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Estimated Thermodynamic Parameters of Nifedipine by Group Contribution Method

Zhao Mingrui[1], Liu Guangyu[2]

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

[2]College of Chemical Engineering, He'nan University of Technology, Zhengzhou, China

Email address:
zhaomingrui99@163.com (Zhao Mingrui)

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Abstract: *Objective*: Nifedipine is a calcium channel antagonist of dihydropyridine. There are many methods to synthesize nifedipine, but the yield is not high. In order to find a suitable process for the synthesis and industrialization of nifedipine, thermodynamic Parameters of Nifedipine had been estimated by Group Contribution Method. *Methods*: the standard molar enthalpy of reaction, standard isobaric heat capacity, residual entropy, the melting temperature and the flash point temperature of nifedipine were estimated by Joback method. *Results*: The results show that the standard molar reaction enthalpy of Nifedipine was estimated estimated by Joback method is $\Delta_f H_m^\theta(298.15K) = 216.47KJ \cdot mol^{-1}$, standard molar isobaric heat capacity is 108800J·mol-1·K-1 and residual entropy of nifedipine estimated by Joback method is $\Delta S_m^\theta\left(398K\right) = 238.8J \cdot K^{-1} \cdot mol^{-1}$ at 290.15 K and atmospheric pressure which match with the datas of experiment. However the melting temperature and the flash point temperatureof nifedipine was estimated by Joback method is 1074.02 K and 969.98 K seperately, which have large gap between the estamated datas and the reality, and still need to revise. *Coclusion*: the thermodynamic parameters of nifedipine can be estimated by Joback group contribution method. Its corresponding data will provide essential support for industrial design and further theoretical studies.

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

1. Introduction

Nifedipine, also known as dimethyl 1, 4 – dihydro - 2, 6-dimethyl - 4 - (2-nitrophenyl) -3, 5 - pyridine dicarboxylate, is a dihydropyridine calcium antagonist with a molecular structure shown in Figure 1, it is used to prevent and treat angina pectoris of coronary heart disease, especially variant angina pectoris and angina pectoris caused by coronary artery spasm [1-5]. It has no adverse effect on respiratory function, so it is suitable for angina pectoris patients with obstructive disease of respiratory tract. Its curative effect is better than that of β receptor antagonist. Also applicable to all types of hypertension, refractory, severe hypertension also has a good effect. Since it can reduce afterload and has good effect on refractory heart failure, it is suitable for long-term use. [6, 7]

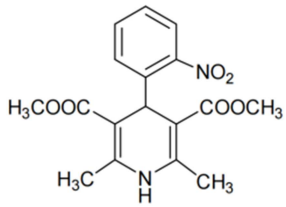

Figure 1. *Molecule structure of Nifedipine.*

2. Physical Properties Estimation

2.1. Selective of Physical Properties Estimation

Chemical reaction, always means the bond of atoms or groups of atoms were broken, and at the same time, the new bond of atoms or groups of atoms were format.

Therefore, according to the change of the bond of atoms or

groups of atoms in the reaction process, the enthalpy of reaction can be estimated [8-10]. The group contribution method, which assumes that the contribution values of the same group in any molecule are the same, and the contributions of their constituent groups to this property sum to build the properties of substances.

With the binding relations of atoms or groups of atoms, meanwhile, the contribution values of the frequencies of atoms in molecules, the physical and thermodynamic properties of pure organic compounds can be estimated. [11-17]

Through Pamphlet, the thermodynamic data and physical data of each component of the reaction system can be gotten, or, physical property estimation had to be carried out. the group contribution method and the contrast state method, were used to estimate physical properties, Group contribution method, which can not be used because the critical parameters of components can not be found, is divided into Joback method, Constantinous method, Benson method and so on [18-20]. The physical properties of nifedipine were estimated by Joback method.

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

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

Group	-NO_2	=C< (Benzene Ring)	>C<(Benzene Ring)	>C<(non-Benzene Ring)	-COO-	-NH-(Benzene Ring)
n_i	1	10	1	4	2	1
$n_i \Delta H_i$	-66.57	464.3	79.72	328.92	-679.84	21.65

