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Sublimation Effects and Volume Effects in the Crystals of Amino Acids, Peptides, and Their Some Acetyl Derivatives

E. Yu. Tyunina and V. G. Badelin

Krestov Institute of Solution Chemistry, Russian Academy of Sciences, ul. Akademicheskaya 1, Ivanovo, 153045 Russia
e-mail: *tey@isc-ras.ru*

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Abstract—The effects of molecular shape, packing density, and electronic characteristics on the sublimation enthalpies of crystalline amino acids, dipeptides, and certain amides and their N-acetyl derivatives were studied on the basis of their experimental thermodynamic parameters (sublimation enthalpies, heat capacities) and steric structures. The sublimation enthalpy of L-α-phenylalanine was determined by Knudsen effusion mass spectrometry. A multiparameter correlation between the sublimation enthalpy and molecular descriptors of the studied compounds was proposed. The contributions of volume factors, electrostatic attraction of zwitterions, and hydrogen bonding in crystals into the sublimation enthalpy were estimated.

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Over the past decades vigorous progress of nanotechnology R&D aimed at creation of structured materials with unique properties has been observed [1–3]. Nanoconstructions can be assembled not only from inorganic atoms, but also from biological molecules. Such systems can be used as biosensors, optical filters, drug carriers, and other biologically active substances [3–5]. A necessary parameter for a theoretical analysis of the stability of various nanostructures is the crystal lattice energy [3] which, under certain conditions, can be considered to be close to the sublimation enthalpy. Thermodynamic characteristics of amino acids, oligopeptides, proteins, polysaccharides, and other biologically active compounds are required for studying both their synthesis and transformations in living bodies, such as enzymatic reactions or conformational transformations of proteins and nucleic acids. For deeper insight into the spacial organization and mechanisms of functioning of complex macromolecules, experimental data are required on the physicochemical properties of the monomeric structural units, thermodynamic parameters of binding between them, and influence of structural modification on the interaction between macromolecules. Thus, the mechanisms of biochemical reactions are studied using the Gibbs energies which allow estimation of the energies of formation of intermediates, conjugates, or complexes between reagents. Of great importance here is also the knowledge of the enthalpies of vaporization (evaporation or sublimation), but they have scarcely been determined for low-volatile biological compounds in view of their tendency to thermal degradation. Moreover, thermochemical characteristics of vaporization make it possible to estimate the energies of bonds responsible for reactivity, which allows, in combination with other methods, the identification and characterization of different types of intra- and intermolecular interactions [6–8]. In this connection, it is quite important, both from the theoretical and practical viewpoints, to establish relationships between the structure of biologically active compounds and their thermodynamic properties.

Even though amino acids, peptides, and their derivatives have long been under the scrutiny of science [9–13], research into the thermodynamics of phase transitions of such molecules could favor a deeper understanding of the crystal state of polar organic compounds having donor and acceptor groups capable of hydrogen bonding [8, 14, 15]. Amino acids and dipeptides containing both the amino (NH_2) and carboxy (COOH) groups crystallize from water as dipolar ions. A zwitterion is an organic molecule which has both positively and negatively charged segments. Evidence for the zwitter-ionic crystal structure of amino acids and peptides is provided by

their fairly high dipole moments ($\leq 50\times10^{-30}$ C m) and high densities and melting (decomposition) points, as well as by the presence of an absorption band at 1610–1550 cm^{-1} in the IR spectra of solid compounds and their solutions [16]. The zwitter-ionic form of amino acids and peptides does not exist in the gas phase, which is experimentally confirmed by microwave spectroscopy [17, 18].

It is commonly accepted that molecular organic crystals feature a dense molecular packing [19]. The packing density is defined as the ratio of the total intrinsic volume of atoms in the crystal lattice to the total volume of the latter. Different types of crystal lattices have different packing densities of atoms, depending on the electronic structure of the atoms and the nature of interatomic bond. Amino acids and peptides in crystal are held together not only by van der Waals forces, but also by hydrogen bonds which are directed, as well as electrostatic forces; as a result, the total energy of their crystal lattices is much higher compared to molecular organic crystals.

