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Estimated Thermodynamic Parameters of Amlodipine by Group Contribution Method

Zhao Mingrui[1, *], Peng Peng[2]

[1]College of Pharmacy, Henan Medical College, Zhengzhou, China

[2]School of Art and Design, Zhengzhou University of Light Industry, Zhengzhou, China

Email address:

zhaomingrui99@163.com (Zhao Mingrui)

[*]Corresponding author

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Abstract: *Objective:* Amlodipine is the third-generation Calcium channel antagonist of dihydropyridine. which belongs to the first-line antihypertensive drug in clinic and used as racemate and levoisomer. The antihypertensive effection of levo-Amlodipine is twice as much as that of racemate. Physical property data of compounds are often used in scientific research, pharmaceutical process design, chemical and pharmaceutical production, synthesis and resolution of chiral drugs, etc., distinct and accurate estimation of physical property data will greatly save time and effort. In particular, thermodynamic parameters such as enthalpy, entropy and heat capacity are state functions, so in practical applications, a state of matter can be arbitrarily chosen as a reference state, and then calculated. In order to provide data support for the separation and industrial production of Amlodipine, the thermodynamic parameters of Amlodipine were estimated by Joback group contribution method which always used to estimated the thermodynamic parameters of industry product. The physical properties of Amlodipine, such as the melting boiling point, are generally related to the structure of matter. In this paper, by comparing the measurement of melting boiling point with the estimated value of group contribution method, it is shown that the group contribution method is reasonable to split the group, and the values of other thermodynamic properties estimated by the group contribution method have a certain degree of credibility, it can be used to calculate physical properties in industrial production. *Method:* The structure of Amlodipine was divided by Joback group contribution method, and the group contribution value was calculated to get the standard enthalpy of formation, Standard molar isobaric heat capacity, and residual entropy of Amlodipine. *Result:* the standard formation enthalpy of Amlodipine is -143.4KJ·mol^{-1}, standard molar isobaric heat capacity of Amlodipine is108500J·K^{-1}·mol^{-1}, and residual entropy of Amlodipine is349.86J·K^{-1}·mol^{-1}. The melting temperature of Amlodipine was also estimated by Joback group contribution method at 1188.74 K, which was 230°C (503.15 K) measured by experiment and average relative error nearly4.05%. The boiling point temperature of Amlodipine was estimated by Joback method is 1005.97 K, which was 527.2°C (800.35 K) by measured. The average relative error ARD is 2.57%. *Conclusion:* The results show that the thermodynamic parameters of Amlodipine can be estimated by Joback group contribution method. Joback method has a high accuracy in estimating the boiling point of Amlodipine, and it quite fit with the melting point after revised.

Keywords: Antihypertensive Drug, Amlodipine, Group Contribution Method, Standard Enthalpy of Formation Method, Group Contribution Method, Joback Method

1. Introduction

Amlodipine is 6-methyl-2-(2-aminoethoxy) methyl-4-(2-chlorophenyl)-1, 4-dihydro-3, 5-ethyl pyridine dicarboxylate, produced by pfizer Co., is the third generation calcium channel antagonist, which is mainly used to treat hypertension and angina pectoris in clinic. [1-5] Because of the solubility problem, at present, the main forms of Amlodipine benzenesulfonate, Amlodipine maleate, Amlodipine mesylate and chiral compound levAmlodipine benzenesulfonate exist in the market.

Amlodipine is a compound of 1, 4-Dihydropyridines (1, 4-DHPs) that was first developed by the German chemist

Arthur Rudolf, Crown Prince of Austria Hantzsch in 1881, but it wasn't until 1975 that it was discovered, the first dihydropyridine drug nifedipine tablets (trade name"Nifedipine") drugs in the German Bayer Company was launched in 1985 nimodipine tablets (trade name "NIMOTOP") on the market. Amlodipine is a chiral drug developed on the basis of Nimodipine [6, 7]. As shown in Figure 1, since the dihydropyridine ring is linked to 2'-chlorophenyl at the 4 position, and the 2, 3, 5, and 6 positions are substituted by different groups, the asymmetry of the molecule is due to the inhibition effect of the chlorine atom, 4-carbon becomes the chiral center, which can produce a pair of enantiomers, namely, left-handed Amlodipine and right-handed Amlodipine.

