Molar Heat Capacities of Some Derivatives of Uridine and 2′-Deoxyuridine

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The molar heat capacities $C_{p,m}$ of seven crystalline compounds (uridine, 2′-deoxyuridine, 5-iodouridine, 5-bromouridine, 5-iodo-2′-deoxyuridine, 5-bromo-2′-deoxyuridine, and 5-methyl-2′-deoxyuridine (thymidine)) were determined using a differential scanning calorimeter (SETARAM TG-DSC 111). The measurements were made over the temperature range from (298.15 to 368.15) K. The values of molar heat capacities versus temperature $C_{p,m} = f(T)$ were determined. The standard molar heat capacities $C_{p,m}^{0}$ were compared with those calculated by the Chickos method. The contributions of the $C-CH_3$ group, as well as Br and I atoms, in the value of $C_{p,m}^{0}$ were evaluated.

Introduction

The thermodynamic properties of differently substituted derivatives of uridine are important in view of their medical application. Some of the halogen derivatives of uridine exhibit a significant pharmacological activity and have been used as antitumor, antibacterial, and antiviral drugs. 5-Iodo-2′-deoxyuridine (IDU, Iduviran), the antiviral nucleoside, first was synthesized by Prusoff.[1] IDU is used in treatment of occular HSV-1 infections such as keratitis.[2] 5-[125I]iodo-2′-deoxyuridine ([125I]IUdR) has long been recognized as possessing therapeutic potential.[3,4]

5-Bromo-2′-deoxyuridine (BrdU), a thymidine analogue, is widely used as a marker of proliferating cells in neuroscience.[5] Three 5-bromo-2′-deoxyuridine derivatives containing glycyl-, glycyl-glycyl-, and glycyl-glycyl-glycyl-residues show high activity against the herpes virus (pseudo rabies virus (PsRV)) and only moderate activity versus HSV-1.[6]

The molar heat capacities $C_{p,m}$ of uridine, 2′-deoxyuridine, and their derivatives over the temperature range from (298.15 to 368.15) K were determined. The functions $C_{p,m} = f(T)$ were evaluated. The contributions of the $C-CH_3$ group, as well as Br and I atoms, in the value of $C_{p,m}^{0}$ were evaluated. Finally, the experimentally determined $C_{p,m}^{0}$ values were compared with those calculated by the Chickos method.[7,8] The $C_{p,m}^{0}$ values for derivatives of uridine were also compared with data obtained for uracil and its halogen derivatives.[9]

This paper constitutes a continuation of investigations of the derivatives of bases of nucleic acid. The heat capacities for halogen, methyl, and amino derivatives of uracil were determined before.[9,10]

Materials and Methods

The compounds used in the experiments were: uridine [1-β-D-ribofuranosyluracil, Fluka, 94320, Chemical Abstract Service Registry Number (CASRN): 58-96-8, purity ≥ 99 %], 5-bromouridine (Aldrich, 850187, CAS: 957-75-5, purity: ≥ 98 %), 5-iodouridine (Fluka 58150, CAS: 1024-99-3, purity ≥ 97 %), 2′-deoxyuridine [(1-(2-deoxy-β-D-ribofuranosyl)uracil), Alfa Aestar, Lot: D8600A, CAS: 951-78-0, purity ≥ 99 %], 5-bromo-2′-deoxyuridine (Fluka, 16880, CAS: 59-14-3, purity ≥ 99 %), 5-iodo-2′-deoxyuridine (Fluka 57830, CAS: 54-42-2, purity ≥ 98 %), 5-methyl-2′-deoxyuridine (Fluka 89270, CAS: 50-89-5, purity ≥ 99 %). Their molar masses were (0.24420, 0.32310, 0.37010, 0.22820, 0.30711, 0.35410, and 0.24223) $kg \cdot mol^{-1}$, respectively. Structural formulas of the studied compounds are presented in Figure 1.