The aim of the present work was to study the effect of steric and electronic molecular characteristics of amino acids and peptides on their sublimation enthalpies by means of multiple regression analysis. This allows quantitative estimation of intermolecular interactions in a crystal. Based on our own and published thermodynamic parameters (sublimation enthalpies Δ_sH, heat capacities $C_{p,s}$) of crystalline dipeptides [$^+NH_3CH(R)CONHCH(R')COO^-$], amino acids [$^+NH_3CH(R)COO^-$], and *N*-acetyl derivatives of amino acid amides [$CH_3CONHCH(R)CONH_2$] (R is the side-chain group) we estimated Δ_sH for these compounds by correlations with various molecular parameters which contribute, to a greater or lesser degree, into the crystal lattice energy. Table 1 lists the structural descriptors used as independent but mutually complementary parameters relating to different types of intermolecular interactions in a crystal. The parameter *M* (molecular mass of a substance) includes molecular size and polarizability. As steric descriptors we took crystal density (d_{cr}), molecular packing parameter $D_{pac} = ZV_w/V_{cell}$ (*Z* is the number of molecules in a cell and V_{cell}, unit cell volume), and van der Waals molecular volume (V_w) [20]. To take into account the possibility of hydrogen bonding, we introduced the parameter N_{HB} which is the maximum possible number of H-bonds for different functional groups containing donor and acceptor atoms [21]. The electrostatic properties of amino acids, dipeptides, and their derivatives were included to a certain extent via the dipole moments of their molecules (μ), which were calculated quantum-chemically.

Using the heat capacities of the solid phase ($C_{p,s}$) and experimental sublimation enthalpies measured at the temperature *T* (Δ_sH^T), we estimated the standard molar sublimation enthalpies (Δ_sH^{298}) of the studied compounds at 298.15 K by Eq. (1) [22].

$$\Delta_sH^{298} = \Delta_sH^T + [0.75+0.15C_{p,s}^{298}][T - 298.15]. \quad (1)$$

The resulting Δ_sH^{298} values for amino acids and their derivatives are presented in Table 2 and those for dipeptides, in Table 3. For correct thermodynamic analysis, volume-specific sublimation enthalpies Δ_sH^{298}/V_w were used [15, 23, 24]. The molecular structure of amino acids, dipeptides, and some *N*-acetyl derivatives of amides were characterized by a set of geometric (steric) (V_w, D_{pac}, *M*) and electronic (μ, N_{HB}) descriptors (Table 1). An approach to the quantitative assessment of the type of interactions in the crystals of the studied compounds by means of a multiparameter correlation equation relating Δ_sH^{298}/V_w to structural molecular descriptors was suggested.

$$(\Delta_sH^{298}/V_w) = a + b_1D_{pac} + b_2N_{HB} + b_3\mu + b_4\,(M/100). \quad (2)$$

Here D_{pac} is the molecular packing parameter; N_{HB}, number of hydrogen bonds (per a molecule); μ, dipole moment; and *M*/100, reduced molecular mass. Analysis of the results for amino acids revealed three groups of compounds: (1) amino acids containing aliphatic radicals; (2) amino acids containing aromatic and heterocyclic fragments and polar groups; and (3) amides of *N*-acetyl derivatives of amino acids.

Table 4 lists the coefficients which correspond to the contributions of different structural descriptors into Δ_sH^{298}/V_w. The analysis of the resulting data showed that from 82 to 99% of variations in this value can be explained in terms of Eq. (2).

