidine skeleton are withdrawn from direct interaction with the hydration shell must be limited only to the methylated derivatives of uracil and cytosine. This is also evident from the data in Table 3 on the increments in $\Delta_{\mathrm{solv}}H_{\mathrm{m}}$, including the distinguished increments $Z_{\{CH_2(C)\}'}$ and $Z_{\{CH_2(C)\}''}$ in Z_{CH_2} corresponding, respectively, to the substitution of the hydrogen atom with the CH_3 group on the skeleton and to the extension of an alkyl side chain by the methylene group. The relevant values are seen to be considerably different.

Similarly as in the case of the enthalpy of solvation, there is an evident influence of the substitution (on carbon or nitrogen) with CH_2 on the V_2^0 and $C_{\mathrm{p},2}^0$ values (Table 4). For uracil and cytosine derivatives, addition of a CH_2 group on the N atoms is equivalent to an increment of $18.0 \pm 0.3\,\mathrm{cm^3\,mol^{-1}}$ in V_2^0, whereas addition to the C atom(s) yields the value $16.2 \pm 0.2\,\mathrm{cm^3\,mol^{-1}}$. In $C_{\mathrm{p},2}^0$, addition of CH_2 on the N atom(s) corresponds to an increment of $81.9 \pm 6.9\,\mathrm{JK^{-1}\,mol^{-1}}$, whereas addition to the C atom yields the value $88.4 \pm 3.2\,\mathrm{JK^{-1}\,mol^{-1}}$.

According to the concept of Spolar et al. [38] and Freire and coworkers [39,40], to explain the effect of the position of substitution on $C_{\mathrm{p},2}^0$ in terms of the perturbations caused by the substituents, it was desirable to establish the relation of $C_{\mathrm{p},2}^0$ to the polar S_{p} and the apolar S_{np} parts of the molecular surface area:

(a) methylated and other alkylated uracils

$$C_{\mathrm{p},2}^0 = 9.7(\pm1.8)S_{\mathrm{p}} + 7.6(\pm0.5)S_{\mathrm{np}} - 595(\pm94), \quad r^2 = 0.979 \tag{8}$$

(b) alkylated methoxy and hydroxy derivatives of cytosine

$$C_{\mathrm{p},2}^0 = 10.8(\pm0.9)S_{\mathrm{p}} + 8.2(\pm0.3))S_{\mathrm{p}} - 725(\pm61), \quad r^2 = 0990 \tag{9}$$

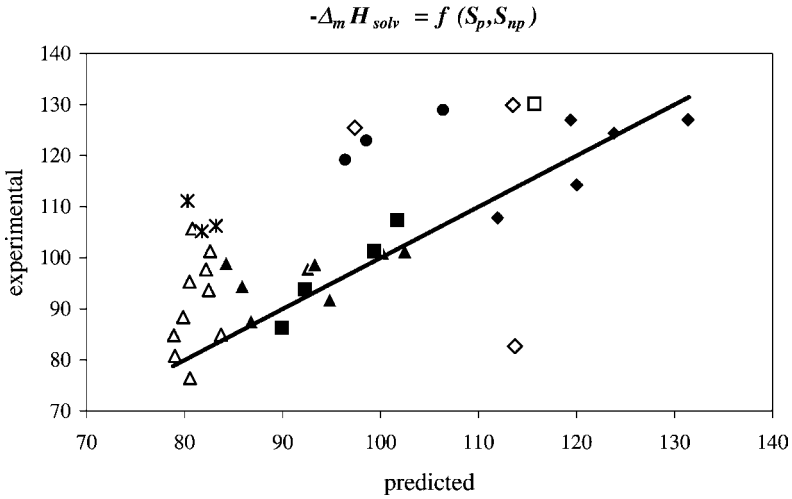

Fig. 3. The enthalpy of solvation of aqueous derivatives of uracil and cytosine plotted against polar and apolar parts of accessible surface areas.

