Electronic Supplementary Information

The bending behaviour of L-phenylalanine monohydrate soft crystal via reversible hydrogen bonds rupture and remodeling

Yaxiang Gong[a, ‡], Yuanfeng Wei[b, ‡], Yuan Gao[b], Zungting Pang[b], Jianjun Zhang[a,*], Shuai Qian[b,*]

[a] School of Pharmacy, China Pharmaceutical University, Nanjing, 211198, China

[b] School of Traditional Chinese Pharmacy, China Pharmaceutical University, Nanjing, 211198, China

---

[‡]Authors contributed equally.

Corresponding authors:

Dr. Jianjun Zhang
School of Pharmacy, China Pharmaceutical University
Tel.: +86 13951974969, Email address: myamicute@163.com

Dr. Shuai Qian
School of Traditional Chinese Pharmacy, China Pharmaceutical University
Tel.: +86 139 15957175, Email address: silence_qs@163.com

1. Lattice energy determination of L-Phe·H_2O

Method

1.1 Differential scanning calorimetry (DSC)

A differential scanning calorimeter (DSC 250, TA Instruments-Waters, U.S.A.) was used to carry out DSC. Approximately 4 mg of sample (L-Phe·H_2O soft crystal and L-Phe (the raw material, RM)) was placed in a nonhermetic aluminum pan, after which it was heated from 25 to 295 °C at a heating rate of 10 °C/min. The dehydration product of L-Phe·H_2O during the heating process was named as L-Phe form-X. Nitrogen gas was used as the purge gas at 20 mL/min. The data was analyzed by Trios software (version 5.1.1.46572). Each experiment was repeated in triplicate.

1.2 Determination of specific heat capacity of L-Phe form X

A differential scanning calorimetry (DSC 250, TA Instruments-Waters, U.S.A.) was used to determine the specific heat capacity of L-Phe form-X was determined by "three-step" method. The empty aluminum pan, sapphire and sample (4 mg) were heated from 150 to 250 °C with a heating rate of 10 °C /min, respectively. The data was analyzed by Trios software (version 5.1.1.46572). The specific heat capacity of L-Phe form-X in the range of 150~250 °C was recorded.

1.3 Lattice energy calculation of L-Phe·H_2O

The lattice energy of L-Phe·H_2O can be calculated by sublimation enthalpy as follow[1-3]:

$$E_{\text{lattice}} = -\Delta H_{\text{sub}}(T) - 2RT \quad (1)$$

Where E_{lattice} represents lattice energy, ΔH_{sub} is the sublimation enthalpy determined at a specific temperature (T), R is the gas constant.

Considering the sublimation of crystalline water and proton transfer energy of L-Phe (the energy to be overcome from amphoteric ions to molecules), Eq.(1) should be modified to:

$$E_{\text{lattice}} = -\Delta H_{\text{sub}}(T) - 2RT - p^{\theta}V_1 + \Delta E_{\text{pt}} \quad (2)$$

Where V_1 represents the molar volume of crystalline water at sublimation temperature, p^{θ} represents the standard gas pressure, ΔE_{pt} is the proton transfer energy of amino acids, which is a constant (-137 kJ·mol^{-1}).[4] Besides, according to Charles' law, [5] V_1 at temperature T_1 can be expressed as:

$$V_1 = V^{\theta}T_1 / T^{\theta} \quad (3)$$

Where T^{θ} represents the Kelvin temperature at 0 ºC, T^{θ}=273 K, V^{θ} represents the molar volume of ideal gas at 273 K, V^{θ}=22.4 L. Thus, making use of Eq (2) and (3), E_{lattice} can be expressed as:

$$E_{\text{lattice}} = -\Delta H_{\text{sub}}(T) - 2RT - p^{\theta}\left(\frac{V^{\theta}T_1}{T^{\theta}}\right) + \Delta E_{\text{pt}} = -\Delta H_{\text{sub}}(T) - 3RT + \Delta E_{\text{pt}} \quad (4)$$

