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Thermochemistry of alkylated uracils in aqueous solutions. Enthalpies of hydration of 3-alkyluracils

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Abstract - Enthalpies of solution in water, ΔH^{o}_{sol}, and enthalpies of sublimation, ΔH^{o}_{sub}, were determined experimentally for a number of crystalline derivatives of uracil: 1,3,5,6-tetramethyluracil, 1,6-dimethyl-3-ethyluracil, 1,6-dimethyl-3-propyluracil 1,6-dimethyl-3-butyluracil. Standard enthalpies of hydration, ΔH^{o}_{hydr}, derived from these data were corrected for the calculated cavity terms, ΔH^{o}_{cav}, to yield enthalpies of interaction, ΔH^{o}_{int}, of the solutes with their hydration shell. The latter are discussed together with those for variously methylated uracils, obtained previously. The data obtained show that dependence of ΔH^{o}_{int} on the number of methylene groups added upon substitution with 3-n-alkyl groups of the diketopirymidine ring, is nonlinear.

INTRODUCTION

Nucleoside bases play an important role in organization of the structure of nucleic acids. Methyl and other alkyl groups on pyrimidine and purine bases are known to contribute significantly to stacking interactions between both purine and pyrimidine (ref. 1-4) bases in aqueous solutions and thus to attainment of biologically active conformations by nucleic acids.

However, little was known experimentally about energy and thermodynamics of hydration in aqueous solution. We initiated thus couple years ago systematic thermochemical studies (refs. 5,6) to determine enthalpies of solute-water interaction, ΔH^{o}_{int}. The latter were calculated from experimental values of enthalpies of sublimation ΔH^{o}_{subl}, enthalpies of solution ΔH^{o}_{sol} and semiempirically determined enthalpies of cavity formation in liquid water ΔH^{o}_{cav}. The present work is an extension of our previous investigations towards 3-alkyluracils with the aim to supplement ealier data on the effect of larger alkyl groups at C(5) and C(6) ring carbons on solvatation properties of the diketopirymidine ring (refs. 5,15).

MATERIALS AND METHODS

The compounds studied: 1,3,5,6-tetramethyluracil ($m_4^{1,3,5,6}$Ura), 1,6-dimethyl-3-ethyluracil ($m_2^{1,6}e^3$Ura), 1,6-dimethyl-3-propyluracil ($m_2^{1,6}p^3$Ura), 1,6-dimethyl-3-butyluracil ($m_2^{1,6}b^3$Ura) were synthesized by Prof.dr M. Dramiński, Military School of Medicine (Łódź, Poland) and purified by repeated crystallization and vacuum sublimation. Their purity was checked by melting point determinations using a Du Pont DSC 910 calorimeter and thermal analyzer type 1090B and chromatographic analysis in several solvent systems. All the compounds proved to be at least 99% pure. The solutions were prepared by weight using degassed and deionized distilled water.

Enthalpies of solution were determined, as it was described previously (ref.5), with use of an isoperibol calorimeter of 80 cm^3 vessel equipped by two 150 Ω thermistors and placed in water thermostat (with an accuracy better than 0.001°C). The calorimeter was calibrated by the electric Joule effect and by determination of the heat of solution of KCl in water. Values of the enthalpy of solution obtained for a series of solute concentrations were numerically extrapolated back to an infinitely diluted solution to yield ΔH^{o}_{sol}. Enthalpies of sublimation were carried out by Knudsen effusion method, described previously (ref.7).

The enthalpy of cavity formation, ΔH^{o}_{int}, were evaluated according to general formula derived by Sinagoglu (ref.8):

$$\Delta H^{o}_{cav} = k_1^{e}(\Phi_{1B}^{-1/3})\ S_B\gamma\ [1 - \frac{\delta \ln \gamma_1}{\delta \ln T} - 2/3\ \alpha_{1\beta}\ T] \qquad (1)$$

where γ_1 is the macroscopic surface tension of the solvent, S_B is solvent - accesible area of the solute, α_{1B} - the coefficient of thermal expansion appropriate to the cavity and closely approximated (ref. 9) by the solvent expansion coefficient, $k_1^e(\phi_{1B}^{-1/3}) = 1 + \phi_{1B}^{2/3}(k_1^e/1/-1)$ is a constant, dependent on the volume fraction $\phi_{1B} = V_1/V_B$. The following values of the solvent constants were used: $V_1 = 29.8$ Å^3, $\alpha_{1B} = 0.235 \cdot 10^{-3}K^{-1}$, $k^e(1) = 1.277$, $\gamma_1 = 72$ dyne cm^{-1} at 25°C.

Water accesible molecular area S_B was calculated, similarly as in the case of 2-alkyl-9-methyladenines (ref.10), by the method of static steric accesibility of atoms developed by Lavery et al (ref.11). The geometry of 3-alkiluracils was generated using mean values for bond lengths and angles from crystallographic data bases as compiled in (refs.1,12). Hydrogen atoms were added assuming C-H distance of 1.09 Å and tetrahedral bond angles. Cartesian coordinates were obtained using EUKLID program (Quantum Chemistry Program Exchange, program N-452). The mean values of solvent accesibilities obtained with radii of attacking sphere at 1.2 Å and 1.4 Å were taken. The Van der Waals volumes V_B were calculated using the program GEOPOL version 12.0 described by Silla et al. (ref.13).

