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Thermodynamic Parameters of Fluoxetine Estimated by Group Contribution Method

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Abstract: *Background*: fluoxetine is a commonly used antidepressant in clinic. There are many synthetic methods, but the total yield is not very high. 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 order to provide data support for industrial production of Fluoxetine, the thermodynamic parameters of fluoxetinewere estimated by Joback group contribution method which always used to estimated the thermodynamic parameters of industry product. 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. Since the melting boiling point is generally related to the structure of the substance, it is found that the measured value is basically consistent with the estimated value by group contribution method. Based on the group contribution method, other thermodynamic properties such as molar melting, standard enthalpy of formation and residual entropy are also estimated to provide data support for the calculation in industrial production. *Subjects and Methods*: The structure of fluoxetine 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 Fluoxetine. *Results*: the standard formation enthalpy of fluoxetineis202.09 $kJ \cdot mol^{-1}$, standard molar isobaric heat capacity of fluoxetineis 54590 $J \cdot mol^{-1} \cdot K^{-1}$, and residual entropy of fluoxetineis 261.5 $J \cdot mol^{-1} \cdot K^{-1}$. The melting temperature of fluoxetinewas also estimated by Joback group contribution method at 825.94 K, which measured by experiment is 158°C, or 456 K, with average relative error ARD = 8.11%. The boiling point temperature of fluoxetine was estimated by Joback method is 733.87 K, which was 569.2°C (867.35K) by measured. The average relative error ARD is 15.38%. *Conclusions*: The results show that the thermodynamic parameters of fluoxetine can be estimated by Joback group contribution method. Joback method has a high accuracy in estimating the boiling point of Fluoxetine, and it quite fit with the melting point after revised.

Keywords: Fluoxetine, Antidepressant Drug, Group Contribution, Standard Enthalpy of Formation, Joback Method

1. Introduction

Depression is a psychotic disorder characterized by morbid changes in mood, Depression, reticence, strong suicidal tendencies, or mania, heightened emotions, and increased activity. [1] the incidence of the disease has increased in recent years. Antidepressants are mainly used in the treatment of depression and a variety of depressive states. The etiology of depression is complex and may be related to a lack of neurotransmitters such as (-)-noradrenaline and 5-hydroxytryptamine in the body [2]. Serotonin-reuptake Inhibitors (SSRIs) are 5-hydroxytryptamine Reuptake inhibitor that selectively inhibit 5-hydroxytryptamine reuptake by nerve cells, increasing their concentration in the synaptic space and acting as antidepressants. Common drugs are fluoxetine.

Fluoxetine (Prozac), N-methyl-3-phenyl-3-(4-trifluoromethyl phenoxy) propylamine hydrochloride, is a new generation of non-tricyclic antidepressants developed by Lilly Co. USA, the structure is shown in Figure 1. Because of its high selectivity, safety and bioavailability, it is widely

used in clinical practice and is one of the essential drugs listed by the World Health Organization (who). It is also an essential drug for the basic health system [3-5]. fluoxetinecontains a chiral center with a pair of enantiomers, namely (R)-and (s)-fluoxetine. A clinical study of chiral (R)-or (s)-fluoxetine by SEPRACOR found that (R)-fluoxetine has a shorter half-life and action time than commercial racemic fluoxetine, it can greatly reduce the adverse side effects of racemic fluoxetine, such as headache, anxiety and suicidal impulse. [1, 6] fluoxetinehydrochloride is widely sold in the market at present.

The fluoxetineis a selective inhibitor of 5-hydroxytryptamine reuptake. It enhances 5-hydroxytryptamine function by inhibiting 5-hydroxytryptamine reuptake in the central nervous system and is used in the treatment of a wide range of depressive disorders, including mild and severe depression, bipolar affective disorder depression, psychogenic depression and depressive neurosis. The main effects of (R)-fluoxetine and (s)-fluoxetine are the treatment of depression and the prevention of Migraine, respectively. [2, 7] the racemic is now on the market. Common preparation steps are shown in figure 2.

