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The thermodynamics of dipeptides in water. Part IV. Calorimetric study of the influence of methyl and isopropyl chains on the free α-carboxyl and free α-amino groups

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Abstract

We have made calorimetric measurements to obtain the ΔH° values for the dissociation processes of an aqueous series of dipeptides at 298.15 K, and have considered these results in relation to those from another series of dipeptides, previously studied, in an effort to compare the effects of different chains on the ionization processes of free α-carboxyl and α-amino groups.

Keywords: Dipeptides; Calorimetry; Heat of ionization; Heat of protonation; Heat of neutralization; Acidity and basicity variations; Zwitterions.

1. Introduction

Calorimetry in the aqueous phase has been found to be a useful tool in the study of the reciprocal influence of the "standard" α-amino acids in the dipeptide structures.

This technique is based on the enthalpy values of the proton dissociation processes of the free α-amino group belonging to the amino terminal residue (N-terminal) and of the free α-carboxyl group belonging to the carboxyl terminal residue (C-terminal). These values can be subsequently compared with those of proton dissociation processes related to the same groups of the corresponding single α-amino acids which are the components of the dipeptides.

Some studies on dipeptides in the aqueous phase have been performed in our laboratory [1–3].

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In the first study [1], the influence of the structure of valine, one of the components of each dipeptide, on a number of other α-amino acids, the second component, and the influence of other α-amino acids on the structure of valine, using valil–valine as a reference structure, were studied.

In the second [2] and third [3] works, the influence of the two components of the dipeptides on the dissociation processes of the free carboxyl and amino groups was studied.

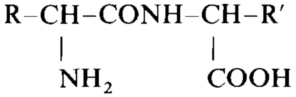
Finally, a calorimetric analysis of the proton transfer processes related to the free amino group of the neutral form of some dipeptides in water, compared with the same processes in the gaseous phase, was presented [4].

It was observed that the thermodynamic quantities related to these proton transfer processes (with valyl–valine as a reference compound) vary as a function of the structure of the second component, so that two relative scales of basicity, in aqueous and gaseous phases, were found.

Experimental evidence also leads to the hypothesis that the α-amino acid structures affect the thermodynamic quantities of these proton transfer processes (and so the basicity) of the dipeptides in different ways in gaseous and aqueous phases. Finally, it was noted that the molecule–proton interactions are not determined at a specific site because of the electron charge delocalization on the neutral molecules of the dipeptides.

The aim of this work was to compare the influence of methyl and isopropyl chains on the functional groups of some dipeptides. For this purpose the following dipeptides were studied: alanyl–lysine (AlaLys), alanyl–tyrosine (AlaTyr), alanyl–tryptophan (AlaTrp), alanyl–valine (AlaVal), alanyl–threonine (AlaThr), alanyl–phenylalanine (AlaPhe), alanyl–leucine (AlaLeu), alanyl–serine (AlaSer) and alanyl–proline (AlaPro).

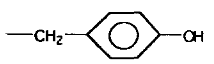
Using some compounds of a series of dipeptides previously studied [1], with valine as the common first term, it was possible to observe the different influence of methyl and isopropyl chains on the α-free carboxyl and amino group dissociation processes.

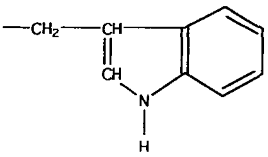


$$\begin{array}{l} \mathrm{R{-}\underset{\displaystyle NH_2}{\underset{|}{CH}}{-}CONH{-}\underset{\displaystyle COOH}{\underset{|}{CH}}{-}R'} \end{array}$$

The pairs considered were AlaTyr/ValTyr, AlaTrp/ValTrp, AlaLys/ValLys, AlaVal/ValVal, AlaLeu/ValLeu, AlaSer/ValSer and AlaPro/ValPro. In structure 1, R for the first series is $-CH_3$, and in the second, $(CH_3)_2-CH-$.