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

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

$$\Delta_f H_m^{\theta}(298K) = 68.29 + \sum_{i=1}^{6} n_i \Delta H_i$$

$$=68.29+148.18$$

$$= 216.47\, kJ \cdot mol^{-1}$$

2.3. The Standard Isobaric Molar Melting $C_{p,m}^{\theta}$ of Nifedipine Was Estimated by Joback Method

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

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

Group	n	$\Delta a J \cdot mol^{-1} \cdot K^{-1}$	$\Delta b J \cdot mol^{-1} \cdot K^{-2}$	$\Delta c J \cdot mol^{-1} \cdot K^{-3}$	$\Delta d J \cdot mol^{-1} \cdot K^{-4}$
-NO_2	1	25.9	-0.00374	1.29×10^{-4}	-8.88×10^{-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}
>C< (non-Benzene Ring)	4	-0.662	0.427	-6.41×10^{-4}	3.01×10^{-7}
-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}

$$\sum_{j=1}^{7} n_j \Delta a = -64.908 J \cdot mol^{-1} \cdot K^{-1}$$

$$\sum_{j=1}^{7} n_j \Delta b = 5.221 J \cdot mol^{-1} \cdot K^{-2}$$

$$\sum_{j=1}^{7} n_j \Delta c = -4.006\times10^{-3} J \cdot mol^{-1} \cdot K^{-3}$$

$$\sum_{j=1}^{7} n_j \Delta d = 4.069\times10^{-3} J \cdot mol^{-1} \cdot K^{-4}$$

$$C_{\mathrm{p,m}}^{\theta}\left(298K\right)=(\sum_{j=1}^{7}n_j\Delta a-37.93)+(\sum_{j=1}^{7}n_j\Delta b+0.21)\times 298$$
$$+(\sum_{j=1}^{7}n_j\Delta c-3.91\times 10^{-4})\times 298^2$$
$$+(\sum_{j=1}^{7}n_j\Delta d+2.06\times 10^{-7})\times 298^3$$

$$=(-64.908-37.93)+(5.221+0.21)\times 298$$
$$+(-4.006\times 10^{-3}-3.91\times 10^{-4})\times 298^2+(4.069\times 10^{-3}\times 298^3)$$
$$=-102.838+1618.438-390.471+1.077\times 10^5$$
$$=1.088\times 10^5\,J\cdot \mathrm{mol}^{-1}\cdot K^{-1}$$

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 Nifedipine are as follows (shown in table 3), Tb, Tc, Pc, Vc of Nifedipine are calculated too.

Table 3. *The Group Division and corresponding parameter value Tb, Tc, Pc, Vc of Nifedipine (total atom number n_A=44).*

Group	-NO_2	=C< (Benzene Ring)	>C<(Benzene Ring)	>C<(non-Benzene Ring)	-COO-	-NH-(Benzene Ring)
n_i	1	10	1	4	2	1
Tf	127.24	37.02	60.15	46.43	53.60	101.51
Tb	152.54	31.01	21.32	18.25	81.10	52.82
Tc	0.0437	0.0143	0.0042	0.0067	0.0481	0.0130
Pc	0.0064	0.0008	0.0061	0.0043	0.0005	0.0114
Vc	91	32	27	27	82	29

2.4.1. Joback Method Calculate the Melting Point of Nifedipine

The methods of parameter measurement cited from [19]

$$\sum T_f=127.24+10\times 37.02+60.15+4\times 46.43+2\times 53.60+101.51$$
$$=952.02K$$

$$\mathrm{Tf}=122+952.02=1074.02\mathrm{K}$$

2.4.2. Joback Method Calculate the Boiling Point of Nifedipine

$$T_b=31.01\times 10+15254+21.32+81.10\times 2+1825\times 4+5282=77198$$

melting point:

$$T_b=198\Sigma\Delta T_b=198+771.98=969.98\mathrm{K}$$

2.4.3. Joback Method Estimate Residual Entropy of Nifedipine

$$\sum\Delta T_i=0.0143\times 10+0.0042+0.0437+0.0481\times 2+0.0067\times 4+0.0130$$
$$=0.3269$$
$$\sum\Delta P_i=0.008\times 10+0.0064+0.0005\times 2+0.0061+0.0043\times 4+0.0114$$
$$=0.0501$$
$$\sum\Delta V_i=32\times 10+91+27+27\times 4+82\times 2+29=739$$

Critical temperature:

$$T_c = T_b\left[0.584 + 0.965\sum \Delta T_i - (\sum \Delta T_i)^2\right]^{-1}$$
$$= 969.98 \times \left[0.584 + 0.965 \times 0.3269 - (0.3269)^2\right]^{-1}$$
$$= 1223.8K$$

Critical pressure:

$$P_C = (0.113 + 0.0032\mathrm{n}_A - \sum \Delta P_i)^{-2}$$
$$= (0.113 + 0.0032 \times 44 - 0.0501)^{-2}$$
$$= 24.1bar$$