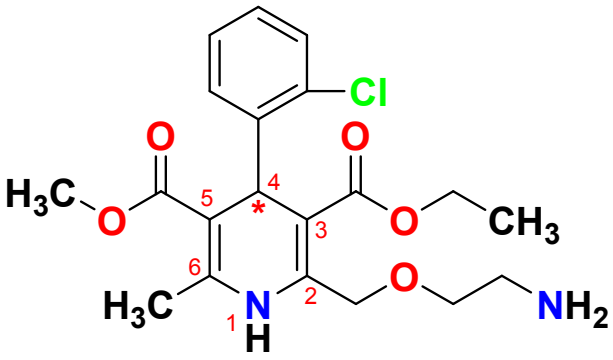

Figure 1. *Molecule structure of Amlodipine.*

2. Materials and Methods

2.1. Physical Properties Estimation

The essence of a chemical reaction is the rearrangement and combination of atoms or atomic groups. The whole process of the reaction is the breaking of the old bond and the formation of the new bond. Therefore, the enthalpy of reaction can be estimated according to the change of bond in the reaction process [8]. The group contribution method assumes that the contribution values of the same group in any molecule are the same, and that the properties of substances are the sum of the contributions of their constituent groups to this property. The intrinsic physicochemical properties of molecules can be estimated by the binding relations of atoms and bonds and the contribution values of the frequencies of atoms in molecules, which can be used to estimate the physical and thermodynamic properties of pure organic compounds. [9, 10] when the physical and thermodynamic data of each component of the reaction system can not completely pass the manual inquiry, it is necessary to carry out physical property estimation [11-17]. There are two methods to estimate physical properties, the group contribution method and the contrast state method, which can not be used because the critical parameters of components can not be found. Group contribution method is divided into Joback method, Constantinous method, Benson method and so on [11, 18-20]. The physical properties of Amlodipine were estimated by Joback method.

2.2. The Standard Enthalpy of Formation of Amlodipine Was Estimated by Joback Method

Table 1. *The Group Division of Amlodipine and Group Contribution values in Joback Method (298.15K).*

Group	-Cl	=C< (Benzene Ring)	>C<(Benzene Ring)	>C<(non-Benzene Ring)	-O-(non-Benzene Ring)	-COO-	-NH-(Benzene Ring)	-NH2
ni	1	10	1	7	1	2	1	1
$n_i\Delta H_i$	-71.55	464.3	79.72	82.23	-132.22	-679.84	21.65	22.02

Note: $\Delta_f H_m^\theta(298.15K)$ is the standard mole formation enthalpy of Amlodipine at 298.15K and standard condition, unit is kJ·mol-1, ni is the number of Group i in Amlodipine; ΔH_i is the corresponding contribution value of Group i in Amlodipine (shown in Table 1)

The calculation result of standard mole formation enthalpy of Amlodipine as follows:

$$\Delta_f H_m^\theta(298K) = 68.29 + \sum_{i=1}^{8} n_i \Delta H_i$$

$$=68.29+(-211.69)$$
$$= -143.4\, kJ \cdot mol^{-1}$$

2.3. The Standard Isobaric Molar Melting of Amlodipine Was Estimated by Joback Method

The standard isobaric molar melting of Amlodipine was estimated by Joback method. The group division and corresponding parameter values of Amlodipine are shown in Table 2.

Table 2. *The Group Division and corresponding parameter value of Amlodipine.*

Group	n	Δa $J \cdot mol^{-1} \cdot K^{-1}$	Δb $J \cdot mol^{-1} \cdot K^{-2}$	Δc $J \cdot mol^{-1} \cdot K^{-3}$	Δd $J \cdot mol^{-1} \cdot K^{-4}$
-Cl	1	33.3	-0.0963	1.87×10^{-4}	-9.96×10^{-8}
=CH- (Benzene Ring)	4	-2.14	0.0574	-1.64×10^{-6}	1.59×10^{-8}
=C< (Benzene Ring)	6	-8.25	0.101	-1.42×10^{-4}	6.78×10^{-4}
>C< (Benzene Ring)	1	-90.9	0.657	-9×10^{-4}	4.69×10^{-7}

Group	n	Δa $J\cdot mol^{-1}\cdot K^{-1}$	Δb $J\cdot mol^{-1}\cdot K^{-2}$	Δc $J\cdot mol^{-1}\cdot K^{-3}$	Δd $J\cdot mol^{-1}\cdot K^{-4}$
>C< (non-Benzene Ring)	7	-0.662	0.427	-6.41×10^{-4}	3.01×10^{-7}
-O-(non-Benzene Ring)	1	25.5	-0.0632	1.11×10^{-4}	-5.48×10^{-8}
-COO-	2	24.5	0.0402	4.02×10^{-5}	-4.52×10^{-8}
-NH- (Benzene Ring)	1	11.8	-0.0230	1.07×10^{-4}	-6.28×10^{-8}
$-NH_2$	1	26.9	-0.0412	1.64×10^{-4}	-9.76×10^{-8}