For both series, R′ is respectively:





$-(CH_2)_4-NH_3^+$

$-CH-(CH_3)_2$

$-CH_2-CH-(CH_3)_2$

$-CH_2OH$

$-CH_2-CH_2-CH_2-$

In addition, the pairs AlaTyr/AlaPhe and AlaTyr/AlaThr were considered. In the former, the two dipeptides differ only in an oxydryl group, while in the latter, the oxydryl group lies respectively in aliphatic and aromatic chains.

2. Experimental and procedure

The compounds (Calbiochem) were weighed and handled in a nitrogen-filled dry box.

The purity of all compounds was between 99 and 100% and was checked by means of the DSC purity method using a Stanton–Redcroft 625 simultaneous TG-DSC (with dynamic purity program supplied by P.L. Thermal Sciences Ltd.) and subsequently by potentiometric titrations.

A Tronac (Model 458) instrument was used to make the measurements. The calorimeter vessel was a rapid-response glass vacuum Dewar of capacity 100 cm^3. The thermostat was maintained at 298.15 K to within 2×10^{-4} K during the calorimetric measurement by employing a Tronac P.T.C. 41 precision temperature controller.

Potential vs. time measurements were made using a Fluke 88100 model digital voltmeter. The unbalance (volts) of the bridge of the calorimeter was fed into a Hitachi 561–1000 2/P strip chart recorder and into a digital voltmeter connected to an Olivetti M24 computer.

Data were acquired by the computer via a data-acquisition system and subsequently read and converted into enthalpy values using a basic program run on the Olivetti M24 computer [5]. All the steps of the measurements (calibration curve, cooling curve, reaction curve and equilibrium temperature) were also described [5]. Data obtained using the chart record may be slightly different from those obtained using the computer and they also give the shape of the thermograms expressed as temperature vs. time curves.

The proton ionization of the free α-carboxyl group and of the free α-amino group of a generic dipeptide can be represented as

$$\mathrm{NH_3^+CHRCONHCHR'COOH(aq)} \rightarrow \mathrm{NH_3^+CHRCONHCHR'COO^-(aq)} + \mathrm{H^+(aq)} \quad (1)$$

and

$$\mathrm{NH_3^+CHRCONHCHR'COO^-(aq)} \rightarrow \mathrm{NH_3^+CHRCONHCHR'COO^-(aq)} + \mathrm{H^+(aq)} \quad (2)$$

The molar enthalpy of dissociation at infinite dilution ΔH_1^0 for the free carboxyl in water is obtained by measuring the following quantities:

(a) The molar enthalpy of solution of the crystalline (cr) $\mathrm{NH_3^+CHRCONHCHR'COO^-}$ zwitterion form in water at a pH close to the isoelectric value

$$\mathrm{NH_3^+CHRCONHCHR'COO^-(cr)} \rightarrow \mathrm{NH_3^+CHRCONHCHR'COO^-(aq)} \quad (3)$$

A pH value of 5.99 ± 0.12 is the mean of the isoelectric pH values; a buffer solution at pH 6.00 ± 0.02 (Carlo Erba RPE at 298.15 K) formed by $\mathrm{KH_2PO_4}$ and $\mathrm{Na_2HPO_4}$ was used. The concentrations of these salts are in the ratio of 1/10 and about fifty times larger than those of the dipeptides. So no variation in pH values for the dissolution of the dipeptides can be hypothesized.

(b) The molar enthalpy of protonation of the same compound in 0.02 M HCl solution

$$\mathrm{NH_3^+CHRCONHCHR'COO(cr) + H^+(aq) \rightarrow NH_3^+CHRCONHCHR'COOH(aq)} \quad (4)$$

Results of at least six determinations of heats of solution of the various compounds (concentrations from 10^{-4} to 10^{-3} molal) have been extrapolated vs. the square root of concentrations, to infinite dilution ΔH_3^0.

