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THERMODYNAMIC PROPERTIES OF AQUEOUS SOLUTION OF 1,N^2-(PROP-1-ENE-1,2-DIYL)ACYCLOVIR

A. Zielenkiewicz[1], *G. L. Perlovich*[1*] *and B. Golankiewicz*[2]

[1]Institute of Physical Chemistry, Polish Academy of Sciences, Kasprzaka 44/52
01-224 Warsaw
[2]Institute of Bioorganic Chemistry, Polish Academy of Sciences, Noskowskiego 12/14
61-704 Poznań, Poland

Abstract

A description of experimental thermodynamic data of aqueous solutions of 1,N^2-(prop-1-ene-1,2-diyl)acyclovir in the range of molality 0.008237–0.018331 mol kg^{-1} is provided on the basis of differential scanning adiabatic calorimetry and densimetry. The enthalpy of hydration from the experimental enthalpy of solution and the enthalpy of sublimation was determined ($\Delta_m H_{hydr}$= −124.1 kJ mol^{-1}). The non-linear variations of apparent molar heat capacities with temperature and concentration were observed. The apparent molar volumes increase with temperature in the range of 25–45°C.

Keywords: 1,N^2-(prop-1-ene-1,2-diyl)acyclovir, antiviral agent, apparent molar volumes and heat capacities, density, enthalpy of hydration, enthalpy of solution

Introduction

The discovery of acyclovir, 9-[(2-hydroxyethoxy)methyl] guanine **1** (Fig. 1), the first potent and selective antiviral drug has stimulated the synthesis of its analogues. Modifications of the acyclic side chain of **1** have given rise to several compounds of significant antiviral activity e.g. ganciclovir, penciclovir. On the contrary for a long time modifications of guanine moiety of **1** were reported as virtually annihilating the antiviral activity.

1,N^2-(prop-1-ene-1,2-diyl)acyclovir **2** (Fig. 1), has been found to be a first base modified analogue of **1** of marked and selective antiherpetic activity [1]. It has become a lead compound for the development of further tricyclic congeners with additional desired properties (e.g. fluorescence) [2, 3].

In this paper the first results of the determinations of the thermodynamic properties of aqueous solutions of **2**, namely the enthalpy of solution, densities,

* Permanent address: Institute of Non-Aqueous Solutions Chemistry, Russian Academy of Sciences, Akademicheskaya 1, 153045 Ivanovo, Russia

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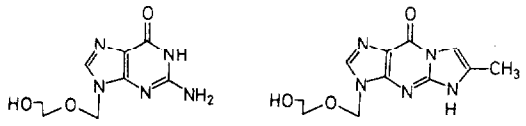

1 2

Fig. 1 Structural formula of 9-([2-hydroxyethoxy)methyl] guanine (1) and 1,N^2-(prop-1-ene-1,2-diyl)acyclovir (2)

variation of the apparent molar volumes and heat capacities as the functions of molality are reported.

Experimental

1,N^7-(prop-1-ene-1,2-diyl)acyclovir* was synthesized in the Institute of Bioorganic Chemistry PAN, Poznań, Poland. It was thoroughly purified by crystallization and then carefully dried. The melting temperature (T_f=201.3°C) was checked by DSC DuPont Thermal Analyzer Model 910.

The solutions were prepared by weight using deionized, distilled water. The densities of the solutions relative to the density of pure water were measured using an Anton Paar DMA 60/602 digital densimeter equipped with a Hetoterm thermostat model C8–7 to ensure the temperature stability of ±0.01°C. The calibration constant of the densimeter was determined daily using reference fluids of well known densities (water and dry air) leading to uncertainties of densities less than $5 \cdot 10^{-6}$ g cm^{-3}.

The heat capacities per unit volume of the solution were measured relatively to that of water using a differential adiabatic scanning microcalorimeter DASM-4 for which the volume of each vessel was 0.47 cm^3. The measurements were performed at fixed heating rate of 1 K min^{-1} in the range of 10–60°C. The instrument and working procedure have been described elsewhere [4].

The apparent molar volumes and heat capacities were determined from experimental densities and heat capacities per unit volume, using the usual expressions [5] and molecular weight equal to 263.28.

Enthalpies of solution at 25°C were determined by the measurements of heat of solution of crystalline sample using an isoperibol, solution calorimeter equipped with an 80 cm^3 steel vessel. Sensitivity of the device was $1 \cdot 10^{-2}$ J min^{-1}. The calorimeter was calibrated by the Joule effect and by the determination of the heat of solution of KCl. The obtained value of the enthalpy of solution of KCl corresponds to 17.59±0.03 kJ mol^{-1} and is in good agreement with the literature data [6].

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* IUPAC systematic name:
3,9-dihydro-3[(2-hydroxyethoxy)-methyl]-6-methyl-9-oxo-5*H*-imidazol[1,2*a*]-purine

The enthalpy of sublimation was obtained (149±1 kJ mol^{-1}) [7] by the determination of vapour pressure using the inert gas flow method [8].