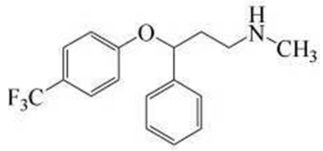

Figure 1. *Molecule structure of Fluoxetine.*

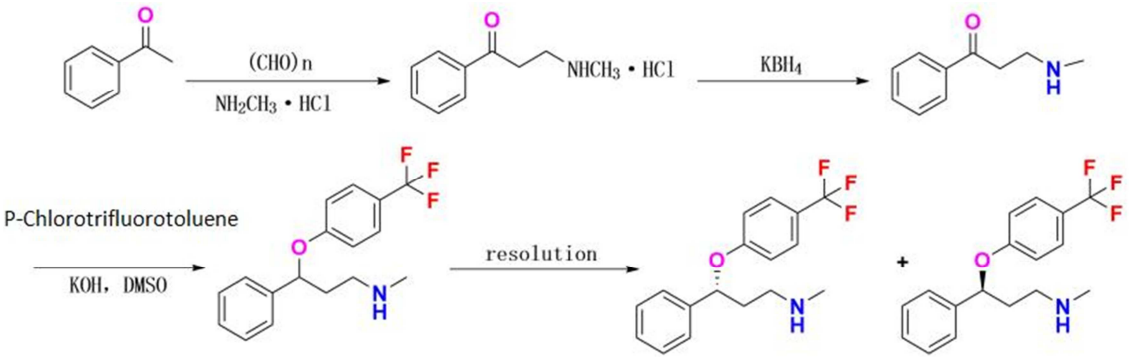

Figure 2. *Preparation steps of fluoxetinehydrochloride salt.*

Although there are many methods for the synthesis and resolution of fluoxetine [8-11], the total yield of fluoxetineis low, about 40%. The thermal effect of chemical reaction is an important basis for reactor design and operation conditions optimization. Therefore, the group contribution method is used to estimate the thermodynamic parameters of the fluoxetinein order to provide data support for the optimization of the preparation process of the fluoxetine.

2. Subjects and Methods

2.1. Selection of 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 [12]. 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. [13, 14] 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 [15-17]. 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 [15, 18-20]. The physical properties of fluoxetine. were estimated by Joback method.

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

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

Group	-F	=C< (Benzene Ring)	>C<(non-Benzene Ring)	-O-(non-Benzene Ring)	-NH-(non-Benzene Ring)
n_i	3	12	5	1	1
$n_i \Delta H_i$	-755.76	557.16	411.15	-132.22	53.47

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

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

$$\Delta_f H_m^{\theta}(298K) = 68.29 + \sum_{i=1}^{5} n_i \Delta H_i = 68.29 + 133.8 = 202.09\text{KJ} \cdot mol^{-1}$$

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

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

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

Group	n	Δ*a* $J \cdot mol^{-1} \cdot K^{-1}$	Δ*b* $J \cdot mol^{-1} \cdot K^{-2}$	Δc $J \cdot mol^{-1} \cdot K^{-3}$	Δd $J \cdot mol^{-1} \cdot K^{-4}$
-F	3	0.265	-0.0913	1.91×10^{-4}	-1.03×10^{-7}
=C< (Benzene Ring)	3	-8.25	0.101	-1.42×10^{-4}	6.78×10^{-4}
>C< (non-Benzene Ring)	5	-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}
-NH- (non-Benzene Ring)	1	-1.12	0.0762	-4.86×10^{-5}	1.05×10^{-8}
=CH- (Benzene Ring)	9	-2.14	0.0574	-1.64×10^{-6}	1.59×10^{-8}

$$\sum_{j=1}^{6} n_j \Delta a = -21.945 J \cdot mol^{-1} \cdot K^{-1}$$

$$\sum_{j=1}^{6} n_j \Delta b = 2.694 J \cdot mol^{-1} \cdot K^{-2}$$

$$\sum_{j=1}^{6} n_j \Delta c = -3.010 \times 10^{-3} J \cdot mol^{-1} \cdot K^{-3}$$

$$\sum_{j=1}^{6} n_j \Delta d = 2.035 \times 10^{-3} J \cdot mol^{-1} \cdot K^{-4}$$

$$C_{p,m}^{\theta}(298K) = (-21.945 - 37.93) + (2.694 + 0.21) \times 298$$
$$+(-3.010 \times 10^{-3} - 3.91 \times 10^{-4}) \times 298^2$$
$$+(2.035 \times 10^{-3} \times 298^3)$$
$$= -59.875 + 865.392 - 64.822 + 5.385 \times 10^4$$
$$= 5.459 \times 10^4 J \cdot mol^{-1} \cdot K^{-1}$$