The $C_{p,m}$ determinations were made with use of the Calvet TG-DSC 111 differential scanning microcalorimeter (Setaram, France).[9] The procedure for determining $C_{p,m}$ was identical to the one applied in our previous study.[9,10] The measurements were performed differentially, relatively to the empty crucible over the temperature range from (298.15 to 368.15) K at a scan rate of 0.5 $K \cdot min^{-1}$. All the samples were prepared in the same way. The investigated compounds were placed in a stainless steal crucible of 150 μL volume. The stainless steel cover was crimped with an aluminum seal with the use of a crimping press. The sample mass was determined with the uncertainty $\pm 1 \cdot 10^{-5}$ g using the balance Mettler AT 261 Delta Range. The uncertainty of the temperature was 0.1 K. The DSC device was calibrated using as a standard substance benzoic acid of purity 99.8 %, received from the Polish Committee for Standardization. The experimentally determined standard molar heat capacity $C_{p,m}^{0}$ value of benzoic acid equal to (146.9 ± 1.32) $J \cdot K^{-1} \cdot mol^{-1}$ was in agreement with those recommended by the IUPAC[11] (146.8 $J \cdot K^{-1} \cdot mol^{-1}$).

The $C_{p,m}$(calcd) data were obtained from $C_{p,m}$(exptl) using the least-squares linear regression method (Excel 2003, Microsoft).[12] The $C_{p,m}^{0}$ data were compared with those obtained by the Chickos procedure $C_{p,m}^{0}$(Chickos) on the basis of heat capacities of functional groups comprising a given compound.[7,8]

For calculation for uridine, we assumed that $C_{p,m}^{0}$ corresponded to the sum of one cyclic secondary group −CONH− (46.4 $J \cdot K^{-1} \cdot mol^{-1}$), one cyclic tertiary amide −CONR− (52.7 $J \cdot K^{-1} \cdot mol^{-1}$), two tertiary aromatic sp^2 C groups =CH− (2·17.5 $J \cdot K^{-1} \cdot mol^{-1}$), group −O− (9.7 $J \cdot K^{-1} \cdot mol^{-1}$), four cyclic tertiary sp^3 C groups −CHR− (4·11.7 $J \cdot K^{-1} \cdot mol^{-1}$), three groups −OH (3·23.5 $J \cdot K^{-1} \cdot mol^{-1}$), and one secondary sp^3 C group $-CH_2-$ (26.9 $J \cdot K^{-1} \cdot mol^{-1}$).

For 2′-deoxyuridine, the $C_{p,m}^{0}$ value was calculated assuming one cyclic secondary sp^3 C group $-CHR_2-$ (24.6 $J \cdot K^{-1} \cdot mol^{-1}$) instead of one cyclic tertiary sp^3 C group

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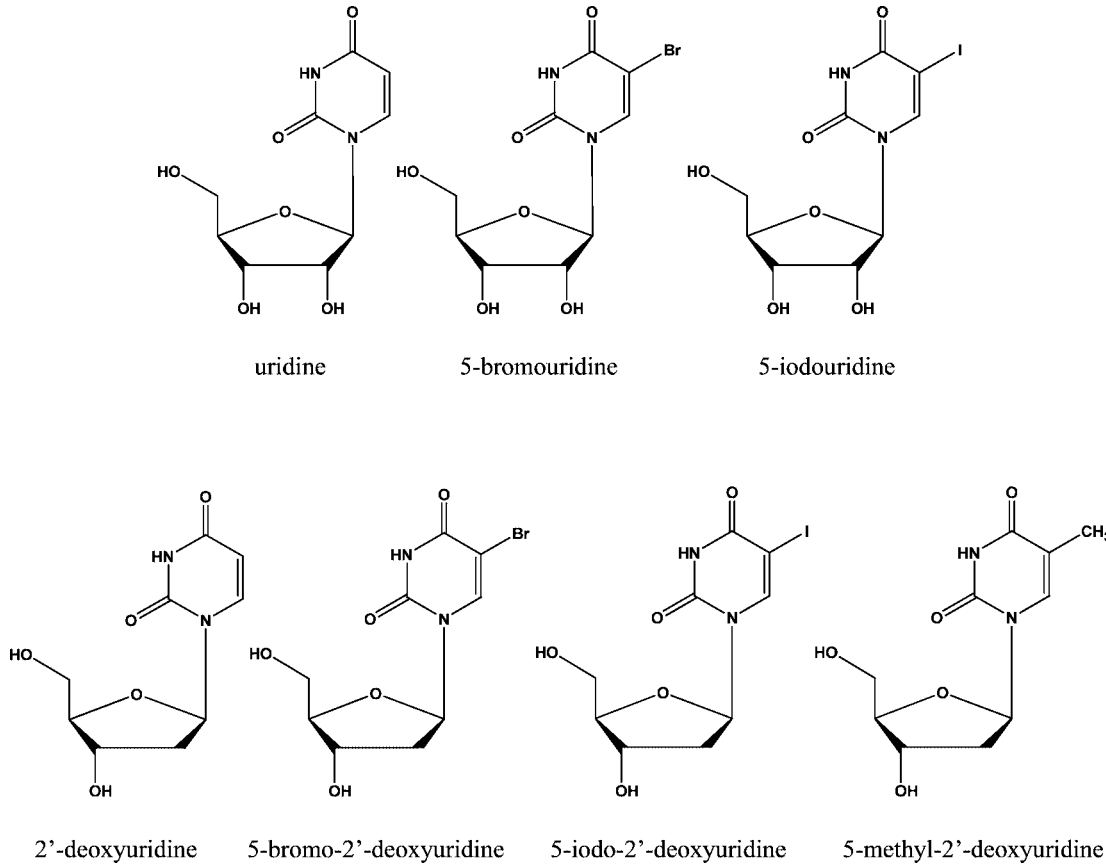