DISCUSSION AND RESULTS

The experimental enthalpies of solution, ΔH^o_{sol}, sublimation, ΔH^o_{subl}, and fusion, ΔH^o_f, for 1,6-dimethyl-3-alkyluracils are collected in Table 1. The enthalpies of solution and sublimation determine the enthalpy of hydration, $\Delta H^o_{hydr} = \Delta H^o_{sol} - \Delta H^o_{subl}$, corresponding to the

Table 1 Enthalpies of solution, ΔH^o_{sol}, enthalpies of sublimation, ΔH^o_{subl}, and enthalpies of fusion, ΔH^o_f.

Compound	ΔH^o_{sol} kJ mol^{-1}	ΔH^o_{subl} kJ mol^{-1}	ΔH_f kJ mol^{-1}
$m_2^{1,6}e^3$Ura	10.15(0.4÷1.3)	77.1(307.9÷313.9)	28.3
$m_2^{1,6}p^3$Ura	12.80(0.8÷2.0)	118.5(312.0-315.8)	31.9
$m_2^{1,6}b^3$Ura	10.80(0.5÷1.3)	91.6(310.5-316.7)	28.1
$m_4^{1,3,5,6}$Ura	10.23(0.8÷1.7)	103.9(316.8-321.8)	24.6

Enthalpies of sublimation were measured over the temperature range indicated in parantheses whilst enthalpies of solution in water were determined at 25°C by measurements of heat of solution in the range of solute molalities mmol kg^{-1} shown in parantheses.

process of transfer of one mole of the solute from the gas phase to the infinitely diluted solution. The enthalpy of hydration, ΔH^o_{hydr}, contains thus the cavity term, ΔH^o_{cav}. The calculated values of ΔH^o_{cav} and then $\Delta H^o_{int} = \Delta H^o_{hydr} - \Delta H^o_{cav}$, for the compounds studied as well as for 1,3-dimethyluracil ($m_2^{1,3}$Ura), 1,3,6-trimethyluracil ($m_3^{1,3,6}$Ura), for which the enthalpies hydration were determined previously (ref. 5). are given in Table 2.

Table 2 Water - accesible molecular areas S_B and volumes V_B and enthalpies of hydration ΔH^o_{hydr}, enthalpies of cavity formation ΔH^o_{cav} and enthalpies of interaction ΔH^o_{int}

Compound	n_{CH_2}	S_B	V_B	$-\Delta H^o_{hydr}$	ΔH^o_{cav}	$-\Delta H^o_{int}$
		Å^2	Å^3		kJmol^{-1}	
$m_2^{1,3}$Ura	2	73.5	115.9	86.0^a	56.5	142.5
$m_3^{1,3,6}$Ura	3	78.4	135.7	94.4^a	59.7	154.1
$m_4^{1,3,5,6}$Ura	4	82.8	152.0	93.7	62.7	156.4
$m_2^{1,6}e^3$Ura	4	83.9	152.1	66.9	63.4	130.3
$m_2^{1,6}p^3$Ura	5	91.6	173.0	105.7	68.7	174.4
$m_2^{1,6}b^3$Ura	6	98.7	181.7	80.8	73.9	154.7

^{a}from (ref. 6)

As it was shown earlier each methyl substitution brings about an increase in the enthalpy of interaction. In the series of 5-alkyluracils contribution of succesive CH_2 groups to ΔH^o_{int} decreased monotonically (ref.5). In the presently studied series of 3-alkyluracils elongation of n-alkyl chain by succesive CH_2 groups is first accompanied by an increase in ΔH^o_{hydr} and ΔH^o_{int} values, which then vary in an erratic way. Namely, the two parameters decrease on going from $m_3^{1,3,6}$Ura to $m_2^{1,6}e^3$Ura, increase for $m_2^{1,6}p^3$Ura and finally again decrease for the last member in the series i.e. $m^{1,6}$but^{3}Ura. Very similar relation between ΔH^o_{hydr} and ΔH^o_{int} has been observed by us for 6-alkyluracils (unpublished). All this indicates that contribution of n-alkyl chains to

ΔH^{o}_{int} and ΔH^{o}_{hydr} is not additive. However, as is it has been demonstrated by Cp^{o}_{2} and V^{o}_{2} determinations (ref. 14), the contribution to ΔH^{o}_{int} from Van der Waals interaction is almost additive. We can thus conclude therefrom, that the effect observed comes for the most part from variation of largerly electrostatic in nature water-solute interaction. In order to get an insight into the underlying varation in the hydration scheme of the diketopirymidine ring, expected to be influenced by conformation of substituted n-alkyl chains, further thermodynamical and NMR spectroscopic studies will be attempted.

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