It was found that the packing parameter D_{pac} contributed mostly to the sublimation enthalpies of crystalline aliphatic amino acids and amides of their *N*-acetyl derivatives, whereas the major contribution into respective values for aromatic amino acids comes from the molecular mass *M*. In going from aliphatic amino acids to amides of their *N*-acetyl derivatives and further to amino acids with aromatic and polar fragments the interactions associated with H-bond formation (N_{HB}) are taking more significance. The contributions of the electrostatic attraction of zwitterions (μ), obtained for amino acids of different

Table 1. Physicochemical parameters of crystalline amino acids, dipeptides, and their derivatives

Compound	V_w, Å^3	M	d_{cr}, g cm^{-3} [9, 14, 34–38]	Z	D_{pac}	μ	N_{HB} [21]
Gly	60.63	75.07	1.598	4	0.799	1.476	2
DL-Ala	76.82	89.09	1.401	4	0.717	0.980	2
L-Ala	76.81	89.09	1.371	4	0.713	1.281	2
β-Ala	76.65	89.09	1.316	8	0.738	0	5
DL-Val	109.47	117.15	1.281	4	0.724	1.010	5
L-Val	109.45	117.15	1.267	4	0.722	1.414	5
DL-Leu	125.49	131.18	1.191	4	0.693	0.995	2
L-Leu	125.48	131.18	1.167	4	0.683	1.277	2
Phe	146.96	165.19	1.315	4	0.557	0.250	1
Arg	151.31	174.20	1.325	2	0.639	3.520	5
Cys	90.83	121.16	1.495	4	0.677	1.930	2
Met	128.61	149.21	1.311	4	0.713	1.770	2
Tyr	154.85	181.19	1.403	4	0.727	1.330	3
Trp	174.68	204.23	1.303	2	0.610	2.180	0
His	127.21	155.16	1.412	4	0.504	3.930	1
Asn	104.43	132.12	1.567	2	0.764	3.510	1
Gln	120.45	147.13	1.497	4	0.871	3.750	2
Lys	132.03	146.19	1.237	4	0.601	1.510	5
Pro	98.82	115.13	1.376	4	0.729	1.490	1
Sar	73.65	89.09	1.271	4	0.651	2.619	1
$AcGlyNH_2$	97.91	116.12	1.319	4	0.669	3.401	2
$AcAlaNH_2$	114.11	130.15	1.203	2	0.608	3.007	2
$AcValNH_2$	146.75	158.20	1.135	4	0.634	1.483	2
$AcLeuNH_2$	162.77	172.22	1.125	4	0.640	2.731	1
$AcIleNH_2$	154.85	172.23	1.165	4	0.726	2.800	1
$AcProNH_2$	136.88	156.18	1.294	4	0.773	3.945	1
$AcSarNH_2$	95.87	130.15	1.276	4	0.862	3.646	2
GlyGly	103.86	132.12	1.534	4	0.873	3.081	4
DL-AlaGly	120.02	146.13	–	4	0.779	3.487	4
Gly-*L*-Ala	120.56	146.13	1.395	4	0.749	2.189	4
L-Ala-*L*-Ala	137.33	160.17	1.276	8	0.743	3.220	8
DL-Ala-*DL*-Val	165.41	188.23	1.069	6	0.733	3.623	8
cGlyGly	88.26	114.10	1.592	4	0.758	0	2
cGlyAla	106.87	128.13	1.421	3	0.742	0.325	2
cAlaAla	120.64	142.15	1.312	3	0.740	0.018	2
cSarSar	123.1	142.16	1.371	3	0.735	3.410	0
$AcGlyAlaNH_2$	146.92	187.20	1.340	4	0.758	6.158	4
$AcAlaAlaNH_2$	163.12	201.23	1.244	4	0.748	4.601	4
$AcProGlyNH_2$	178.59	212.99	1.342	4	0.721	5.803	3

Table 2. Sublimation enthalpies and heat capacities of crystalline amino acids and their derivatives