Figure 1. Structural formulas of uridine, 2′-deoxyuridine, and their derivatives.

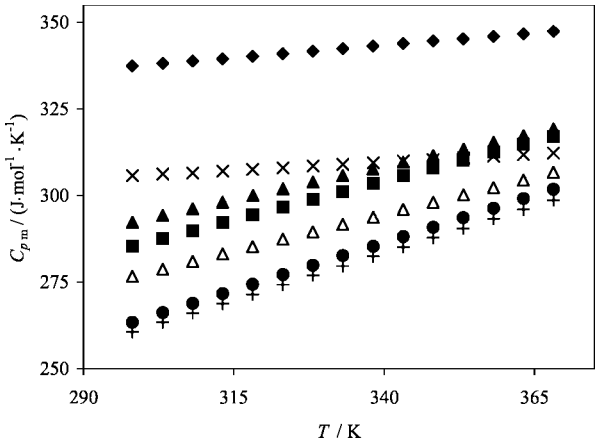

Figure 2. Temperature dependence $C_{p,m}$ of +, 5-bromo-2′-deoxyuridine; ●, 2′-deoxyuridine; Δ, 5-methyl-2′-deoxyuridine; ■, 5-iodo-2′-deoxyuridine; ▲, uridine; ×, 5-bromouridine; ◆, 5-iodouridine.

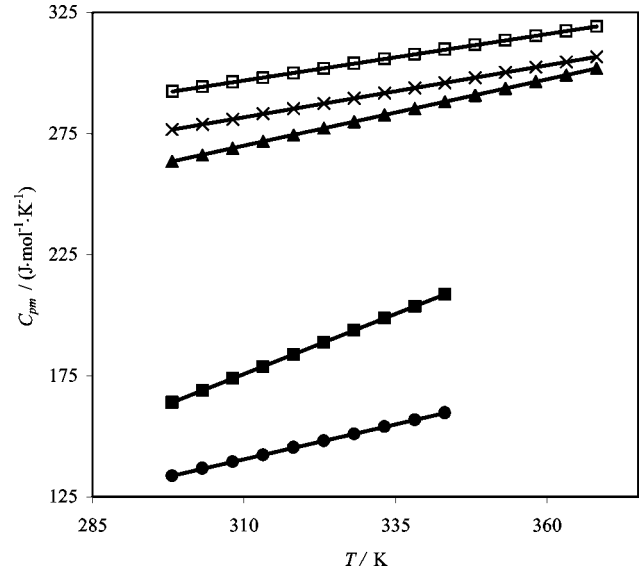

Figure 3. Temperature dependence $C_{p,m}$ of ●, uracil; ■, 5-methyluracil; ▲, 2′-deoxyuridine; ×, 5-methyl-2′- deoxyuridine; □, uridine.

−CHR− (11.7 J·K^{-1}·mol^{-1}) and one −OH group (23.5 J·K^{-1}·mol^{-1}). For calculation by the Chickos method, the $C_{p,m}{}^{0}$(Chickos) value was accepted be equal to 288.0 J·K^{-1}·mol^{-1}, whereas for 2′-deoxyuridine, the $C_{p,m}{}^{0}$ value was equal to 277.4 J·K^{-1}·mol^{-1}.

Results and Discussion

The experimentally determined $C_{p,m}$(exptl) data, the relations expressing the functions $C_{p,m} = f(T)$, and calculated values of $C_{p,m}$(calcd) were presented in Table 1. The obtained dependences $C_{p,m} = f(T)$ for seven investigated compounds are shown in Figure 2, whereas Figure 3 shows the dependences $C_{p,m} = f(T)$ for uridine, 2′-deoxyuridine, 5-methyl-2′-deoxyuridine, uracil,[9] and 5-methyluracil.[9] This comparison shows considerable differences in the values of heat capacity for derivatives of uridine and derivatives of uracil. The values of heat capacity of the presented compounds increase with an increase in their molar masses.