Critical volume:

$$V_c = 17.5 + \sum \Delta V_i = 17.5 + 739 = 756.5\mathrm{cm}^3 \cdot mol^{-1}$$

$$T_{\mathrm{br}} = T_b / T_c = \frac{969.98}{1223.8} = 0.79$$

eccentricity factor:

$$\omega = \frac{3T_{\mathrm{br}}}{7(1 - T_{br})}\log P_c - 1 = \frac{3}{7} \times \frac{0.79}{1 - 0.79} \times \log 24.1 - 1 = 1.23$$

Estimate residual entropy at temperature is 125°C and pressure is 1000kPa, suppose criterion pressureP_0=100kPa and temperature T_0=273.15 k.

$$P_{\mathrm{r}} = \frac{P}{P_C} = \frac{1000KPa}{2410KPa} = 0.41$$
$$T_r = \frac{T}{T_C} = \frac{(273.15+125)K}{1223.8K} = 0.33$$

$$\left(\frac{S_{\mathrm{m}}^{\theta} - S_m}{R}\right)^{(0)} = 7.529$$

$$\left(\frac{S_{\mathrm{m}}^{\theta} - S_m}{R}\right)^{(1)} = 15.359$$

According to Lee-Kesler method,

$$\Delta S_m^{\theta} = R\left[\left(\frac{S_m^{\theta} - S_m}{R}\right)^{(0)} + \omega\left(\frac{S_m^{\theta} - {}_m}{R}\right)^{(1)}\right] - R\ln\frac{p_0}{p}$$
$$= 8.314 \times (7.529 + 1.23 \times 15.359) - 8.314 \times \ln\frac{100kpa}{1000kpa}$$
$$= 238.8J \cdot K^{-1} \cdot \mathrm{mol}^{-1}$$

3. Results

3.1. Measurement of the Melting Point and the Boiling Point of Nifedipine

The apparatus and method used to measure the melting point and the boiling point of Nifedipine are the same as in our former work. Moreover, to verify the uncertainty of the measurement, a laser monitoring technique has been used to measure the experimental values, and compared with literature values, it proved that this experimental technique was reliable.

3.2. Ir Spectra of Nifedipine

X-ray diffraction patterns were recorded with an X-ray

diffractometer (smar9kw, Japan). Infrared spectra were measured by Nicolet 380 (USA) FTIR photometer. Infrared Spectrum of Nifedipine is as follow.

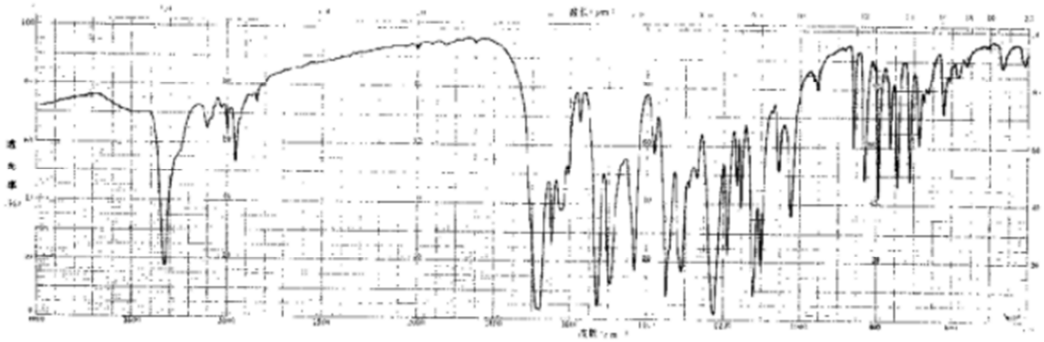

Figure 2. *Infrared Spectrum of Nifedipine.*

4. Conclusion

The standard molar reaction enthalpy of Nifedipine was estimated by Joback method and the value is 216.47kJ·mol^{-1}, Standard molar isobaric heat capacity value is 108800J·mol^{-1}·K^{-1} and the residual entropy is 238.8J·mol^{-1}·K^{-1} at290.15 K and atmospheric pressure. Its corresponding data will provide essential support for industrial design and further theoretical studies.

The melting point of Nifedipine was 1074.02 K estimated by Joback group contribution method. The boiling point of Nifedipine was 969.98 K estimated by Joback group contribution method. The results show that the thermodynamic parameters of Nifedipine can be estimated by Joback group contribution method. The Joback method has high accuracy in estimating boiling point temperature of Nifedipine, but the difference of melting point is large, which needs to be revised.

Acknowledgments

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