Results

DSC is a common method for determining sublimation enthalpy.[6,7] The DSC curves of L-Phe·H_2O and L-Phe (RM) were shown in Fig. S1. For L-Phe·H_2O, the endothermic peaks at 127 ºC (400 K, ΔH_{Dehy} =163.2±2.8 kJ·mol^{-1}) and 274 ºC (547 K, ΔH_{fus}=64.3±1.2 kJ·mol^{-1}) were attributed to dehydration and melting of L-Phe·H_2O, respectively. After dehydration, the specific heat capacity of L-Phe form-X ($C_{\text{p,form-X}}$) was determined to be 197.8±6.4 J·mol^{-1}·K^{-1}. In addition, for L-Phe (RM), only a melting endothermic peak was observed at 274 ºC (547K, ΔH_{fus}=62.1±1.2 kJ·mol^{-1}).

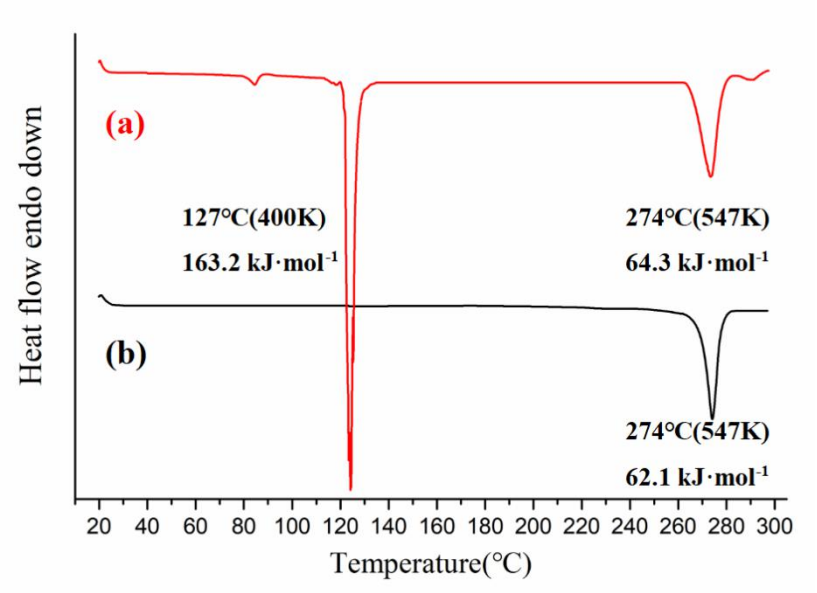

Fig. S1 DSC curves of (a) L-Phe·H_2O and (b) L-Phe (RM).

At 400 K, the sublimation reaction of L-Phe·H_2O could be described as follow:

$$\text{L-Phe}\cdot\text{H}_2\text{O}(s,\ 400\text{K}) \rightarrow \text{L-Phe}(g,\ 400\text{K}) + \text{H}_2\text{O}(g,\ 400\text{K}),\ \Delta H_{\text{sub}}(\text{L-Phe}\cdot\text{H}_2\text{O}) \quad (5)$$

The reaction (5) could be regarded as the sum of Eq. (6), Eq. (7) and Eq. (8):

$$\text{L-Phe}\cdot\text{H}_2\text{O}(s,\ 400K) \rightarrow \text{L-Phe}\cdot\text{H}_2\text{O}(\text{form-X},\ 400K) + \text{H}_2\text{O}(\text{g},\ 400\text{K})$$

$$\Delta H_{\text{Dehy}} = 163.2 \pm 2.8\text{kJ}\cdot\text{mol}^{-1} \quad (6)$$

$$\text{L-Phe}(\text{form-X},\ 400K) \rightarrow \text{L-Phe}(\text{RM},\ 400K),\ \Delta H_{\text{trans}}(400K) \quad (7)$$

$$\text{L-Phe}(\text{RM},\ 400K) \rightarrow \text{L-Phe}(g,\ 400K),\ \Delta H_{\text{sub}}(\text{L-Phe, RM, }400K) \quad (8)$$