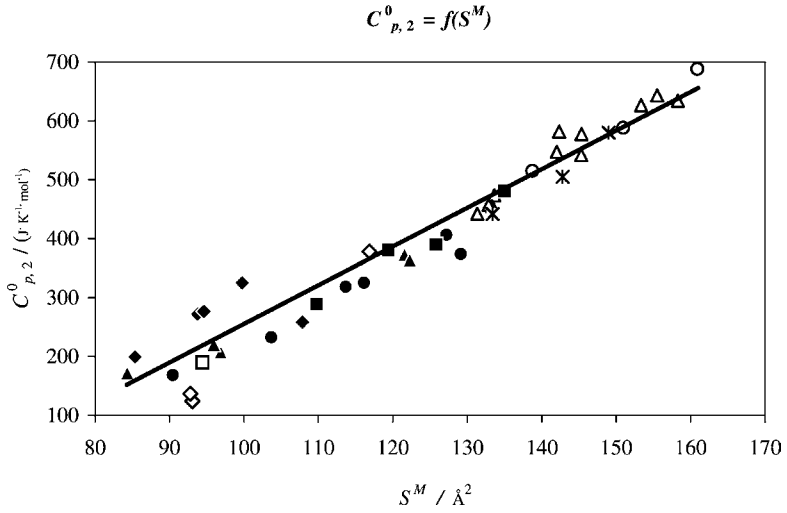

Fig. 4. Partial molar heat capacities vs. accessible molecular surface area.

(c) however, jointly for the derivatives of uracil and cytosine, the only relation possible to establish was that of $C^0_{p,2}$ to the accessible molecular surface area, as expressed by Eq. (10)

$$C^0_{p,2} = 6.8(\pm 0.2)S^M - 725(\pm 61), \quad r^2 = 0949 \tag{10}$$

This correlation is presented graphically in Fig. 4.

The correlations of the partial molar volume data with the structural parameters were developed by using the suggested model based on the assumption that the relative density of the solvation shell, α, depends on the structure and polarity P of the compounds studied. This assumption was confirmed by the calculations carried out for the aqueous solutions of the compounds in several series, e.g. alkanes, amines, diamines, amides, alcohols and diols, cyclic ethers and oxanes, ketones, cyclic ketones [25] and uracil derivatives [7]. By way of illustration, the α-values for alkylated uracils are given in Fig. 5. The value of α is seen to vary with the number of methylene groups attached to the molecule; again, the α-values exhibit differences caused by screening of the carbon atoms (C(5), C(6)) and nitrogen atoms (N(1), N(3)) in the uracil skeleton by methyl groups. The α-value is always negative, a fact indicating the mean water density in the solvation shell to be lower than that of pure water, and always decreases as the hydrophobicity of the solute is increased. It must be inherently connected with the decrease in energy associated with the loss of energy of polar interactions.

The quantity α was assumed to be related to polarity P as follows

$$\alpha = \alpha_0 + bP \tag{11}$$

where α_0 is the correction for the change in the solvent density caused by the completely apolar solute introduced into the solvent.

For uracil and cytosine and their derivatives, the function $\alpha = f(P)$ was found to be

$$\alpha = -0.111(\pm 0.001) + 0.083(\pm 0.004)P, \quad r^2 = 0.914 \tag{12}$$

which is presented graphically in Fig. 6.

For the uracil derivatives excluding the alkylated uracil derivatives carrying long alkyl side chains,