$$\sum_{j=1}^{8} n_j \Delta a = -7.094 J\cdot mol^{-1}\cdot K^{-1}$$

$$\sum_{j=1}^{8} n_j \Delta b = 4.3383 J\cdot mol^{-1}\cdot K^{-2}$$

$$\sum_{j=1}^{8} n_j \Delta c = -5.596\times10^{-3} J\cdot mol^{-1}\cdot K^{-3}$$

$$\sum_{j=1}^{8} n_j \Delta d = 4.070\times10^{-3} J\cdot mol^{-1}\cdot K^{-4}$$

$$C^{\theta}_{\mathrm{p,m}}(298K) = (\sum_{j=1}^{8} n_j \Delta a - 37.93) + (\sum_{j=1}^{8} n_j \Delta b + 0.21)\times 298$$

$$+(\sum_{j=1}^{8} n_j \Delta c - 3.91\times10^{-4})\times 298^2$$

$$+(\sum_{j=1}^{8} n_j \Delta d + 2.06\times10^{-7})\times 298^3$$

$$= (-7.094 - 37.93) + (4.3383 + 0.21)\times 298$$

$$+(-5.596\times10^{-3} - 3.91\times10^{-4})\times 298^2 + (4.070\times10^{-3}\times 298^3)$$

$$= -45.024 + 1355.393 - 531.670 + 1.077\times10^{5}$$

$$= 1.085\times10^{5} J\cdot \mathrm{mol}^{-1}\cdot K^{-1}$$

2.4. Residual Entropy Was Estimated by Group Contribution Method

Residual entropy was estimated by Joback group contribution method, the Group Division and corresponding parameter value of Amlodipine are as follows (shown in table 3), Tb, Tc, Pc, Vc of Amlodipine are calculated too.

Table 3. *The Group Division and corresponding parameter value Tb, Tc, Pc, Vc of Amlodipine (total atom number n_A=53).*

Group	-Cl	=C< (Benzene Ring)	>C<(Benzene Ring)	>C<(non-Benzene Ring)	-O-(non-Benzene Ring)	-COO-	-NH-(Benzene Ring)	$-NH_2$
n_i	1	10	1	7	1	2	1	1
Tf	13.55	37.02	60.15	46.43	22.23	53.60	101.51	66.89
Tb	38.13	31.01	21.32	18.25	22.42	81.10	52.82	73.23
Tc	0.0105	0.0143	0.0042	0.0067	0.0168	0.0481	0.0130	0.0243
Pc	-0.0049	0.008	0.0061	0.0043	0.0015	0.0005	0.0114	0.0109
Vc	58	32	27	27	18	82	29	38

2.4.1. Joback Method Calculate the Melting Point of Amlodipine

$$\sum T_f = 13.55 + 10\times 37.02 + 60.15 + 7\times 46.43 + 22.23 + 2\times 53.60 + 101.51 + 66.89 = 1066.74K$$

$$\mathrm{Tf}=122+\sum T_{\mathrm{f}}$$

$$=122+1066.74=1188.74\mathrm{K}$$

2.4.2. Joback Method Calculate the Boiling Point of Amlodipine

$$\sum \Delta T_{\mathrm{b}} = 31.01\times10 + 38.13 + 21.32 + 18.25\times7 + 81.10\times2 + 22.42 + 52.82 + 73.23 = 807.97K$$

melting point:

$$T_b = 198 + \sum \Delta T_b = 198 + 807.97 = 1005.97K$$

2.4.3. Joback Method Estimate Residual Entropy of Amlodipine

$$\sum \Delta T_i = 0.0143\times10 + 0.0105 + 0.0042 + 0.0067\times7 + 0.0481\times2 + 0.0168 + 0.0130 + 0.0243 = 0.3549$$

$$\sum \Delta p_i = 0.008\times10 + (-0.0049) + 0.0061 + (0.0043\times7) + (0.0005\times2) + 0.0015 + 0.0114 + 0.0109 = 0.1361$$

$$\sum \Delta V_i = 32\times10 + 58 + 27 + 27\times7 + 82\times2 + 18 + 29 + 38 = 843$$

Critical temperature:

$$\begin{aligned} T_c &= T_b\left[0.584 + 0.965\sum \Delta T_i - \left(\sum \Delta T_i\right)^2\right]^{-1} \\ &= 1005.97\times\left[0.584 + 0.965\times0.3549 - (0.3549)^2\right]^{-1} \\ &= 1256.64K \end{aligned}$$

Critical pressure:

$$\begin{aligned} P_c &= \left(0.113 + 0.0032n_A - \sum \Delta P_{\mathrm{i}}\right)^{-2} \\ &= (0.113 + 0.0032\times53 - 0.1361)^{-2} \\ &= 46.59\mathrm{bar} \end{aligned}$$

