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Thermodynamic Characteristics of Protolytic Equilibria of L-valyl-L-valine in Aqueous Solution

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Abstract—Direct calorimetric method was used to determine the heat of reaction of L-valyl-L-valine stepwise dissociation. The standard thermodynamic characteristics of the studied equilibria were established. The results are compared with the corresponding data for related compounds.

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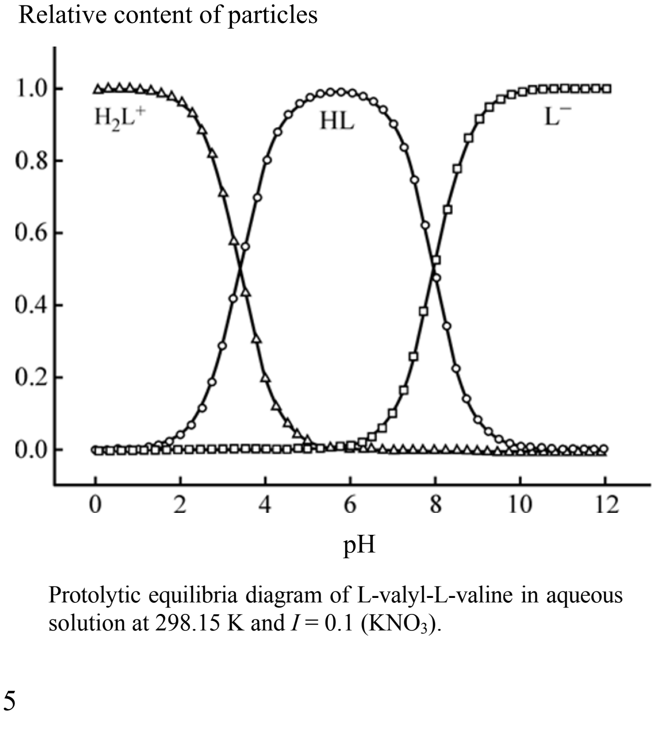
A single paper is published [1] on the determination of the thermal effects of the processes of acid–base interactions in solutions of L-valyl-L-valine (HL). Heats of dissolution of the crystalline dipeptide in water were measured at 298.15K (–13.48 kJ mol^{-1}) and 1.0 m solutions of hydrochloric acid and sodium hydroxide (–11.68 and –21.76 kJ mol^{-1}, respectively). From these data the heat effects of the reaction of stepwise dissociation [$\Delta_{dis}H^0$ (H_2L^+) –1.80 and $\Delta_{dis}H^0$ (HL) 47.67 kJ mol^{-1}] were estimated and reduced to the standard state. In general, this approach is not quite correct, because the measured values correspond to different final states. In addition, there are no data on the concentration dependence of the thermal effects of the processes studied. The absence of such important information necessitates additional calorimetric studies of protolytic equilibria of L-valyl-L-valine. The purpose of this paper is to measure the thermal effects of dissociation of this dipeptide at several ionic strengths and to determine standard thermodynamic characteristics of the equilibria.

The equilibrium diagram (see figure) shows that the thermal effects of dissociation of the species H_2L^+ and HL can be found as a difference between the respective heats of mixing and dilution:

$$\Delta_{dis}H = -(\Delta_{mix}H - \Delta_{dil}H)/\alpha, \quad (1)$$

where $\Delta_{mix}H$ is the heat of mixing of the solution with a solution of L-valyl-L-valine in HNO_3 in the presence of the "background" electrolyte in the respective area of pH; $\Delta_{dil}H$ is the heat of dilution of HNO_3 solution in the "background" electrolyte at the same ionic strength; a is the completeness of the protonation reactions of the particles HL and L^-. The obtained values of the thermal effects of dissociation of L-valyl-L-valine at 298.15K and I = 0.1, 0.5, 1.0 (KNO_3) are shown in Table 1. The $\Delta_{dis}H$ values found in this paper at I = 1.0 are consistent within the experimental error with the results of [1] obtained under similar concentration conditions (1.0 M HCl and NaOH).

The found $\Delta_{dis}H$ values at a fixed ionic strength allow the calculation of the standard thermodynamic characteristics of the investigated equilibria. To extrapolate the concentration of thermal effects to zero



Protolytic equilibria diagram of L-valyl-L-valine in aqueous solution at 298.15 K and I = 0.1 (KNO_3).