Compound	R	$\Delta_s H^{298}_{exp}$, kJ mol^{-1}	$C_{p,s}$, J mol^{-1} K^{-1}	$\Delta_s H^{298}_{calc}$, kJ mol^{-1}	$(\pm\Delta)^a$ kJ mol^{-1}
Aliphatic amino acids					
Gly	H	138.9±2 [22]	95 [41]	139	0.1
DL-Ala	CH_3	141.2±8 [34]	114 [42]	142	0.8
L-Ala	CH_3	144.8±4 [22]	115 [41]	144	0.8
β-Ala	CH_3	134.2±2 [22]	–	134	0.2
DL-Val	$CH(CH_3)_2$	–	165 [42]	161	–
L-Val	$CH(CH_3)_2$	166.8±8 [22]	168.9 [43]	166	0.8
DL-Leu	$CH_2CH(CH_3)_2$	155.3±2 [22]	195.3 [42]	155	0.3
L-Leu	$CH_2CH(CH_3)_2$	–	191 [43]	157	–
Amino acids containing aromatic and heterocyclic fragments and polar groups					
Phe	$CH_2(C_6H_5)$	149±6	203 [44]	139	9.4
Arg	$(CH_2)_3NHC(=NH)NH_2$	–	247 [42]	113	–
Cys	CH_2SH	116.4±8 [22]	–	111	5.0
Met	$CH_2CH_2SCH_3$	142±8 [22]	290.2 [22]	150	8.0
Tyr	$CH_2(C_6H_4OH)$	–	216.5 [42]	109	–
Trp	CH_2(indol-3-yl)	–	238.2 [44]	127	–
His	CH_2(imidazol-4-yl)	147.4±8 [33]	249 [45]	140	7.4
Asn	$CH_2C(=O)NH_2$	–	–	109	–
Gln	$CH_2CH_2C(=O)NH_2$	–	–	120	–
Lys	$CH_2CH_2CH_2CH_2NH_2$	102±9 [22]	239 [45]	124	22.1
Pro	$(CH_2CH_2CH_2)$	151±4 [22]	151.2 [44]	139	11.0
Sar	NCH_3, H	146±8 [22]	–	150	8.3
N-acetyl derivatives of amino acid amides					
$AcGlyNH_2$	H	126.3±4 [14]	152.7 [39]	129	3.1
$AcAlaNH_2$	CH_3	118.7±2 [14]	181.3 [39]	114	4.3
$AcValNH_2$	$CH(CH_3)_2$	133.1±6 [14]	232.1 [39]	133	0.1
$AcLeuNH_2$	$CH_2CH(CH_3)_2$	120.3±4 [14]	259.6 [39]	129	9.4
$AcIleNH_2$	$CH_2CH(CH_3)_2$	147.5±6 [14]	261.9 [14]	139	7.9
$AcProNH_2$	$(CH_2CH_2CH_2)$	146.1±4 [14]	208.9 [14]	146	0.1
$AcSarNH_2$	NCH_3, H	142.4±8 [40]	–	142	0.4

[a] $(\pm\Delta) = \Delta_s H^{298}_{exp} - \Delta_s H^{298}_{calc}$.

structures but having the same charged centers COO^- and NH_3^+ are almost comparable with each other and were by an order-of-magnitude higher than those of N-acetyl derivatives of amino acid amides which contain no charged terminal groups. These results provide evidence for the prevalence of van der Waals interactions in the studied organic compounds, and, therewith, specific interactions prevail over electrostatic effects in aromatic and heterocyclic amino acids and amides of their *N*-acetyl derivatives, unlike the effects in aliphatic amino acids.

As to peptides, Eq. (2) is suitable for calculation of the sublimation enthalpies of cyclic dipeptides and *N*-acetyl derivatives of dipeptide amides. At the same time, for aliphatic dipeptides, in view of the lack of

Table 3. Sublimation enthalpies and heat capacities of crystalline dipeptides and their derivatives

