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THERMODYNAMIC INVESTIGATIONS OF INTERACTION OF AQUEOUS SOLUTIONS OF 2',3'-DIDEOXYINOSINE AND 2',3'-DIDEOXY-ADENOSINE WITH GLYCYL–GLYCINE

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Abstract

2'3'-dideoxyinosine (ddI) and 2'3'-dideoxyadenosine (ddA) are known to exhibit relatively selective activity *vs.* HIV strains in cell cultures and low toxicity *in vivo*; ddI has been approved for the treatment of HIV infection in humans. It is therefore interesting to determine the thermodynamic properties of aqueous solutions of these compounds. For this purpose, we determined their apparent molar volumes V_φ and heat capacities $C_{p\varphi}$. The preliminary measurements of interaction of these compounds with peptides were made. The volume and molar heat capacities of transfer of ddI and ddA from aqueous solutions to glycyl–glycine (Gly–Gly) ones were calculated. For both compounds the significant values of $C_{p\varphi 3,tr}$ which depended on the concentration of Gly–Gly were observed.

Keywords: 2'3'-dideoxyinosine, 2'3'-dideoxyadenosine, interactions with glycyl–glycine

Introduction

Since the discovery of the human immunodeficiency virus (HIV) as the etiological agent of AIDS, a number of nucleoside analogues have been developed as potential anti-AIDS drugs. Of the compounds characterized in terms of anti-HIV activity in the pioneering work of Mitsuya and Broder [1], 2'3'-dideoxyinosine (ddI) and 2'3'-dideoxyadenosine (ddA) – Fig. 1 have been shown to exhibit relatively selective activity against HIV strains in cell culture and low toxicity *in vivo*; ddI has recently been approved for the treatment of HIV infection in humans (for recent reviews see references [2, 3]).

Finding the thermodynamic properties of aqueous solutions of ddI and ddA is therefore of interest as a basis for further work aimed towards determination of the interactions of these compounds with amino acids, peptides and proteins.

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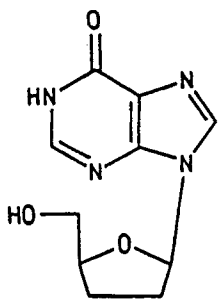
As an example of the procedure chosen for the determination of the interactions of aqueous solutions of **1** and **2** with peptides, the results of experiments with glycyl–glycine (Gly–Gly) are now presented.

Table 1 Partial molar heat capacities and volumes of ddI and ddA in aqueous solutions at 25°C

Compound	m_2 / mol·kg^{-1}	d_2 / g·cm^{-3}	$V_{\varphi 2}$ / cm^3·mol^{-1}	$C_{p\varphi 2}$ / J·K^{-1}·mol^{-1}
ddI	0.038103	0.999895	161.25	487.9
	0.038111	0.999917	160.68	490.0
	0.041356	1.000157	160.75	489.0
		average:	160.89(0.2)	489.0(0.6)
ddA	0.032913	0.999174	170.57	622.4
	0.037048	0.999500	168.92	626.6
	0.037101	0.999518	168.53	624.6
	0.037133	0.999525	168.39	629.7
	0.037161	0.999487	169.48	634.8
	0.037232	0.999495	169.39	634.0
		average:	169.21(0.3)	628.7(2.0)

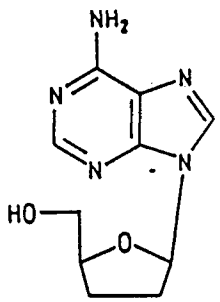
Materials and methods

2'3'-dideoxyinosine was synthesized in the Institute of Bioorganic Chemistry using modified procedure of Webb II *et al.* [4]. 2'3'-dideoxyadenosine and glycyl–glycine were commercial products obtained from Sigma. The solutions were prepared by weight using degassed and deionized distilled water.