2.4. Residual Entropy Was Estimated by Group Contribution Method

Joback group contribution method used to estimate the residual entropy of fluoxetine, follows are the Group Division and corresponding parameter value (shown in table 3), Tb, Tc, Pc, Vc of fluoxetine are calculated too.

Table 3. *The group division and corresponding parameter value Tb, Tc, Pc, Vc of fluoxetine. (total atom number n_A=40).*

Group	-F	=C< (Benzene Ring)	>C<(non-Benzene Ring)	-O-(non-Benzene Ring)	-NH-(non-Benzene Ring)
n_i	3	12	5	1	1
Tf	-15.78	37.02	46.43	22.23	52.66
Tb	-0.03	31.01	18.25	22.42	50.17
Tc	0.0111	0.0143	0.0067	0.0168	0.0295
Pc	-0.0057	0.0008	0.0043	0.0015	0.0077
Vc	27	32	27	18	35

2.4.1. Joback Method Calculate the Melting Point of Fluoxetine

$$\sum T_f = 3\times(-15.78) + 12\times37.02 + 5\times46.43 + 22.23 + 52.66$$
$$= 703.94K$$

T_f=122+703.94=825.94k

2.4.2. Joback Method Calculate the Boiling Point of Fluoxetine

The methods of parameter measurement cited from [19]

$$\sum \Delta T_b = (-0.03) \times 3 + 31.01 \times 12 + 18.25 \times 5 + 22.42 + 50.17$$
$$= 535.87K$$

melting point:

$$T_b = 198 + \sum \Delta T_b = 198 + 535.87 = 733.87K$$

2.4.3. Joback Method Estimate Residual Entropy of Fluoxetine

$$\sum \Delta T_i = 0.111 \times 3 + 0.0143 \times 12 + 0.0067 \times 5 + 0.0168 + 0.0295 = 0.5844$$
$$\sum \Delta P_i = (-0.0057) \times 3 + 0.0008 \times 12 + 0.0043 \times 5 + 0.0015 + 0.0077 = 0.0232$$
$$\sum \Delta V_i = 27 \times 3 + 32 \times 12 + 27 \times 5 + 18 + 35 = 653$$

Critical temperature:

$$T_C = T_b \left[0.584 + 0.965 \sum \Delta T_i - (\sum \Delta T_i)^2\right]^{-1}$$
$$= 733.87 \times \left[0.584 + 0.965 \times 0.5844 - (0.5844)^2\right]^{-1}$$
$$= 910.03K$$

Critical pressure:

$$P_c = (0.113 + 0.0032 n_A - \sum \Delta P_i)^{-2}$$
$$= (0.113 + 0.0032 \times 40 - 0.0232)^{-2}$$
$$= 21.08bar$$

Critical volume:

$$V_c = 17.5 + \sum \Delta V_i = 17.5 + 653 = 670.5 cm^3 \cdot mol^{-1}$$

$$T_{br} = T_b / T_c = \frac{733.87}{910.03} = 0.81$$

The eccentricity factor ω, which reflects the degree of eccentricity or non-sphericity of a molecule, is used to measure the complexity of the geometry and polarity of a molecule to some extent.
eccentricity factor:

$$\omega = \frac{3T_{br}}{7(1 - T_{br})} \log P_C - 1 = \frac{3 \times 0.81}{7 \times (1 - 0.81)} \times \log 21.08 - 1 = 1.42$$

Estimate residual entropy at temperature is 25°C and pressure is 100kPa, suppose criterion pressure P0=100kPa and temperature T0=273.15.