$$\alpha = -0.107(\pm 0.002) + 0.078(\pm 0.007)P \quad r^2 = 0.928 \tag{13}$$

and for cytosine and cytosine derivatives

$$\alpha = -0.112(\pm 0.002) + 0.084(\pm 0.004)P \quad r^2 = 0.919 \tag{14}$$

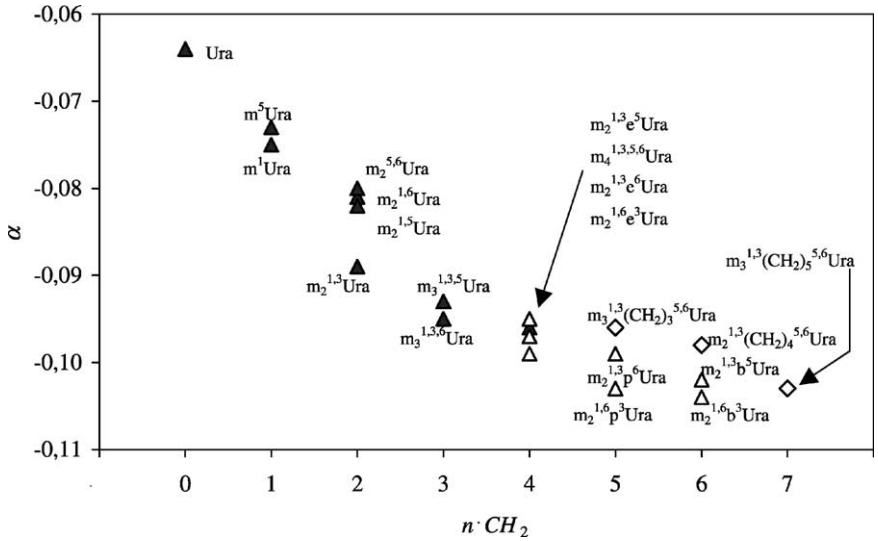

Fig. 5. Values of α for variously methylated uracils.

The relations $\alpha = f(P)$ expressed by Eqs. (12)–(14) reaffirmed the former conclusion emphasizing the fundamental contribution of polar interactions to solute–solvent interactions.

As mentioned before, the model based on the assumption that the relative density of the solvation shell depends on the structure and the polarity of the compounds investigated enables their properties to be examined also in terms of parameter β. This parameter was assumed to be proportional to changes in free-energy, ΔG. This assumption is based on the fact that, for alkanes, the β-values calculated by us and compared with Lee's [41] "experimental" free-energy ΔG data for solvent reorganization upon formation of a cavity, produce a linear plot. Furthermore, with entropy changes assumed to be negligible, trials were made to relate β-values to the enthalpy of solvation as also to the partial molar heat capacity. The calculations performed are presented graphically in Figs. 6 and 7. The data presented in Fig. 6 show that

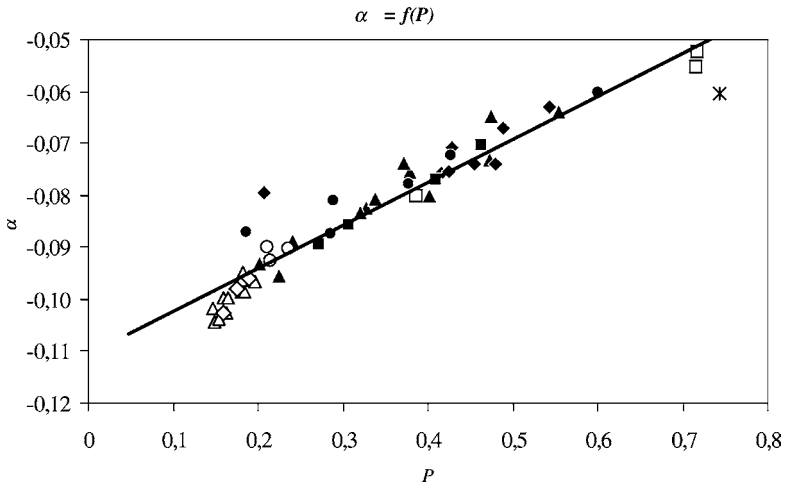

Fig. 6. Solvation shell's relative density α vs. polarity P.

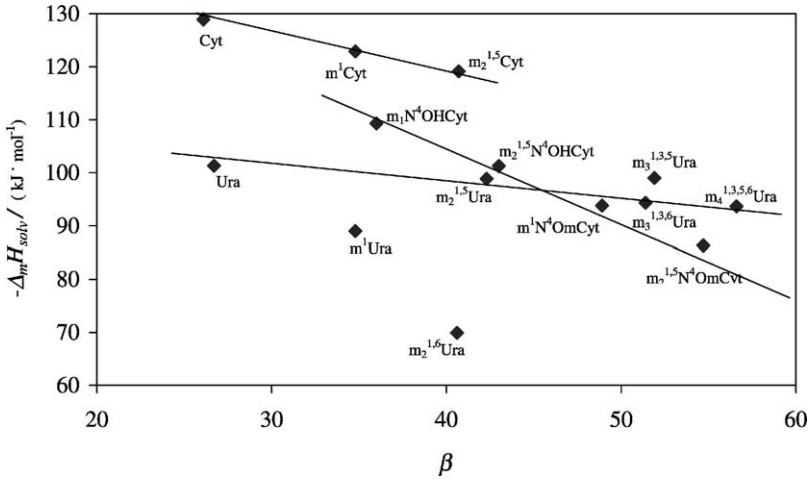

Fig. 7. Enthalpy of solvation plotted against parameter β.