2',3'-dideoxyinosine

(ddI)



2',3'-dideoxyadenosine

(ddA)

Fig. 1 The structural formulas of 2'3'-dideoxyinosine and 2'3'-dideoxyadenosine

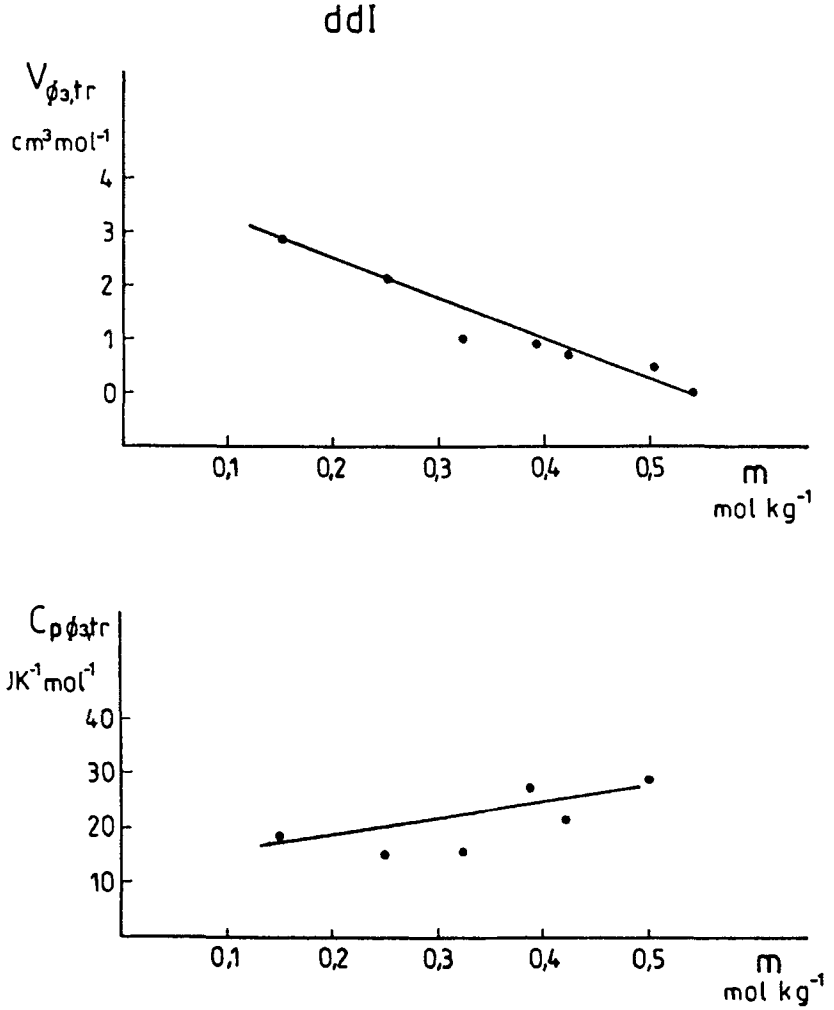


Fig. 2 The transfer properties $V_{\varphi 3,tr}$ and $C_{p\varphi 3,tr}$ of 2'3'-dideoxyinosine along with the molality of Gly–Gly solutions

The densities were determined with Anton Paar DMA 60/602 ZM digital densimeter. Measurements were carried out in the micro cell of 0.3 cm^3 volume at 298.15 ±0.05 K. The temperature stability obtained by Heto Model CB-7 thermostat was ±0.002 deg. All the solution densities were measured relative to that of pure water. The calibration constant of the densimeter was determined daily using the known densities of water and dry air. Under these conditions the uncertainties was equal to $1 \cdot 10^{-5} g \cdot cm^{-3}$.