The values of $C_{p,m}{}^{0}$(exptl) and $C_{p,m}{}^{0}$(Chickos) were given in Table 2. In this table also were presented the differences ($\Delta = C_{p,m}{}^{0}$(exptl) − $C_{p,m}{}^{0}$(Chickos)) calculated on the basis of the values of the heat capacities determined experimentally and evaluated by the Chickos method. As can be seen from the data collected in Table 2, the $C_{p,m}{}^{0}$(Chickos) values differ from the

Table 1. Experimental (C_p(exptl)) and Approximated (C_p(calcd)) Values of Molar Heat Capacity and the Correlation Functions of Uridine, 2′-Deoxyuridine, and Their Derivatives $C_{p,m} = f(T)$

	J·K^{-1}·mol^{-1}			J·K^{-1}·mol^{-1}	
T/K	$C_{p,m}$(exptl)	$C_{p,m}$(calcd)	T/K	$C_{p,m}$(exptl)	$C_{p,m}$(calcd)
Uridine $C_{p,m}$/(J·K^{-1}·mol^{-1}) = 77.90(± 0.012) + (0.383)T/K, rmsd[a]/(J·K^{-1}·mol^{-1}) = 0.00304			5-Bromouridine $C_{p,m}$/(J·K^{-1}·mol^{-1}) = 277.58(± 0.012) + (0.094)T/K, rmsd[a]/(J·K^{-1}·mol^{-1}) = 0.00315		
298.15	292.34	292.34	298.15	305.69	305.69
303.15	294.26	294.26	303.15	306.16	306.16
308.15	296.18	296.17	308.15	306.64	306.63
313.15	298.10	298.09	313.15	307.11	307.10
318.15	300.02	300.02	318.15	307.58	307.58
323.15	301.93	301.93	323.15	308.05	308.05
328.15	303.86	303.85	328.15	308.52	308.52
333.15	305.77	305.77	333.15	308.99	308.99
338.15	307.69	307.69	338.15	309.47	309.46
343.15	309.61	309.61	343.15	309.94	309.93
348.15	311.53	311.53	348.15	310.41	310.40
353.15	313.45	313.45	353.15	310.88	310.88
358.15	315.37	315.37	358.15	311.35	311.35
363.15	317.29	317.29	363.15	311.82	311.82
368.15	319.21	319.21	368.15	312.29	312.29
5-Iodouridine $C_{p,m}$/(J·K^{-1}·mol^{-1}) = 294(± 0.012) + (0.143)T/K, rmsd[a]/(J·K^{-1}·mol^{-1}) = 0.0038			2′-Deoxyuridine $C_{p,m}$/(J·K^{-1}·mol^{-1}) = 99.72(± 0.018) + (0.550)T/K, rmsd[a]/(J·K^{-1}·mol^{-1}) = 0.00460		
298.15	337.43	337.43	298.15	263.41	263.41
303.15	338.14	338.14	303.15	266.16	266.16
308.15	338.86	338.86	308.15	268.90	268.90
313.15	339.57	339.57	313.15	271.65	271.65
318.15	340.29	340.28	318.15	274.39	274.39
323.15	341.00	341.00	323.15	277.14	277.14
328.15	341.72	341.72	328.15	279.89	279.88
333.15	342.43	342.43	333.15	282.63	282.63
338.15	343.15	343.14	338.15	285.38	285.37
343.15	343.86	343.86	343.15	288.12	288.12
348.15	344.58	344.58	348.15	290.86	290.86
353.15	345.29	345.29	353.15	293.60	293.61
358.15	346.01	346.01	358.15	296.36	296.35
363.15	346.72	346.72	363.15	299.10	299.10
368.15	347.44	347.44	368.15	301.84	301.84
5-Bromo-2′-deoxyuridine $C_{p,m}$/(J·K^{-1}·mol^{-1}) = 98.73(± 0.014) + (0.543)T/K, rmsd[a]/(J·K^{-1}·mol^{-1}) = 0.00355			5-Iodo-2′-deoxyuridine $C_{p,m}$/(J·K^{-1}·mol^{-1}) = 150.14(± 0.027) + (0.453)T/K, rmsd[a]/(J·K^{-1}·mol^{-1}) = 0.00680		
298.15	260.65	260.65	298.15	285.34	285.35
303.15	263.37	263.36	303.15	287.61	287.61
308.15	266.08	266.08	308.15	289.88	289.88
313.15	268.80	268.80	313.15	292.15	292.15
318.15	271.51	271.51	318.15	294.43	294.42
323.15	274.23	274.23	323.15	296.69	296.68
328.15	276.94	276.94	328.15	298.96	298.95
333.15	279.66	279.66	333.15	301.22	301.22
338.15	282.38	282.37	338.15	303.48	303.49
343.15	285.09	285.09	343.15	305.76	305.75
348.15	287.81	287.80	348.15	308.02	308.02
353.15	290.52	290.52	353.15	310.30	310.30
358.15	293.24	293.23	358.15	312.55	312.56
363.15	295.95	295.95	363.15	314.82	314.82
368.15	298.66	298.66	368.15	317.09	317.09
5-Methyl-2′-deoxyuridine (thymidine) $C_{p,m}$/(J·K^{-1}·mol^{-1}) =149.12(± 0.012) + (0.428)T/K, rmsd[a]/(J·K^{-1}·mol^{-1}) = 0.00309					
298.15	276.70	276.69			
303.15	278.84	278.84			
308.15	280.97	280.97			
313.15	283.12	283.12			
318.15	285.25	285.25			
323.15	287.40	287.40			
328.15	289.53	289.53			
333.15	291.68	291.67			
338.15	293.81	293.81			
343.15	295.95	295.95			
348.15	298.09	298.08			
353.15	300.23	300.23			
358.15	302.37	302.37			
363.15	304.51	304.51			
368.15	306.65	306.65			