Compound	$\Delta_s H^{298}_{exp}$, kJ mol^{-1}	$C_{p,s}$, J mol^{-1} K^{-1}	$\Delta_s H^{298}_{calc}$, kJ mol^{-1}	$(\pm\Delta)^a$ kJ mol^{-1}
Aliphatic dipeptides				
GlyGly	190±5 [15]	158 [47]	189	0.45
DL-AlaGly	173±24 [15]	181 [47]	174	1.23
Gly-*L*-Ala	113±9 [32]	168 [46]	112	0.71
L-Ala-*L*-Ala	118±8 [32]	195 [47]	121	3.22
DL-Ala-*DL*-Val	160±5 [32]	240 [46]	156	3.87
Cyclic dipeptides and amides of *N*-acetyl derivatives of dipeptides				
cGlyGly	118±7 [14]	155.4 [14]	128	9.5
cGlyAla	143±2 [14]	175.4 [14]	142	0.71
cAlaAla	137±6 [14]	195.4 [14]	123	14.1
cSarSar	93±3 [14]	–	92	0.55
$AcGlyAlaNH_2$	263±5 [9]	255 [9]	250	12.4
$AcAlaAlaNH_2$	198±2 [9]	284 [9]	207	9.0
$AcProGlyNH_2$	167±8 [9]	283 [9]	176	8.72

[a] $(\pm\Delta) = \Delta_s H^{298}_{exp} - \Delta_s H^{298}_{calc}$.

sufficient information on their sublimation enthalpies, we derived Eq. (3) with the same structural descriptor as for Eq. (2).

$$(\Delta_s H^{298}/V_w) = a + b_1 D_{pac} + b_2 N_{HB} + b_3 \mu. \quad (3)$$

The coefficients for the contributions of these descriptors into $\Delta_s H^{298}/V_w$ are listed in Table 5. The highest regression coefficients at D_{pac} suggest that the packing effect in peptides contributed more to the sublimation enthalpies than in amino acids. The sensitivity of the volume-specific sublimation enthalpy to specific interactions (H-bond formation) between structural units in crystalline peptides reveals itself in the regression coefficients b_i in Eqs. (2) and (3) at the N_{HB} term whose values for a number of cyclic and substituted dipeptides are much higher compared to those for aliphatic peptides. This contribution increases in going from amino acids to cyclic and substituted dipeptides, which can be explained by the appearance of the peptide group CONH that is capable for H-bond formations. At the same time, these contributions for amino acids and dipeptides containing aliphatic side chains are close to each other. The contributions of the electrostatic attraction of zwitterions (μ) into the sublimation enthalpies of aliphatic dipeptides exceed twice those of the other dipeptides which have no charged groups. It should also be borne in mind that this contribution strongly increases in going from amino acids to dipeptides, probably, due to a change in the molecular polarizability with increasing hydrocarbon chain length, which is accompanied by an increase in the volume of cavity this molecule occupies in the crystal.

Tables 2 and 3 list the sublimation enthalpies calculated by Eqs. (2) and (3), as well as the absolute errors of the calculation $(\pm\Delta) = \Delta_s H^{298}_{exp} - \Delta_s H^{298}_{calc}$. The average relative errors of such estimates were 7.5% for aromatic, heterocyclic, and polar amino acids, 0.3% for aliphatic amino acids, 2.9% for *N*-acetyl derivatives of their amides, 1.3% for aliphatic dipeptides, and 4.9% for cyclic dipeptides and their derivatives. This is comparable with the errors in the estimates for various physicochemical parameters from correlation equations (6–12%) [25].

It was found that the volume-specific sublimation enthalpies decrease in the following orders: Gly > *L*-Ala > *DL*-Ala > β-Ala > *L*-Val > *DL*-Val > *L*-Leu > *DL*-Leu; Sar > Pro > Cys > Asn > Gln > His > Met > Phe > Arg > Lys > Tyr > Trp; Ac-Sar-NH_2 > Ac-Gly-

Table 4. Coefficients of Eq. (2) for calculation of the sublimation enthalpies of amino acids and amides of their

a_0	b_1	b_2	b_3	b_4	r_{corr} (r^2_{adj}, %)	SD	$F_{statistic}$	n
Amino acids with an aliphatic side-chain radical								
1.231 ±0.19	2.339 ±0.23	–0.0064 ±0.004	0.1306 ±0.012	–1.323 ±0.04	0.9997 (99.88)	0.012	1069.0	8
Amino acids containing aromatic and heterocyclic fragments and polar groups								
2.103 ±1.0	0.518 ±0.29	–0.1647 ±0.079	0.116 ±0.08	–0.791 ±0.35	0.9369 (82.85)	0.151	18.56	8
N-acetyl derivatives of amino acid amides								
1.703 ±0.44	1.208 ±0.29	–0.0243 ±0.013	–0.011 ±0.007	–0.928 ±0.15	0.9769 (93.08)	0.065	31.64	7