Again, results of at least six determinations of heats of protonation were extrapolated vs. the square root of concentrations of the protonated dipeptide.

The molar enthalpy of process (1) ΔH_1^0 at infinite dilution can be obtained by subtracting ΔH_4^0 from ΔH_3^0.

These values refer to the proton dissociation of one mole of $\mathrm{NH_3^+CHRCONHCHR'COOH}$ at infinite dilution in water, yielding one mole of $\mathrm{NH_3^+CHRCONHCHR'COO^-}$ and one mole of protons.

For compounds containing carboxyl and amino groups, the dissociation processes in water are complicated by tautomeric equilibria and zwitterion formation [6–7].

While a generic dipeptide in acid solution can be represented by the form $\mathrm{NH_3^+CHRCONHCHR'COOH}$, in a solution approaching pH 7.00 the principal species are neutral molecules, which may be either the $\mathrm{NH_2CHRCONHCHR'COOH}$ (aq) form or the zwitterion form.

Thus, only the $\mathrm{NH_3^+CHRCONHCHR'COOH}$ form is represented in Eq. (4) for acid solution, while in Eq. (3) this is not the case. The isoelectric pH values for some of the compounds examined can be calculated by means of the dissociation constants [8–10]. If this is not possible, it can be noted that the isoelectric values of dipeptides are close to those of the corresponding free α-amino acids, by virtue of the small differences in the $\mathrm{p}K_a$ values of their carboxyl and aminic groups. It can therefore be assumed that in this solution the zwitterion form is predominant. In this way, the carboxyl proton dissociation enthalpy values can be calculated.

The molar enthalpy at infinite dilution ΔH_2^0 of the second proton dissociation process of $\mathrm{NH_3^+CHRCONHCHR'COO^-}$ is obtained by measuring the molar enthalpy of neutralization of the crystalline compound in 2×10^{-2} M NaOH solution.

$$\mathrm{NH_3^+CHRCONHCHR'COO^-(cr) + OH^-(aq) \rightarrow}$$
$$\mathrm{NH_2CHRCONHCHR'COO^-(aq) + H_2O(l)} \quad (5)$$

The enthalpy values of process (5) were extrapolated vs. the square root of concentrations of the anion form.

If the solution process enthalpy values ΔH_3^0 and the ΔH_6^0 molar value in water (Ref. [11], value 55.94 kJ $\mathrm{mol^{-1}}$) related to process (6)

$$\mathrm{H^+(aq) + OH^-(aq) \rightarrow H_2O(l)} \quad (6)$$

are subtracted from ΔH_5^0 values, then the relation $\Delta H_5^0 - (\Delta H_3^0 + \Delta H_6^0)$ supplies the enthalpy values of process (2).

These values refer to the proton dissociation of one mole of $NH_3^+CHRCONHCHR'COO^-$ at infinite dilution in water, yielding one mole of $NH_2CHRCONHCHR'COO^-$ and one mole of protons.

It has been noted that process (4) occurs in basic solution so that only the $NH_2CHRCONHCHR'COO^-$ form is present.

Finally it was noted that in process (5) the second free amino group of alanyl–lysine and the hydroxyl group of alanyl–tyrosine are converted respectively to amide and ester of trifluoroacetate because the heat of neutralization of process (5) must be referred to only one amino group. In addition, all the values are the total uncertainties (calorimetric, chemical and extrapolation).

3. Results and discussion

The enthalpy values of solution ΔH_3^0, protonation ΔH_4^0 and neutralization ΔH_5^0 of all the compounds cited are reported in Table 1.

Table 1 also gives the ionization enthalpy values for the free carboxyl groups (ΔH_1^0) and for the free amino groups (ΔH_2^0) of the dipeptides.