Table 1. Thermal effects of dissociation of L-valyl-L-valine at 298.15 K

Process	$\Delta_{dis}H$, kJ mol^{-1}		
	$I = 0.1$	$I = 0.5$	$I = 1.0$
$H_2L^+ = H^+ + HL$	–1932±250	–1621±235	–1663±271
$HL = H^+ + L^-$	46455±397	47411±324	47784±316
$H_2L^+ = 2H^+ + L^-$	44523±469	45790±400	46121±416

ionic strength, we used the equation with one individual parameter [2].

$$\Delta_{dis}H - \Delta z^2\Psi(I) = \Delta_{dis}H^0 + bI, \quad (2)$$

where $\Delta_{dis}H$ and $\Delta_{dis}H^0$ are changes of the reaction enthalpy at the final and zero ionic strength, b is empirical coefficient, Δz^2 is the difference between the squares of the charges of the reaction products and the reacting species; $\Psi(I)$ is a function of ionic strength, calculated theoretically [2]. The corresponding values of the thermodynamic dissociation constants of L-valyl-L-valine were calculated according to the Vasil'ev equation [2].

$$pK^0 = pK + A\Delta z^2[I^{1/2}/(1 + 1.6I^{1/2}) - 0.05I] + 0.05I. \quad (3)$$

Here K^0 and K are thermodynamic and concentration dissociation constants, respectively, A is the Debye–Huckel constant. Concentration dissociation constant values of dipeptide were found in [3]. Standard thermodynamic characteristics of dissociation of L-valyl-L-valine are shown in Table 2. The table also presents the results of calorimetric studies of D,L-alanyl-D,L-leucine [4], D,L-alanyl-D,L-alanine [5], D,L-

Table 2. The standard thermodynamic characteristics of dissociation of some dipeptides in aqueous solution

Dipeptide	pK^0	$\Delta_{dis}G^0$, kJ mol^{-1}	$\Delta_{dis}H^0$, kJ mol^{-1}	$-\Delta_{dis}S^0$, J mol^{-1} K^{-1}
L-valyl-L-valine, $H_3N^+CH(CH(CH_3)_2)CONHCH[CH(CH_3)_2]COO^-$ (1.3+1.3)[a]				
$H_2L^+ = H^+ + HL$	3.38±0.01	19.29±0.06	–1.89±0.26	71.0±0.9
$HL = H^+ + L^-$	8.18±0.03	46.69±0.17	46.04±0.40	2.2±1.5
D,L-alanyl-D,L-leucine, $H_3N^+CH(CH_3)CONHCH[CH_2CH(CH_3)_2]COO^-$ (0.5+1.8)[a]				
$H_2L^+ = H^+ + HL$	3.24±0.01	18.49±0.06	–1.54±0.17	67.2±0.6
$HL = H^+ + L^-$	8.48±0.03	48.40±0.17	45.97±0.23	8.2±1.0
D,L-alanyl-D,L-alanine, $H_3N^+CH(CH_3)CONHCH(CH_3)COO^-$ (0.5+0.5)[a]				
$H_2L^+ = H^+ + HL$	3.12±0.01	17.81±0.06	–1.72±0.11	65.5±0.5
$HL = H^+ + L^-$	8.54±0.01	48.75±0.06	45.89±0.56	9.6±1.9
D,L-alanyl-glycine, $H_3N^+CH(CH_3)CONHCH_2COO^-$ (0.5+0.0)[a]				
$H_2L^+ = H^+ + HL$	3.18±0.03	18.15±0.17	0.74±0.11	58.4±0.7
$HL = H^+ + L^-$	8.35±0.03	47.66±0.17	45.14±0.22	8.5±0.9
Glycyl-glycine, $H_3N^+CH_2CONHCH_2COO^-$ (0.0+0.0)[a]				
$H_2L^+ = H^+ + HL$	3.16±0.01	18.04±0.06	0.61±0.14	58.5±0.5
$HL = H^+ + L^-$	8.31±0.01	47.43±0.06	44.19±0.33	10.9±1.1
Glycyl-β-alanine, $H_3N^+CH_2CONHCH_2CH_2COO^-$				
$H_2L^+ = H^+ + HL$	4.04±0.02	23.06±0.29	1.36±0.18	72.8±1.1
$HL = H^+ + L^-$	8.37±0.06	47.78±0.34	42.97±0.28	16.1±1.5
β-Alanyl-β-alanine, $H_3N^+CH_2CH_2CONHCH_2CH_2COO^-$				
$H_2L^+ = H^+ + HL$	4.02±0.02	22.93±0.11	2.42±0.28	68.8 ± 1.0
$HL = H^+ + L^-$	9.59±0.03	54.74±0.15	46.70±0.28	27.0 ± 1.3
β-Alanyl-glycine, $H_3N^+CH_2CH_2CONHCH_2COO^-$				
$H_2L^+ = H^+ + HL$	3.24±0.03	18.49±0.15	1.24±0.15	57.9±0.7
$HL = H^+ + L^-$	9.62±0.08	54.91±0.46	47.83±0.21	23.7±1.7