Critical volume:

$$V_{\mathrm{C}} = 17.5 + \sum \Delta V_{\mathrm{i}} = 17.5 + 843 = 860.5cm^3\cdot mol^{-1}$$

$$T_{\mathrm{br}} = T_{\mathrm{b}} / T_C = 1005.97 \div 1256.64 = 0.8$$

eccentricity factor:

$$\omega = \frac{3T_{br}}{7(1-T_{\mathrm{br}})}\log p_C - 1 = \frac{3}{7}\times\frac{0.8}{1-0.8}\log46.59 - 1 = 1.86$$

Estimate residual entropy at temperature is 125°C and pressure is 1000kPa, suppose criterion pressureP0=100kPa and temperature T0=273.15.

$$P_{\mathrm{r}} = \frac{P}{P_C} = \frac{1000KPa}{4659KPa} = 0.21$$

$$T_r = \frac{T}{T_C} = \frac{(273.15+125)K}{1256.64K} = 0.32$$

$$\left(\frac{S_{\mathrm{m}}^{\theta} - S_m}{R}\right)^{(0)} = 8.635$$

$$\left(\frac{S_{\mathrm{m}}^{\theta} - S_m}{R}\right)^{(1)} = 16.744$$

According to Lee-Kesler method,

$$\Delta S_m^\theta = R\left[\left(\frac{S_m^\theta - S_m}{R}\right)^{(0)} + \omega\left(\frac{S_m^\theta - {}_m}{R}\right)^{(1)}\right] - R\ln\frac{p_0}{p}$$

$$= 8.314\times\left(8.635 + 1.86\times 16.744\right) - 8.314\times\ln\frac{100kpa}{1000kpa}$$

$$= 349.86J\cdot K^{-1}\cdot \text{mol}^{-1}$$

3. Results

3.1. Measurement of the Melting Point of Amlodipine

Take a 6-8cm long capillary with an inner diameter of about 1mm and seal one end of it on the alcohol lamp. Take a small amount of sample on the surface dish and stack it into a small pile. Insert the open end of the capillary into the pile, i. e. a small amount of sample is squeezed into the capillary tube. A glass tube about 20-30cm in length is erected on the clean surface, and the open end of the capillary tube containing the sample is thrown upward from the upper end of the glass tube to make it fall freely. This repeated several times, until the sample in the capillary height of 2-3 mm, no gap in the middle until. Put silicone oil into the Thiele tube, place the sample capillary in the silicone oil, and fix the melting point meter. At the same time, the sample in the capillary was observed carefully, and the heating rate was controlled at 3 ~ 4°C /min, then slowly increased to 1 ~ 2°C /min. When the sample begins to collapse and a liquid appears, it is the first melting. The heat source should be removed immediately. The melting point of Amlodipine was determined to be 230°C or 403 K.

3.2. Measurement of the Boiling Point of Amlodipine

The boiling point of Amlodipine was 527.2°C (800.35 K) by distillation and determined by boiling point meter.

4. Conclusion

4.1 The Melting Point of Amlodipine

The melting point of Amlodipine was determined to be 230°C (503K). The melting point of Amlodipine was estimated by Joback group contribution method to be 1188.74 K with an average relative error of ARD= $\frac{1}{N}\sum$calculate-experiment/experiment =151.32%. (N is the number of measurement). But if the number of groups is not considered in the estimation of Joback group contribution method, only the type of groups is considered, the melting point of Amlodipine is calculated by Joback group addition method.

$$\sum T_f = 13.55 + 37.02 + 60.15 + 46.43 + 22.23 + 53.60 + 101.51 + 66.89 = 401.38K$$

Tf=122+401.38=523.38K

Then average relative error ARD only is 4.05%.

4.2. The Boiling Point of Amlodipine

The boiling point of Amlodipine was determined to be 527.2 °C (800.35 K). The boiling point of Amlodipine was estimated to be 1005.97 K by Joback group contribution method, and the average relative error ARD is 2.57%. The results show that the thermodynamic parameters of Amlodipine can be estimated by Joback group contribution method. The Joback method has high accuracy in estimating boiling point temperature of Amlodipine, but the difference of melting point is large, which needs to be revised. If only the type of resolution group is considered, the accuracy of the estimation result is high, and the relative error is 4.05%.

4.3. Standard Molar Enthalpy, Standard Molar Isobaric Heat Capacity and Residual Entropy of Amlodipine

The standard molar reaction enthalpy of Amlodipine was estimated by Joback method and the value is -143.4kJ·mol^{-1}, Standard molar isobaric heat capacity value is 108500J·mol^{-1}·K^{-1} and the residual entropy is 349.86J·mol^{-1}·K^{-1}.

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