[a] rmsd means root mean square deviation calculated from linear regression. The standard deviation of the given parameters was shown in parentheses.

$C_{p,m}{}^0$(exptl) data from (−40.15 to 30.53) J·K^{-1}·mol^{-1}. The smallest difference is in the case of uridine, 4.34 J·K^{-1}·mol^{-1}. The larger differences were observed in the case of derivatives of 2′-deoxyuridine.

Table 2. Molar Heat Capacity Data of Uridine, 2′-Deoxyuridine, and Their Derivatives at 298.15 K

		$J \cdot K^{-1} \cdot mol^{-1}$		
no.	compounds	$C_{p,m}^0$(exptl)[a]	$C_{p,m}^0$(Chickos)[b]	$C_{p,m}^0$(exptl) − $C_{p,m}^0$(Chickos)
1	uridine	292.34	288.00	4.34
2	5-bromouridine	305.69	311.40	−5.71
3	5-iodouridine	337.43	306.90	30.53
4	2′-deoxyuridine	263.41	277.40	−13.99
5	5-bromo-2′-deoxyuridine	260.65	300.80	−40.15
6	5-iodo-2′-deoxyuridine	285.34	296.30	−10.96
7	5-methyl-2′-deoxyuridine	276.70	305.00	−28.30

[a] $C_{p,m}^0$, see Table 1. [b] $C_{p,m}^0$(Chickos) values calculated using the Chickos group additivity method.[7,8]

Table 3. Contribution of Groups −OH, −Br, −I, $-CH_3$, β-D-Ribofuranosyl-, 2-Deoxy-β-D-ribofuranosyl- to $C_{p,m}^0$ at 298.15 K of Uridine and 2′-Deoxyuridine[a]