[a] In the parentheses the values of the Ganesh indices characterizing the hydrophobicity of the side aliphatic substituents in the corresponding "betaine" and carboxylate fragments of dipeptides are given [12].

alanyl-glycine [6], glycyl-glycine [7] glycyl-β-alanine [8], β-alanyl-β-alanine [9] and β-alanyl-glycine [10] performed in our laboratory previously using similar experimental procedure.

Comparison of the acid–base properties of these compounds shows that the dissociation of "betaine" groups is characterized by similar values of the thermodynamic properties in the series L-valyl-L-valine–D,L-alanyl-D,L-leucine–D,L-alanyl-D, L-alanine–D,L-alanyl-glycine–glycyl-glycine. At the same time, there is a significant change in the thermal effect and the entropy of the dissociation of the carboxyl group in going from L-valyl-L-valine, D,L-alanyl-D,L-leucine, and D,L-alanyl-D,L- alanine to D,L-alanyl-glycine and glycyl-glycine. Exothermicity of the dissociation of the carboxy groups of L-valyl-L-valine, D,L-alanyl-D,L-leucine and D,L-alanyl-D,L-alanine is due apparently to the presence of hydrophobic substituents in both dipeptide fragments: Alkyl groups of these dipeptides form a medium with low dielectric constant, thus increasing the interaction of ammonium cation and carboxylate anion [5]. The increased interaction of oppositely charged ions can also affect the distribution of the solvent molecules around the solvated molecules of dipeptides and, therefore, cause a decrease in $\Delta_{\text{dis}}S^0$ of the carboxy groups dissociation generated by "binding" a large number of water molecules by the zwitter-ions of L-valyl-L-valine D,L-alanyl-D,L-leucine, and D,L-alanyl-D,L-alanine, compared with D,L-alanine-glycine and glycyl-glycine. The introduction of additional methylene units in the glycine fragments of the dipeptides in going from glycyl-glycine to glycyl-β-alanine, β-alanyl-glycine and further to β-alanyl-β-alanine significantly lowers acidity of the corresponding carboxylic acid or "betaine" group by increasing the inductive effect of the hydrocarbon chain and, in addition, increases the hydration of dipeptides by increasing the distance between the carriers of positive and negative charges. Such a change in the thermodynamic characteristics at replacing of glycine fragments by β-alanine is observed [11] for the protolytic equilibria of several amino acids and complexing agents.

EXPERIMENTAL

We used in this paper L-valyl-L-valine of analytical grade from "Reanal" company (Hungary). Dipeptide solutions were prepared by dissolving the weighed samples in freshly double-distilled water immediately prior to the experiment. KNO_3 and KOH solutions were prepared from chemically pure reagents. The working solutions concentration was determined by the usual titrimetric methods. Reagent KNO_3 (analytical grade) used to support the ionic strength was previously twice recrystallized from double-distilled water.

To perform calorimetric measurements an ampule calorimeter was used with an isothermal shell and thermistor temperature sensor, with automatic recording of temperature changes over time. At 298.15 K and ionic strength 0.1, 0.5, 1.0 (KNO_3) were measured the thermal effects of mixing a solution of HNO_3 (0.9439 mol kg^{-1} of solution) with a 0.0054–0.0080 M solution of dipeptide at pH 4.9→2.7 and 8.4→7.5. To introduce the necessary corrections the heats of dilution of HNO_3 solution in the "background" electrolyte with the corresponding values of the ionic strength were also measured.

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