Eq. (7) could be regarded as the transition from L-Phe form-X to L-Phe RM at 400 K, and the enthalpy change of this process (ΔH_{trans} (400 K)) could be calculated as follow:

$$\text{L-Phe}(\text{form-X},\ 547K) \rightarrow \text{L-Phe}(l,\ 547K),\ \Delta H_{\text{fus}}(\text{form-X},\ 547K) = 64.3\text{kJ}\cdot\text{mol}^{-1} \quad (9)$$

$$\text{L-Phe}(\text{RM},\ 547K) \rightarrow \text{L-Phe}(l,\ 547K),\ \Delta H_{\text{fus}}(\text{RM},\ 547K) = 62.1\text{kJ}\cdot\text{mol}^{-1} \quad (10)$$

$$\text{L-Phe}(\text{form-X},\ 547K) \rightarrow \text{L-Phe}(\text{RM},\ 547K) \quad (11)$$

$$\Delta H_{\text{trans}}\left(547K\right)=\Delta H_{\text{fus}}\left(\text{form-X, }547K\right)-\Delta H_{\text{fus}}\left(\text{RM, }547K\right)=2.2\text{kJ}\cdot\text{mol}^{-1}$$

$$\Delta H_{\text{trans}}\left(400K\right)=\Delta H_{\text{trans}}\left(547K\right)+\left(C_{\text{p,form-X}}-C_{\text{p,RM}}\right)\left(400K-547K\right)=2.3\text{kJ}\cdot\text{mol}^{-1} \quad (12)$$

Where $C_{\text{p,form-X}}$ and $C_{\text{p,RM}}$ were the specific heat capacity of L-Phe form-X and L-Phe RM. $C_{\text{p,RM}}$ was reported to be 203.1±1.5 J·mol^{-1}·K^{-1}. [8]

Eq. (8) was the sublimation process of L-Phe at 400K, and the enthalpy change of this process (ΔH_{sub} (L-Phe, 400 K)) could be described as follow:

$$\Delta H_{\text{sub}}\left(\text{RM},400K\right)=\Delta H_{\text{sub}}\left(\text{RM},298K\right)+\int_{298K}^{400K}\left(C_{\text{p,g}}-C_{\text{p,RM}}\right)dT=158.7\text{kJ}\cdot\text{mol}^{-1} \quad (13)$$

Where $C_{\text{p,g}}$ was the specific heat capacity of gaseous L-Phe, $C_{\text{p,g}}$= 184±1 J·mol^{-1}·K^{-1}.[8]

Combined with Eq. (6), Eq. (12) and Eq. (13), the sublimation enthalpy of L-Phe·H_2O at 400 K could be described as follow:

$$\Delta H_{\text{sub}}\left(\text{L-Phe}\cdot\text{H}_2\text{O},400K\right)=\Delta H_{\text{Dehy}}\left(400K\right)+\Delta H_{\text{trans}}\left(400K\right)+\Delta H_{\text{sub}}\left(\text{L-Phe, RM},400K\right)$$
$$=\left(163.2+2.3+158.7\right)\text{kJ}\cdot\text{mol}^{-1}=324.2\text{kJ}\cdot\text{mol}^{-1}$$

When the calculation result of sublimation enthalpy was sustituted into Eq. (4), the lattice energy of L-Phe·H_2O was obtained to be -112.56 kcal·mol^{-1}.