Table 5. Coefficients of correlation Eqs. (2) and (3) for calculation of the sublimation enthalpies of peptides

a_0	b_1	b_2	b_3	b_4	r_{corr} (r^2_{adj}, %)	SD	$F_{statistic}$	n
Eq. (2)								
Cyclic dipeptides Amides of *N*-acetyl derivatives of peptides								
7.84 ±5.8	–6.50 ±4.5	0.399 ±0.14	0.144 ±0.07	–1.971 ±0.85	0.9454 (82.94)	0.136	19.849	7
Eq. (3)								
Aliphatic dipeptides								
–3.263 ±0.33	5.190 ±0.41	–0.0076 ±0.004	0.2806 ±0.039	–	0.9982 (99.27)	0.035	183.43	5

NH_2 >> Ac-Pro-NH_2 > Ac-Ala-NH_2 > Ac-Val-NH_2 > Ac-Leu-NH_2; Ac-GlyAla-NH_2 > cGlyGly > cGlyAla > Ac-AlaAla-NH_2 > cAlaAla > Ac-ProGly-NH_2 > cSarSar; GlyGly > *DL*-AlaGly > *DL*-AlaVal > GlyAla > *L*-AlaAla. The sublimation enthalpies of aliphatic amino acids and their derivatives are, to a first approximation, directly related to their crystal densities. In aliphatic amino acids and their amides, a decrease in D_{pac} is accompanied by a decrease in $\Delta_s H^{298}/V_w$. In the other compounds, the correlation between these two parameters is not so unambiguous. Since the studied compounds have different molecular shapes and sizes, their packing densities vary from 0.5 to 0.8. It was found that aliphatic amino acids and dipeptides with small molecular volumes (V_w) have a more efficient packing. The same tendency is also characteristic of such amides as Ac-Sar-NH_2, Ac-Pro-NH_2, Ac-Ile-NH_2, whereas the *N*-acetyl derivatives of glycine, valine, and leucine amides have fairly close D_{pac} values. Amino acids containing aromatic and heterocyclic fragments and polar groups show the tendency for an increase in the density of molecular packing with molecular volume V_w for structurally similar compounds: Gln > Asn, Arg > Lys, Met > Cys, Trp > Phe > His, Tyr > Phe. Highly dense packings are observed in the crystals of compounds both with and without H-bonds. Therefore, we can suggest a lack of simple correlation between packing density and crystal lattice energy (or sublimation enthalpy) for biological compounds of different structures.

Thus, the results of the present work provide evidence that the calculated coefficients b_i and multiparameter equations can be used to analyze the contributions and obtain qualitative information on the type of intermolecular interactions in the crystals of biologically active compounds. Correlations between the sublimation enthalpies and molecular descriptors of amino acids, dipeptides, and some of their derivatives were proposed, with special attention given to

Table 6. EI mass spectra of L-phenylalanine (E_{ion} 70 eV, T 439 K)

m/z	Ions	I_{rel}, %
18	H_2O^+	8
29	$[NH_2CH]^+$	36
39	$[C_3H_3]^+$	16
45	$[COOH]^+$	38
51	$[C_4H_3]^+$	14
65	$[C_5H_5]^+$	41
74	$\{M-[C_7H_7]\}^+$	100
77	$[C_6H_5]^+$	27
91	$[PhCH_2]^+$	98
103	$[PhC_2H_2]^+$	31
121	$\{M-[COOH]\}^+$	33
165	M^+	8

accounting for steric structural factors (packing density, van der Waals volume). It was shown that a higher packing density is characteristic of compact molecules with small molecular volumes. Alkyl, acetyl, or amino substitution decreases the packing density and the sublimation enthalpies in the series of aliphatic amino acids, dipeptides, and their derivatives. The contribution of the electrostatic attraction of zwitterions (μ) into the sublimation enthalpy decreases in the order: aliphatic dipeptides, cyclic and substituted dipeptides, aliphatic amino acids, amino acids with polar and heterocyclic fragments, acetyl derivatives of amino acid amides. It was found that the direct correlation between crystal density and sublimation enthalpy holds not for all compounds having chemically different side-chain groups. Hydrogen bonds, while favoring stronger cohesion in the crystals of amino acids, peptides, and their derivatives, not always favor a denser molecular crystal packing.