functions $\beta = f(\Delta_{\text{solv}}H_{\text{m}})$ can be distinguished for: (a) methylated cytosines, (b) methylated uracils and (c) hydroxy and methoxy cytosines. In the case of functions $\beta = f(C^0_{\text{p},2})$, a straight-line relationship could be established for all the compounds investigated in this work:

$$C^0_{\text{p},2} = -211(\pm 2.4) + 11.5(\pm 0.4)\beta \qquad (15)$$

The function is presented graphically in Fig. 8.

As evident from the present considerations, correlation of the enthalpy of solvation with the structural data allows compound properties to be much more precisely differentiated than this is possible by the correlation with partial molar quantities. To interpret this fact, further studies are required; similarly, more studies are required to establish the range within which the correlations $\beta = f(\Delta_{\text{solv}}H_{\text{m}})$ and $\beta = f(C^0_{\text{p},2})$ can be used to predict the direction of changes consistent with those observed in free-energy ΔG. This would make it possible, for example, to use only two volumetric property data, V_2^0 and $V_2^{\text{M}}(\beta = V_2^0 - V_2^{\text{M}})$, to predict the solubilities of the compounds examined.

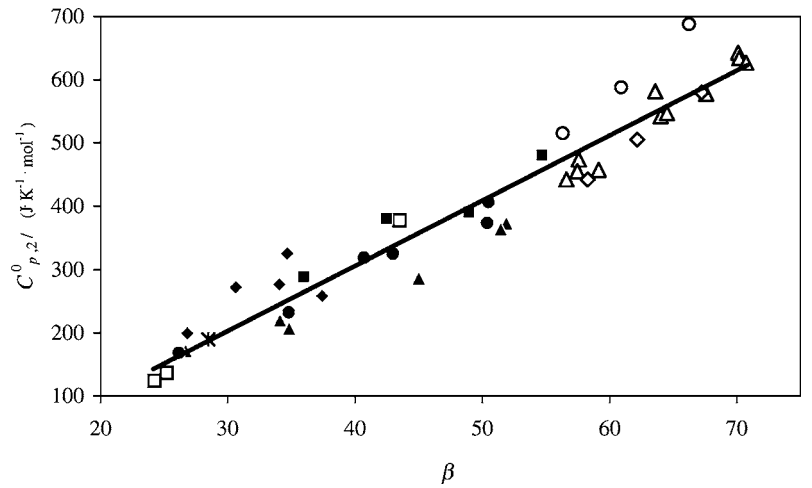

Fig. 8. Relation between partial molar heat capacity and β.

Formerly, such a prediction was shown to be possible in the case of acyclovir analogs [42].

In a number of the correlations presented in this study, use was made of the enthalpies of solvation calculated from the experimentally determined enthalpies of solution and enthalpies of sublimation. Since van't Hoff enthalpies of sublimation $\Delta_s^g H_m^0$ are difficult to measure because of the low saturated vapor pressures of the compounds investigated and the considerable experimental errors involved, in thermochemical studies it is often decided to abandon the measurement of $\Delta_{solv}H_m$. Inference on solute–solvent interactions is then based on the determination of the enthalpy of solution or dilution of the substance examined in various solvents or in mixed solvents. The use of methanol and *N*,*N*-dimethylformamide solutions, in addition to aqueous solutions, has allowed to establish correlations similar to the present correlations for a sizable group of uracil and cytosine derivatives [42]. This fact demonstrates that the technique applied in this study can be used to analyze solute–solvent interactions in various solvents.

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