Results

The results of determination of densities, apparent molar volumes and heat capacities of the aqueous solutions of the solute at 25, 35, 45°C are reported in Table 1, where m, d and V_φ, are molality, density of solution, and apparent molar volume, respectively. Due to the magnitude of experimental error, it was assumed, that calculated mean values of V_φ in the concentration range studied are identical to the partial molar volumes V_2^0 and correspond to 163.2±0.2, 164.7±0.3 and 166.8±0.2 cm^3 mol^{-1} for 25, 35 and 45°C, respectively. The determined values of apparent molar heat capacities $C_{p\varphi}$ calculated for m=0.008237 mol kg^{-1} and temperatures 25, 35 and 45°C correspond to 480.4 J K^{-1} mol^{-1}, 500.8 J K^{-1} mol^{-1}, 487 J K^{-1} mol^{-1}, respectively. As results from these data, at the temperature 35°C the calculated $C_{p\varphi}$ has the greatest value. The non-linear variations of $C_{p\varphi}$ with temperature are observed in the whole range of the concentration studied as follows from microcalorimetric DASM recordings (Fig. 2).

Table 1 Apparent molar volumes of 1,N^2-(prop-1-ene-1,2-diyl)acyclovir

25°C		35°C			45°C	
m/ mol kg^{-1}	d/ g cm^{-3}	V_φ/ cm^3 mol^{-1}	d/ g cm^{-3}	V_φ/ cm^3 mol^{-1}	d/ g cm^{-3}	V_φ/ cm^3 mol^{-1}
0.008237	0.997859	164.1	0.994840	165.1	0.991010	166.4
0.010086	0.998052	163.1	0.995033	164.0	0.991190	166.4
0.012504	0.998290	163.4	0.995260	165.1	0.991411	167.5
0.013369	0.998373	163.6	0.995339	165.5	0.991494	167.6
0.015195	0.998572	162.5	0.995534	164.4	0.991684	166.6
0.018331	0.998881	162.8	0.995853	163.9	0.991990	166.4

The variation of $C_{p\varphi}$ with concentration can be also noticed (Fig. 3). From the molality 0.008237 mol kg^{-1} to 0.015195 mol kg^{-1} the increments of $C_{p\varphi}$ correspond to: 9.0 J K^{-1} mol^{-1}, at 25°C; 11.3 J K^{-1} mol^{-1} at 35°C and 16.9 J K^{-1} mol^{-1} at 45°C.

The results of determination of the enthalpy of solution in water at 25°C are reported in Table 2, where m, m_2, m_{H_2O}, $\Delta_m H_{sol}$ are molality of solution, mass of solute, mass of water and enthalpy of solution at molality m, respectively. Due to low range of concentrations studied it was assumed that the mean value of the determined enthalpies of solution of determined is equal to the enthalpy of solution at infinite dilution $\Delta_m H^0_{sol}$=24.9±0.2 kJ mol^{-1}. Taking into account the value of the

enthalpy of sublimation the enthalpy of hydration corresponds to $\Delta_m H_{hydr}$= −124.1 kJ mol^{-1}.

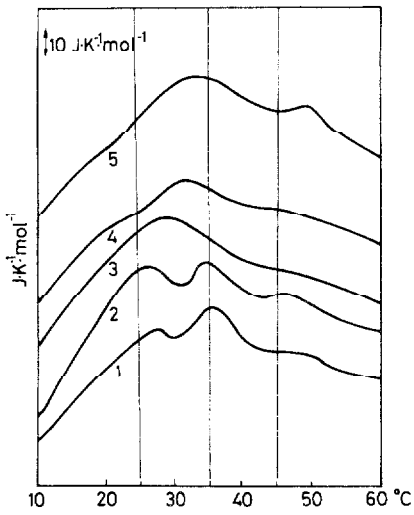

Fig. 2 DSC plots for various molalities of 1,N^2-(prop-1-ene-1,2-diyl)acyclovir 1 – 0.008237 mol kg^{-1}; 2 – 0.010086 mol kg^{-1}; 3 – 0.012504 mol kg^{-1}; 4 – 0.013368 mol kg^{-1}; 5 – 0.015195 mol kg^{-1}

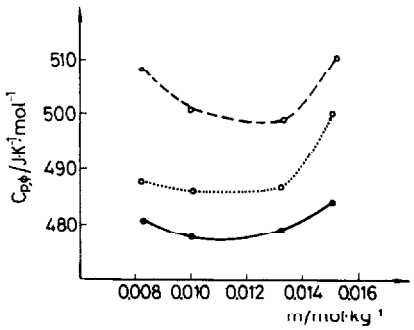

Fig. 3 Apparent molar heat capacity as a function of molality at 25°C (—), 35°C (- - -) and 45°C (···)

Table 2 Enthalpy of solution at 25°C

m/ mol kg^{-1}	m_2/ 10^{-3} g	m_{H_2O}/ g	$\Delta_m H_{sol}$/ kJ mol^{-1}
0.000338	5.71	64.2190	24.9
0.000363	6.15	64.3502	25.8
0.000389	6.57	64.0340	24.4
0.000378	6.38	64.0526	24.6

The determination of the densities, the standard enthalpy of solution and the enthalpy of hydration of the antiviral agent studied can be useful in understanding of its interactions with enzymes. The observed variation of $C_{p\varphi}$ with temperature and concentration is so intriguing that it should also be analyzed by other physicochemical techniques.

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