A technique used previously [1–3] to study the influence of the various structures upon the free carboxyl and free amino groups of dipeptides can be described by the following relations

$$\frac{\Delta H_{1(\mathrm{AlaA})}^0 - \Delta H_{1(\mathrm{A})}^0}{\Delta H_{1(\mathrm{A})}^0} \qquad (5a)$$

$$\frac{\Delta H_{2(\mathrm{AlaA})}^0 - \Delta H_{2(\mathrm{A})}^0}{\Delta H_{2(\mathrm{Ala})}^0} \qquad (5b)$$

where $\Delta H_{1(\mathrm{AlaA})}^0$ represents the ionization process values of the free carboxyl groups of dipeptides having α-alanine as the first component, $\Delta H_{1(\mathrm{A})}^0$ represents the values of the dissociation process of the carboxyl group of the corresponding single α-amino acids A, $\Delta H_{2(\mathrm{AlaA})}^0$ represents the ionization process values of the free amino groups of various dipeptides, and $\Delta H_{2(\mathrm{Ala})}^0$ is the enthalpy dissociation value of the amino group of α-alanine.

The values related to the effect of α-alanine upon the free carboxyl groups of dipeptides, and to the effects of the various α-amino acids upon the free amino group of α-alanine (which is the first common term of the series considered) are given in Table 1.

It can be seen that in the first ionization process, the influence of α-alanine favours the dissociation, from the enthalpic point of view, of the free α-carboxyl groups, with respect to those of the corresponding single α-amino acids, for lysine, valine, phenylalanine, tryptophan, tyrosine, leucine, serine and proline.

For these compounds, the carboxyl groups of the dipeptides show heats of dissociation larger than those of the corresponding single α-amino acids.

The influence of different α-amino acids on the amino group of α-alanine, using the second dissociation processes, was also considered.

Table 1
Enthalpy values (kJ mol^{-1}) of processes (1), (2), (3), (4) and (5), and values obtained by using relations (5a) and (5b) for some dipeptides having α-alanine as the first common term, in water at 298.15 K

Compounds	ΔH_1^0	ΔH_2^0	ΔH_3^0	ΔH_4^0	ΔH_5^0	(5a)	(5b)
AlaLys	-0.21 ± 0.06	47.07 ± 0.12	-2.97 ± 0.01	-2.76 ± 0.08	-11.85 ± 0.15	-1.15	0.05
AlaTyr	-1.99 ± 0.22	33.33 ± 0.11	24.13 ± 0.13	26.12 ± 0.19	1.19 ± 0.01	-0.64	-0.27
AlaTrp	-2.74 ± 0.06	34.09 ± 0.16	11.06 ± 0.03	13.80 ± 0.06	-10.80 ± 0.19	-0.93	-0.26
AlaVal	-1.62 ± 0.04	63.08 ± 0.09	-4.44 ± 0.01	-2.82 ± 0.04	-2.70 ± 0.01	-3.28	0.04
AlaThr	2.01 ± 0.02	43.08 ± 0.16	-3.68 ± 0.02	-5.69 ± 0.01	-16.57 ± 0.21	0.30	0.05
AlaPhe	0.34 ± 0.03	49.20 ± 0.75	0.41 ± 0.04	0.07 ± 0.01	-12.64 ± 0.04	-0.42	0.05
AlaLeu	-1.40 ± 0.53	45.87 ± 0.41	-17.45 ± 0.45	-16.05 ± 0.31	-27.52 ± 0.05	-1.93	0.03
AlaSer	0.76 ± 0.10	45.83 ± 0.18	1.64 ± 0.12	0.88 ± 0.02	-8.47 ± 0.13	-0.43	0.01
AlaPro	-2.96 ± 0.45	42.58 ± 0.45	-19.49 ± 0.26	-16.52 ± 0.38	-32.85 ± 0.31	-11.21	-0.08

The proton dissociation process of the free amino group of α-alanine is hindered by valine, threonine and lysine, while tryptophan, phenylalanine, tyrosine, leucine, serine and proline favour the dissociation process of the free amino group.