The present results for amino acids and peptides can be of interest for studying relationships between the molecular structure of oligopeptides and their thermodynamic characterisitics and also can form the basis for targeted synthesis of peptide antibiotics and modeling complicated high-temperature processes involving phase transformations of biological compounds.

EXPERIMENTAL

The sublimation enthalpy of L-α-phenylalanine was determined by Knudsen effusion mass spectrometry by a procedure described in [15], using a MI 1201 mass spectrometer, ionizaing electrons energy 70 eV. L-α-phenylalanine (CAS 63-91-2; 99%; Sigma–Aldrich) was dried in a vacuum at 323 K for 48 h just before use. The sample was sublimed from a molybdenum effusion cell with the evaporation-to-orifice surface area ratio of about 1000. The temperature was measured with a VR-5/20 tungsten–rhenium thermocouple. The EI mass spectra of L-α-phenylalanine at one of the experimental temperatures are presented in Table 6. Comparison of the measured mass spectra with published data [27–30] provides evidence for their reliability and shows that the fragmentation pathways of dipeptides and amino acids are quite similar. The experimental data were used to construct temperature dependence of ion currents (IT) for the studied amino acid: ln (IT) = $f(1/T)$. These dependences were linear (r_{corr} 0.987) and could be used to estimate the sublimation enthalpy of L-α-phenylalanine by a procedure based on an isobaric equation [15, 31]. The resulting ($\Delta_s H^T$) value was 145±6 kJ/mol (T 439 K).

The experimental sublimation enthalpies of aliphatic dipeptides we determined previously [32], and the corresponding values for other compounds were taken from [22, 33]. The crystal densities (d_{cr}) and heat capacities ($C_{p,s}$) were taken from [9, 14, 34–38] and [9, 14, 39–47], respectively.

The crystal structures were taken from the Cambridge Structural Database [48]. The molecular van der Waals volumes were calculated using the atomic volume increments δV_i obtained by numerical integration in [20]. This methods allows accounting for the spacial overlap of three and more van der Waals spheres of valence-nonbonded atoms in one point, which is of crucial importance in terms of accuracy of estimation of volumes for sterically complex molecules and molecules containing intramolecular H-bonds. Geometry optimization of amino acids, dipeptides, and their derivatives was performed by the AM1 semiempirical method in the isolated molecule approximation, which is known to well reproduce electronic parameters, molecular geometry, etc. [49]. The quantum-chemical calculations were performed with full geometry optimization (gradient norm ≤ 0.001 kcal mol^{-1}) and without inclusion of electron correlation effects; the most energetically stable

conformers with the lowest formation enthalpies and positive vibration frequencies were chosen.

Regression analysis [50, 51] was used to obtain statistically significant structure–sublimation enthalpy correlations for amino acids, dipeptides, and certain amides of their *N*-acetyl derivatives. Statistical analysis of Eqs. (2) and (3) was performed by the multiple correlation technique using the ORIGIN7 software. The correlation accuracy for small sample sizes was estimated by the correlation coefficients r_{corr} and determination coefficient r^2_{adj} [51]. In addition, the fit of the correlation dependences to experimental data was estimated by means of the minimum dispersion (*SD*) which is also called the standard regression deviation, as well as by the Fisher criterion (F_{stat}) for a 0.95 confidence level (Tables 4 and 5). The statistical analysis showed a fair level of reliability of the calculated coefficients b_i in Eqs. (2) and (3).

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