2. Crystallographic information for L-Phe·H_2O

Table S1 Crystallographic data of L-Phe·H_2O

Formula	$C_9H_{13}NO_3$
Molecular weight	183.20
Crystal system	monoclinic
Space group	P 2_1 (4)
a (Å)	13.0612 (5)
b (Å)	5.4197 (2)
c (Å)	13.8643 (6)
α (°)	90
β (°)	102.611
γ (°)	90
Volume ($Å^3$)	957.746
Z	Z=4
ρ_{calc} (g/cm^3)	1.271
2θ	2.841 to 50.011
F (000)	392
R_1	0.0318
wR_2	0.0825
Goodness-of-fit (GOF)	1.047
Temperature (K)	193 (2)
CCDC No.	2009781

Table S2 The intermolecular hydrogen bond parameters of L-Phe·H_2O

No.	Donor-H···Acceptor	D-A/ Å	H···A/ Å	D-H···A/ °
1	O6-H6B(H_2O)···O1(L-Phe)	0.846	1.830	9.634
2	N1-H1A(L-Phe)···O6(H_2O)	0.910	1.849	176.645
3	O5-H5B(H_2O)···O4(L-Phe)	0.874	1.984	149.043
4	N2-H2A(L-Phe)···O4(L-Phe)	0.910	2.020	78.701
5	N2-H2B(L-Phe)···O3(L-Phe)	0.910	1.878	173.345
6	N1-H1C(L-Phe)···O3(L-Phe)	0.910	2.070	139.319
7	N1-H1C(L-Phe)···O2(L-Phe)	0.910	2.388	97.980
8	N2-H2C(L-Phe)···O2(L-Phe)	0.910	1.965	152.045
9	N2-H2C(L-Phe)···O3(L-Phe)	0.910	2.412	110.203

3. Analysis the bending region by *in situ* micro-infrared and *in situ* micro-Raman

Table S3 Micro-infrared assignments for L-Phe·H_2O

Wavenumber (cm^{-1}) in straight state	Wavenumber (cm^{-1}) in bent state	Wavenumber difference (cm^{-1})	Assignments
3358 ± 0.23	**3363 ± 0.43**	**5**	**O-H str.**
3028 ± 0.44	**3062 ± 0.57**	**34**	**NH_3^+ asym. str.**
2846 ± 0.40	2846 ± 0.29	0	C-H str.
1598 ± 0.48	**1560 ± 0.51**	**38**	**NH_3^+ asym.bending and COO^- asym. str.**
1508 ± 0.40	**1500 ± 0.32**	**8**	**NH_3^+ sym.bending**
1404 ± 0.17	**1417 ± 0.22**	**13**	**COO^- asym. str.**
1311 ± 0.13	1311 ± 0.49	0	CH_2 wagging
1197 ± 0.38	1200 ± 0.43	3	C-CH bending
1148 ± 0.22	1150 ± 0.76	2	CH_2 twisting
1041 ± 0.67	1038 ± 0.91	3	C-C str.
980 ± 0.53	979 ± 0.43	1	CH_2 rocking
915 ± 0.31	918 ± 0.35	3	C-CH bending
857 ± 0.88	859 ± 0.64	2	C-H out-of plane deformation
779 ± 0.65	782 ± 0.82	3	C-C skeletal str.
694 ± 0.50	695 ± 0.46	1	C-H out-of plane deformation
516 ± 0.66	**521 ± 0.19**	**5**	**C-COO^- deformation**