These proton dissociation trends could be related to the increase or decrease of the electron charge localized on the carboxyl or amino groups of the dipeptides with respect to the charge localized on the same groups of single α-amino acids. For the carboxyl groups, this trend agrees with the results of the Hückel–McLachlan molecular orbital calculations which show the decrease of the electron charge density on the carboxyl groups of the dipeptides (Table 2) with respect to the density charge localized on the carboxyl groups of the corresponding single α-amino acids (Table 3). The Hückel–McLachlan charge distribution was calculated by a computer program using the values [12]: $h_{\ddot{N}} = 0.5$, $h_{\ddot{O}} = 2$, $h_{\dot{O}} = 1$, $K_{CC} = 1$, $K_{C=O} = 1$, $K_{C-O} = 0.8$, $K_{C-N} = 0.8$ and $K_{C-C} = 0.8$, where h is the Couloumb integral (interaction energy between each electron and its respective nucleus) increment and K is the bond integral which represents the energy of interaction of two atomic orbitals; C–C symbolizes a single bond, C = O a double bond and CC an aromatic bond.

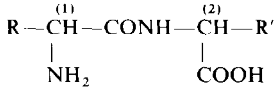
Let us compare the results of relations (5a) and (5b) in Table 1 with the analogous relations (Table 4) relating to the series (previously studied [1]) with valine as the first common term.

Valine increases, from the enthalpic point of view, the dissociation processes related to the free carboxyl groups of tryptophan, lysine, valine, leucine and proline, while it decreases those of tyrosine and serine, with respect to the dissociation processes of the corresponding single α-amino acids. Tyrosine and proline increase the dissociation process related to the α-amino group of valine, while the other amino acids increase it.

α-Alanine and valine show the same influence vs. lysine, tryptophan, valine, leucine and proline, while an opposite influence versus tyrosine and serine was found. However, α-alanine and valine undergo the same effects from tyrosine, lysine, valine, proline and the opposite influence from tryptophan, leucine and serine.

Table 2
Hückel–McLachlan charge density distributions for some dipeptides in netural form

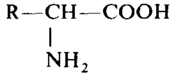
Compounds	$CH^{(1)}$	NH_2	CONH	$CH^{(2)}$	COOH
AlaLys	0.80646	0.48810	1.00364	0.70796	0.40321
AlaTyr	0.62380	0.34293	0.94924	0.55987	0.32209
AlaTrp	0.83506	0.50194	0.73826	0.74820	0.49592
AlaVal	0.76930	0.44935	0.94376	0.64304	0.30094
AlaThr	0.68549	0.36727	0.90940	0.50753	0.36687
AlaPhe	0.80646	0.48810	1.00364	0.70796	0.40322
AlaLeu	0.69171	0.38457	0.95478	0.56348	0.25335
AlaSer	0.82117	0.51047	1.05535	0.72807	0.46795
AlaPro	0.81624	0.50257	1.09400	0.48268	0.20944



$$R-\overset{(1)}{\underset{\displaystyle NH_2}{CH}}-CONH-\overset{(2)}{\underset{\displaystyle COOH}{CH}}-R'$$

Table 3
Hückel–McLachlan charge density distributions for some α-amino acids in neutral form

Compounds	CH	NH_2	COOH
Ala	0.06797	0.01034	1.91500
Tyr	0.76717	0.38818	0.43920
Lys	0.07001	0.00106	1.90911
Trp	0.76885	0.39767	1.55808
Val	0.07216	0.01096	1.90376
Thr	0.07400	0.01123	1.89662
Phe	0.02970	0.00280	1.96369
Leu	0.07630	0.01069	1.48889
Ser	0.07619	0.01155	1.47627
Pro	0.40291	0.78321	0.22140



$$\mathrm{R{-}\underset{\displaystyle NH_2}{\underset{|}{CH}}{-}COOH}$$

Therefore it can be assumed that methyl and isopropyl chains influence in the same way the variations, with respect to the single α-amino acids, of most of the dissociation processes related to the free carboxyl groups for the two series of dipeptides, whereas this is only partially the case for the variations of the free amino groups.