$$P_r = \frac{P}{P_C} = \frac{100kPa}{2108kPa} = 0.0474$$

$$T_r = \frac{T}{T_C} = \frac{(273.15 + 25)K}{910.03K} = 0.327$$

$$\left(\frac{S_m^\theta - S_m}{R}\right)^{(0)} = 9.579$$

$$\left(\frac{S_m^\theta - S_m}{R}\right)^{(1)} = 15.408$$

According to Lee-Kesler method,

$$\Delta S_m^\theta = R\left[\left(\frac{S_m^\theta - S_m}{R}\right)^{(0)} + \omega\left(\frac{S_m^\theta - S_m}{R}\right)^{(1)}\right] - R\ln\frac{p_0}{p}$$
$$= 8.314 \times (9.579 + 1.42 \times 15.408) - 8.314 \times \ln\frac{100kpa}{100kpa}$$
$$= 261.5 J \cdot K^{-1} \cdot mol^{-1}$$

3. Measurement of Gibbs Free Energy of Fluoxetine

Using a bonded stationary phase to separate enantiomers of chiral drugs and to analyze the mechanism of chiral recognition, Jiaxi Li et al. [19] used molecular simulation techniques to calculate the thermodynamic parameters during the separation of High-performance liquid chromatography, the results show that the peak level of enantiomers corresponds to the binding free energy, which provides a good prospect for further understanding the mechanism of chiral recognition. Paulo S. Carvalho et al. [20] calculated the thermodynamic parameters and melting heat of fluoxetinenitrate (molecular structure as shown in figure 3) and showed that the Gibbs Free Energy at 300 K were 21.599 KJ·mol^{-1} and 20.098 KJ·mol^{-1}, respectively.

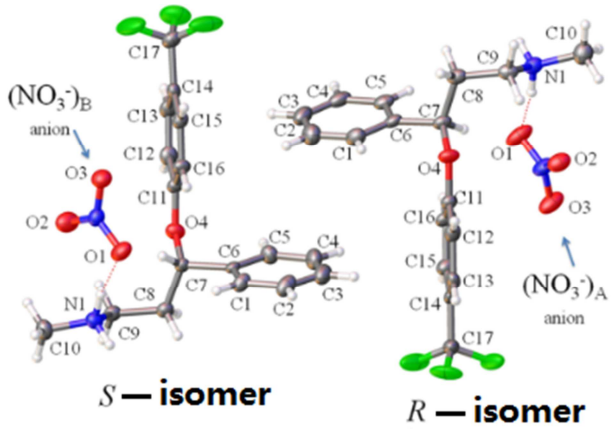

Figure 3. *Molecular structure of fluoxetinenitrate [20].*

4. Discussion

4.1. The Melting Point of Fluoxetine

The melting point of fluoxetine was determined to be 156.8°C (456K). The melting point of fluoxetine estimated by Joback group contribution method to be 825.94K with an average relative error (ARD) is 8.11%.

4.2. The Boiling Point of Fluoxetine

The boiling point of fluoxetinewas determined to be 569.2°C (867.35K). The boiling point of fluoxetinewas estimated to be 733.87K by Joback group contribution method, and the average relative error ARD is 15.38%. The results show that the thermodynamic parameters of fluoxetine can be estimated by Joback group contribution method. The Joback

method has high accuracy in estimating boiling point temperature of fluoxetine.

4.3. Standard Molar Enthalpy

Standard molar isobaric heat capacity, residual entropy of fluoxetine and the standard molar reaction enthalpy of fluoxetinewas estimated by Joback method and the value is 202.09kJ·mol^{-1}, Standard molar isobaric heat capacity value is 54590J·mol^{-1}·K^{-1} and the residual entropy is 261.5J·mol^{-1}·K^{-1}.

5. Conclusion

The apparatus and method used to measure the melting point and the boiling point of fluoxetine are the same as in our former work. The melting point of fluoxetine was determined to be 158°C or 456K. The boiling point of fluoxetine is 569.2°C (867.35K) by distillation and determined by boiling point meter. Laser monitoring technique has been used to measure the experimental values, and compared with literature values, The average relative error of above system can be neglect, so it was proven that this experimental technique was reliable.

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