Table S4 Micro-Raman assignments for L-Phe·H_2O

Wavenumber (cm^{-1}) in straight state	Wavenumber (cm^{-1}) in bent state	Wavenumber difference (cm^{-1})	Assignments
138 ± 0.50	146 ± 0.38	8	Lattice modes
251 ± 0.57	269 ± 0.55	18	Lattice modes
346 ± 0.78	347 ± 0.60	1	C-C-C-C in phase vibration
426 ± 0.41	**432 ± 0.50**	**6**	**COO^- rocking**
497 ± 0.60	**489 ± 0.43**	**9**	**H_2O**
541 ± 0.34	539 ± 0.22	2	C_6H_5-C in plane deformation
618 ± 0.69	**624 ± 0.78**	**6**	**COO^- rocking**
823 ± 0.46	822 ± 0.61	1	CH_2 rocking
846 ± 0.50	**853 ± 0.74**	**7**	**NH_3^+ deformation**
1006 ± 0.37	1004 ± 0.50	2	C-C of the benzene ring sym. str
1169 ± 0.65	1177 ± 0.27	8	C-N str.
1194 ± 0.56	**1186 ± 0.84**	**8**	**NH_3^+ rocking**
1310 ± 0.94	1311 ± 0.59	1	CH_2 rocking
1416 ± 0.30	**1422 ± 0.47**	**6**	**COO^- sym. str**
1498 ± 0.29	**1506 ± 0.35**	**8**	**NH_3^+ sym. str**
1587 ± 0.86	1588 ± 0.53	1	C-C ring sym. str of the benzene
1607 ± 0.73	1607 ± 0.84	0	C-C ring sym. str of the benzene

4. **Difference between the calculated lattice energy and experimental value**

Table S5 Lattice energies of L-Phe·H_2O using different combination of force fields and charge assignment rules

Force field/Charge rule	Calculated values (kcal/mol)	Experimental values (kcal/mol)	The difference between experimental and calculated values (kcal/mol)
COMPASS/Forcefield assigned	-29.683	-112.56	-82.877
COMPASS/Gasteiger	-102.121		-10.439
COMPASS/Qeq	-55.048		-57.512
CVFF/Forcefield assigned	-29.421		-83.139
CVFF/Qeq	-51.438		-61.122
CVFF/Gasteiger	-95.941		-16.619
Universal/Qeq	-73.995		-38.565
Universal/Gasteiger	-58.001		-54.559
Dreiding/Gasteiger	**-115.105**		**2.545**
Dreiding/Qeq	-66.901		-45.659
PCFF/Forcefield assigned	-26.730		-85.83
PCFF/Gasteiger	-95.941		-16.619
PCFF/Qeq	-56.484		56.076

5. Attachment energy calculation

Table S6 Attachment energies and molecular interaction energies in each direction of L-Phe·H_2O soft crystal

h k l	E_{att}(Total)	E_{att}(vdW)	E_{att}(Electrostatic)	E_{att}(H-bond)
[0 1 0]	-76.858 kcal/mol	-4.187 kcal/mol	-62.447 kcal/mol	-10.223 kcal/mol
[1 0 0]	-18.078 kcal/mol	-2.26 kcal/mol	-14.187 kcal/mol	-1.627 kcal/mol
[0 1 1]	-65.453 kcal/mol	-3.061 kcal/mol	-55.276 kcal/mol	-7.117 kcal/mol
[1 1 0]	-68.153 kcal/mol	-2.960 kcal/mol	-57.103 kcal/mol	-8.089 kcal/mol

References

1. C. Ouvrard and J. B. Mitchell, *Acta Crystallographica Section B: Structural Science*, 2003, **59**, 676-685.
2. M. Salahinejad, T. C. Le and D. A. Winkler, *Journal of chemical information and modeling*, 2013, **53**, 223-229.
3. A. Hagler, E. Huler and S. Lifson, *Journal of the American Chemical Society*, 1974, **96**, 5319-5327.
4. V. Bisker-Leib and M. F. Doherty, *Crystal Growth & Design*, 2015, **3**, 221-237.
5. G. Chandan and M. Cascella, 2019.
6. J. P. Murray and J. O. Hill, *Thermochimica Acta*, 1984, **72**, 341-347.
7. A. Rojas-Aguilar, E. Orozco-Guare?O, Mart?, M. Amp, #x and nez-Herrera, *Journal of Chemical Thermodynamics*, 2001, **33**, 1405-1418.
8. V. V. Tyunina, A. V. Krasnov, E. Y. Tyunina, V. G. Badelin and G. V. Girichev, *Journal of Chemical Thermodynamics*, 2014, **74**, 221-226.