		$J \cdot K^{-1} \cdot mol^{-1}$		$J \cdot K^{-1} \cdot mol^{-1}$	
substituent	compound (1)	$C_{p,m}^0$(1)	compound (2)	$C_{p,m}^0$(2)	contribution $\Delta C_{p,m}^0$
β-D-Ribofuranosyl-	uridine	292.34	uracil[9]	131.80	160.54
β-D-Ribofuranosyl-	5-bromouridine	305.69	5-bromouracil[9]	144.70	160.99
β-D-Ribofuranosyl-	5-iodouridine	337.43	5-iodouracil[9]	150.90	186.53
−OH (2′)	uridine	292.34	2′-deoxyuridine	263.41	28.93
−OH (2′)	5-bromouridine	305.69	5-bromo-2′-deoxyuridine	260.65	45.04
−OH (2′)	5-iodouridine	337.43	5-iodo-2′-deoxyuridine	285.34	52.09
2-Deoxy-β-D-ribofuranosyl-	2′-deoxyuridine	263.41	uracil[9]	131.80	131.61
2-Deoxy-β-D-ribofuranosyl-	5-bromo-2′-deoxyuridine	260.65	5-bromouracil[9]	144.70	115.95
2-Deoxy-β-D-ribofuranosyl-	5-iodo-2′-deoxyuridine	285.34	5-iodouracil[9]	150.90	134.44
2-Deoxy-β-D-ribofuranosyl-	5-methyl-2′-deoxyuridine	276.70	5-methyluracil[9]	163.00	113.7
−Br (5)	5-bromouracil[9]	144.70	uracil[9]	131.80	12.90
−Br (5)	5-bromouridine	305.69	uridine	292.34	13.35
−Br (5)	5-bromo-2′-deoxyuridine	260.65	2′-deoxyuridine	263.41	−2.76
−I (5)	5-iodouracil[9]	150.90	uracil[9]	131.80	19.10
−I (5)	5-iodouridine	337.43	uridine	292.34	45.09
−I (5)	5-iodo-2′-deoxyuridine	285.34	2′-deoxyuridine	263.41	21.93
$-CH_3$ (5)	5-methyluracil[9]	163.00	uracil[9]	131.80	31.20
$-CH_3$ (5)	5-methyl-2′-deoxyuridine	276.70	2′-deoxyuridine	263.41	13.29

[a] The contributions were calculated on the basis of the difference between two suitable compounds: $\Delta C_{p,m}^0 = C_{p,m}^0(1) - C_{p,m}^0(2)$.

In the case of derivatives of uridine and 2′-deoxyuridine, the obtained differences show that the Chickos method does not allow for accurate determination of the $C_{p,m}^0$ value.

In Table 3 are presented the contributions of −OH (2′), −Br (5), −I (5), $-CH_3$ (5), β-D-ribofuranosyl-, and 2-deoxy-β-D-ribofuranosyl- to $C_{p,m}^0$ of uridine and 2′-deoxyuridine. The contributions $\Delta C_{p,m}^0$ were calculated on the basis of the difference of two suitable compounds: $\Delta C_{p,m}^0 = C_{p,m}^0(1) - C_{p,m}^0(2)$.

The contributions of the substituent of β-D-ribofuranosyl in uridine, 5-bromouridine, and 5-iodouridine are, respectively, (160.54, 160.99, and 186.53) $J \cdot K^{-1} \cdot mol^{-1}$.

The contributions of group −OH in position 2′ in the ring uridine in the cases of 5-bromouridine, 5-iodouridine, and uridine are as follows: (45.04, 52.09, and 28.93) $J \cdot K^{-1} \cdot mol^{-1}$, respectively. The similarity the contribution in the case of halogenated derivatives is connected with the influence of the atom of bromine and iodine.

The contributions of the substituent of 2-deoxy-β-D-ribofuranosyl in 2′-deoxyuridine, 5-bromo-2′-deoxyuridine, 5-iodo-2′-deoxyuridine, and 5-methyl-2′-deoxyuridine are as follows: (131.61, 115.95, 134.44, and 113.7) $J \cdot K^{-1} \cdot mol^{-1}$, respectively.

The contributions of the atom of bromine (Br) in the ring uracil and uridine are similar (12.90 $J \cdot K^{-1} \cdot mol^{-1}$ and 13.35 $J \cdot K^{-1} \cdot mol^{-1}$). The large differences exist in the substitution of 2′-deoxyuridine by the atom bromine (Br) (−2.76 $J \cdot K^{-1} \cdot mol^{-1}$), whereas the contributions of the atom of iodine(I) in the ring uracil, uridine, and 2′-deoxyuridine are as follows: (19.10, 45.09, and 21.93) $J \cdot K^{-1} \cdot mol^{-1}$, respectively.

The contributions of the $-CH_3$ group in the ring uracil and 2′-deoxyuridine are, respectively, (31.20 and 13.29) $J \cdot K^{-1} \cdot mol^{-1}$.

The obtained contributions (Table 3) are difficult to compare with the contribution obtained by Chickos. The contributions of Chickos[7,8] for Br, I, and CH_3 are, respectively, (23.4, 18.9, and 27.6) $J \cdot K^{-1} \cdot mol^{-1}$, and only the contribution of the atom of iodine in the case uracil and 2′-deoxyuridine, (19.10 and 21.93) $J \cdot K^{-1} \cdot mol^{-1}$, and the contribution of CH_3 (31.20 $J \cdot K^{-1} \cdot mol^{-1}$) in the case of uracil are similar to the value of Chickos.

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