A further contribution to the comprehension of the reciprocal influence of valine, α-alanine and the other α-amino acids can be obtained in the following way.

The quantities $\delta\Delta H_1^0 = \Delta H^0_{1(\mathrm{AlaA})} - \Delta H^0_{1(\mathrm{ValA})}$ and $\delta\Delta H_2^0 = \Delta H^0_{2(\mathrm{AlaA})} - \Delta H^0_{2(\mathrm{ValA})}$ are reported in Table 5, where $\Delta H^0_{1(\mathrm{AlaA})}$ and $\Delta H^0_{1(\mathrm{ValA})}$ are related to the first ionization process values whereas $\Delta H^0_{2(\mathrm{AlaA})}$ and $\Delta H^0_{2(\mathrm{ValA})}$ are related to the second ionization process values for the two series of dipeptides.

It can be observed that, as regards the first ionization process, AlaLys, AlaTyr, AlaTrp and AlaSer are, from the enthalpic point of view, more dissociated, while AlaVal, AlaLeu and AlaPro are less dissociated than the corresponding compounds of the series having valine as the first common term.

Thus, compared with valine, α-alanine makes the carboxyl groups of lysine, tyrosine, tryptophan, serine more dissociated, and those of valine, leucine, proline less dissociated.

In contrast, lysine, tyrosine, valine and proline, as the second component, decrease the dissociation process of the amino group of α-alanine with respect to that of valine.

This behaviour can be explained by considering (Table 6) the relative solvations of the indissociate molecules: $\delta\Delta H_4^0 = \Delta H^0_{4(\mathrm{AlaA})} - \Delta H^0_{4(\mathrm{ValA})}$ and those of the zwitterions $\delta\Delta H_3^0 = \Delta H^0_{3(\mathrm{AlaA})} - \Delta H^0_{3(\mathrm{ValA})}$ of the two series of the dipeptides.

For the AlaLys/ValLys, AlaTyr/ValTyr, AlaTrp/ValTrp and AlaSer/ValSer pairs, the relative solvations of the zwitterions prevail over those of the undissociated molecules, while for the AlaVal/ValVal, AlaLeu/ValLeu and AlaPro/ValPro pairs, the relative solvations of the undissociated molecules play a major role.

The second process can be explained by considering the relative solvations of the zwitterions $\delta\Delta H_3^0$, and the relative solvations of the anions forming NH_2

Table 4
Enthalpy values (kJ mol^{-1}) of processes (1), (2), (3), (4) and (5), and values obtained by using relations (5a) and (5b) for some dipeptides, having valine as the first common term, at 298.15 K in water

Compounds	ΔH_1^0	ΔH_2^0	ΔH_3^0	ΔH_4^0	ΔH_5^0	(5a)	(5b)
ValLys	0.71 ± 0.06	39.20 ± 0.14	0.21 ± 0.01	−0.50 ± 0.08	−9.29 ± 0.19	−1.70	0.51
ValTyr	2.38 ± 0.02	32.17 ± 0.23	2.68 ± 0.02	0.29 ± 0.01	−41.21 ± 0.32	+2.97	−0.05
ValTrp	−2.43 ± 0.53	50.84 ± 0.35	16.61 ± 0.45	19.04 ± 0.30	−11.51 ± 0.10	−0.50	0.16
ValVal	−1.80 ± 0.17	47.66 ± 0.14	−13.47 ± 0.15	−11.67 ± 0.09	−21.75 ± 0.05	−3.53	0.41
ValLeu	−1.59 ± 0.35	45.90 ± 0.43	−24.31 ± 0.39	−22.72 ± 0.10	−34.35 ± 0.31	−2.05	0.36
ValSer	1.46 ± 0.03	55.90 ± 0.16	−10.50 ± 0.02	11.97 ± 0.03	−11.25 ± 0.20	0.09	0.64
ValPro	−3.43 ± 0.07	−5.31 ± 0.23	−2.26 ± 0.01	1.17 ± 0.09	−63.55 ± 0.34	−12.83	−1.16