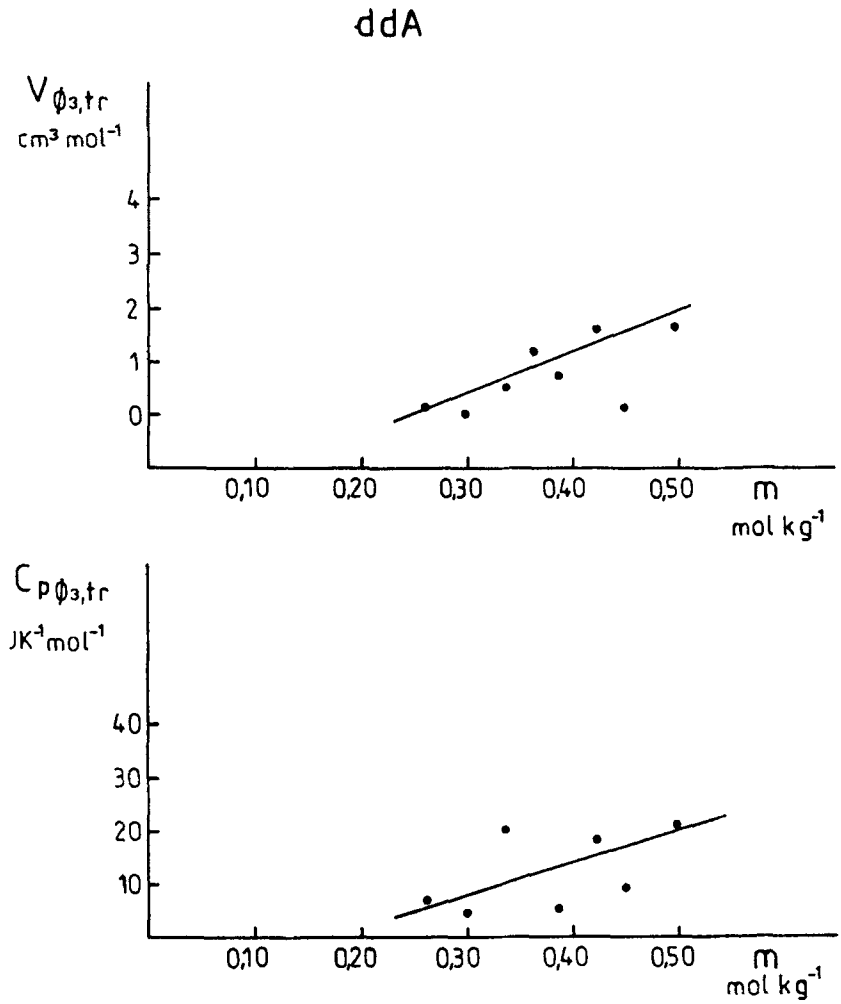


Fig. 3 The transfer properties $V_{\varphi 3,tr}$ and $C_{p\varphi 3,tr}$ of 2'3'-dideoxyadenosine along with the molality of Gly–Gly solutions

The apparent molar volumes V_φ of the solutes were calculated from the experimental values of density (Table 2) according to the relation

$$V_\varphi = \frac{M}{d} - 1000\,\frac{d - d_o}{mdd_o}$$

where M is the molar mass of the solute; d and d_o are the densities of the solution and solvent, respectively, and m is the molality of the solution.

Table 2 Partial molar heat capacities and volumes of ddI (3) and ddA (3) in aqueous solutions of Gly–Gly (2) at 25°C

Compound	m_2 /	m_3 /	d_2 /	d_3 /	$V_{\varphi 2}$ /	$V_{\varphi 3}$ /	$C_{p\varphi 3}$ /
	mol·kg^{-1}		g·cm^{-3}		cm^3·mol^{-1}		J·K^{-1}·mol^{-1}
ddI	0.541380	0.038334	1.025846	1.028624	76.79	160.95	–
	0.505868	0.038399	1.023991	1.026762	76.86	161.41	517.4
	0.424404	0.038119	1.019733	1.022492	76.99	161.59	510.1
	0.391492	0.038097	1.018013	1.020767	77.02	161.83	516.1
	0.324957	0.037818	1.014536	1.017279	77.03	161.91	505.0
	0.250433	0.038077	1.010642	1.013372	76.86	163.08	504.0
	0.151107	0.037954	1.005451	1.008165	75.93	163.74	508.4
ddA	0.495939	0.036913	1.013709	1.023384	77.06	170.80	648.5
	0.456555	0.037124	1.021360	1.023707	–	169.34	637.8
	0.429091	0.037200	1.015596	1.019938	77.08	170.81	646.5
	0.386643	0.036786	1.017750	1.018897	77.05	169.85	632.9
	0.363650	0.037183	1.016565	1.020071	77.02	170.34	–
	0.341228	0.037133	1.015409	1.017767	76.97	169.70	648.8
	0.299020	0.036777	1.013233	1.022239	76.82	169.20	632.5
	0.262076	0.037009	1.011328	1.025653	76.60	169.31	634.3

For the measurements in water d_o represents the density of water and d – the density of ddI (or ddA) in water. For measurements in Gly–Gly solutions, d_o denotes the density of aqueous Gly–Gly solutions whereas d – the density of solution of ddI (or ddA) in the water/Gly–Gly mixture.

Table 3 Partial molar heat capacities and volumes of transfer

Compound	m_2 / mol·kg^{-1} Gly–Gly	$V_{\varphi 3,tr}$ / cm^3·mol^{-1}	$C_{p\varphi 3,tr}$ / J·K^{-1}·mol^{-1}
ddI	0.541380	0.06	–
	0.505868	0.52	28.4
	0.424404	0.70	21.1
	0.391492	0.94	27.1
	0.324957	1.02	16.0
	0.250433	2.19	15.0
	0.151107	2.85	19.4
ddA	0.495939	1.59	19.8
	0.456555	0.13	9.1
	0.429091	1.60	17.8
	0.386643	0.64	4.2
	0.363650	1.13	–
	0.341228	0.49	20.1
	0.299020	-0.01	3.8
	0.262076	0.10	5.6

Apparent molar heat capacities $C_{p\varphi}$ of the compounds studied in aqueous binary and ternary solutions (ddI or ddA + water + Gly–Gly) were obtained in the temperature range 10–30°C, using the differential adiabatic scanning microcalorimeter, model DASM-4. The instrument and working procedure have been described elsewhere [5]. The measurements were performed at heating rate of 1 deg·min^{-1}. The volume of each vessel was 0.47 ml. The actual parameter measured in this microcalorimeter is the compensation power ΔP, which is related to $C_{p\varphi}$ at a given temperature according to the following equation

$$C_{p\varphi} = C_{p1}^{o} \cdot V_2 \cdot V^{-1} - \Delta P \cdot m_2^{-1}$$

where C_{p1}^{o} is the specific heat of liquid water, V_1 its specific volume; V_2 the specific volume of the solute and m_2 its mass content per 1 ml of solution.

Results

All the experimental results are shown in Tables 1 and 2.

According to data in Table 1 the apparent molar volume of ddI correspond to 160.9(0.2) $cm^3 \cdot mol^{-1}$ whereas that of ddA is 169.2(0.3) $cm^3 \cdot mol^{-1}$; the values of apparent molar specific heat are 489.0(0.6) $J \cdot K^{-1} \cdot mol^{-1}$ and 628.7(2.0) $J \cdot K^{-1} \cdot mol^{-1}$, respectively.

The $V_{\varphi 3,tr}$ and $C_{p\varphi 3,tr}$ values are given in Table 3 and presented on Figs 2 and 3. It is interesting that whereas $V_{\varphi 3,tr}$ shows increasing tendency with increasing Gly–Gly concentration, this tendency is reverse for ddI. $C_{p\varphi 3,tr}$ values always increase with Gly–Gly concentration.

There observations, which should be only treated as qualitative and introductory, will be further investigated in our studies of interactions of underside analogues with peptides.

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Zusammenfassung — 2',3'-Didesoxyinosin (ddI) und 2'3'-Didesoxyadenosin (ddA) sind bekannt für ihre relativ hohe selektive Aktivität gegenüber HIV-Rassen in Zellkulturen und für ihre niedrige *in vivo* Toxizität; ddI wird für die Behandlung von HIV-Infektionen beim Menschen empfohlen. Es ist deshalb von Interesse, die thermodynamischen Eigenschaften wäßriger Lösungen dieser Verbindungen zu bestimmen. Hierzu bestimmten wir deren scheinbares molares Volumen V_φ und die Wärmekapazitäten $C_{p\varphi}$. Einführende Messungen an den Wechselwirkungen dieser Verbindungen mit Peptiden wurden unternommen. Das Volumen und die molaren Wärmekapazitäten des Überganges von ddI und ddA aus der wäßrigen Lösung in Glycylglycinlösungen (Gly-Gly) wurden berechnet. Bei beiden Verbindungen wurden die signifikanten Werte für $C_{p\varphi 3,tr}$ beobachtet, die von der Konzentration von Gly-Gly abhängen.