Table 5
Differences in enthalpy values (kJ mol^{-1}) of the first and second ionization processes for two series of dipeptides having α-alanine and valine as the first common term and for two pairs of dipeptides having α-alanine as the first common term

Compounds	$\delta\Delta H_1^0$	$\delta\Delta H_2^0$
AlaLys/ValLys	−0.92	7.87
AlaTyr/ValTyr	−4.37	1.16
AlaTrp/ValTrp	−0.31	−16.75
AlaVal/ValVal	0.18	15.42
AlaTyr/AlaPhe	−2.33	−15.47
AlaTyr/AlaThr	−4.00	−9.75
AlaLeu/ValLeu	0.19	−0.03
AlaSer/ValSer	−0.70	−9.36
AlaPro/ValPro	0.47	47.89

Table 6
Differences in enthalpy values (kJ mol^{-1}) of processes (3), (4) and (5) for two series of dipeptides having α-alanine and valine as the first common term and for two pairs of dipeptides having α-alanine as the first common term

Compounds	$\delta\Delta H_3^0$	$\delta\Delta H_4^0$	$\delta\Delta H_5^0$
AlaLys/ValLys	−3.18	−2.26	−2.56
AlaTyr/ValTyr	21.45	25.83	43.60
AlaTrp/ValTrp	−5.55	−5.24	+22.31
AlaVal/ValVal	9.03	8.85	+19.05
AlaTyr/AlaPhe	23.72	26.05	14.55
AlaTyr/AlaThr	27.81	31.81	18.48
AlaLeu/ValLeu	6.86	6.67	6.83
AlaSer/ValSer	12.14	12.85	2.87
AlaPro/ValPro	−17.23	−17.69	30.70

CHRCONHR'COO$^-$, $\delta\Delta H_5^0 = \Delta H^0_{5(\mathrm{AlaA})} - \Delta H^0_{5(\mathrm{ValA})}$ of the above cited dipeptides (Table 6).

For all the pairs, with the exception of AlaTrp/ValTrp, AlaLeu/ValLeu and AlaSer/ValSer, the relative solvations of the zwitterions predominate in the relative solvations of the anions formed, so that the decrease in the dissociation process of the amino group of the first series is explained.

Thus, comparing directly the two series, it can be observed that the methyl chain plays a predominant role with respect to that of the isopropyl chain in determining the dissociation processes of the carboxyl and amino groups of dipeptides.

Finally, for the pairs AlaTyr/AlaPhe and AlaTyr/AlaThr, it can be noted that phenylalanine and threonine make the amino group of α-alanine less dissociated than tyrosine does.

4. Conclusions

In two series of dipeptides, valine and α-alanine influence in the same way, from the enthalpic point of view, the variation in the dissociation processes of the free α-carboxyl groups with respect to those of the corresponding single α-amino acids.

In a direct comparison of the two series, α-alanine makes the free carboxyl groups of most of the α-amino acids which form the second component of the dipeptides more dissociated than valine does, and the dissociation process of α-alanine is decreased with respect to that of valine by most of the above cited α-amino acids.

This can be explained in terms of the electron-withdrawing effect (on the carboxyl group) of the NH_3^+ group, which is less neutralized by the electron donor effect of the methyl group side chain. Finally, as regards the AlaTyr/AlaPhe and AlaTyr/AlaThr pairs, the benzene ring of phenylalanine and the hydroxyl group of threonine stabilizes the NH_3^+ group of α-alanine more than the hydroxyl group of tyrosine does.

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