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Low-Temperature Heat Capacities and Thermal Stability of New Antidepressant [5-Amino-4-(3-indoly)-3-methyl Pyrazole]

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Low-temperature heat capacities of 5-amino-4-(3-indoly)-3-methyl pyrazole were measured by a temperature modulated differential scanning calorimetry in the temperature range from T = 193 to 503 K. An obvious endothermic process took place in the temperature range of 463-483 K. The peak in the heat capacity curve was correspondent to the fusion. The experimental molar heat capacities in the temperature range of 243-443 K were fitted to the polynomial. The peak temperature, molar enthalpy and entropy of the phase change had been determined to be 476 K, 27.618 kJ mol^{-1} and 58.389 J mol^{-1} k^{-1} by the repeated heat capacity measurements in the temperature region of 193-503 K. The thermodynamic functions, (H_T-$H_{298.15}$ K) and (S_T-$S_{298.15}$ K), of the compound had been calculated by the numerical integral of the heat-capacity polynomial. In addition, TG-DTG techniques were used for further study of thermal behaviour of the compound and showed that the compound began to decompose at 500 K.

Key Words: Differential scanning calorimetry, Heat capacity, Thermal decomposition.

INTRODUCTION

Depression is a chronic, recurring and potentially life-threatening illness that affects *ca.* 20 % of the population across the globe. It is one of the top ten causes of morbidity and mortality worldwide based on a survey by the World Health Organization[1]. Although today's treatments for depression are generally safe and effective, they are far from ideal. In addition to the need to administer the drugs for 3-6 weeks to see clinical benefit, side effects are still a serious problem even with the newer medications. It is important to note that fewer than 50 % of all patients with depression show full remission with optimized treatment, including trials on numerous medications with and without concurrent psychotherapy[2]. So there is still a great need for faster acting, safer and more effective treatments for depression. CRF_1 antigonists is a new kind of antidepressant, which shows a fast action in clinical trials and

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animal models. The research of CRF_1 antagonists[3-5] properly helps to find new fast action and highly effective antidepressants. 5-Amino-4-(3-indoly)-3-methyl pyrazole (m.w.: 212.11) is a key intermediate of a CRF_1 antidepressant.

In the present work, the low-temperature heat capacity of 5-amino-4-(3-indoly)-3-methyl pyrazole has been measured over the temperature range from 190-510 K. The thermal decomposition characteristics of this compound are investigated by thermogravimetric analysis (TG-DTG). The aim of the work is to provide thermal properties before the drug is applied to the clinical experiments.

EXPERIMENTAL

The sample was synthesized in our laboratory and its formula was identified as 5-amino-4-(3-indoly)-3-methyl pyrazole; ^{1}H NMR (DMSO-d_6, ppm) δ: 2.08 (3H, s, CH_3), 4.20 (1H, br, NH_2), 6.99 (1H, t, 5'-H), 7.09 (1H, t, 6'-H), 7.25 (s, 1H, 2'-H), 7.43 (d, 2H, 4'-H, 7'-H), 11.13 (s, 1H, NH) performed in JNM-ECA-400 400 MHz superconducting NMR. Its purity is higher than 99 %. The sample mass of 5-amino-4-(3-indoly)-3-methyl pyrazole (m.w.: 212.11) used for heat capacity measurement was 5 mg, which is equivalent to 0.0236 mmol, based on its molar mass of 212 g mol^{-1}.

The heat capacity measurements were carried out by temperature modulated differential scanning calorimetry (TMDSC) on a Q1000 from TA instruments under N_2 atmosphere[6], in a temperature range from 190-510 K, at a heating rate of 10 K min^{-1}. The temperature scale of the instrument was calibrated at a heating rate of 20 K min^{-1} with the melting points of indium. The energy scales were calibrated with the heat of fusion of indium. Crimp aluminum alloy pans were used under dry nitrogen flow (50 mL min^{-1}). Standard modulation conditions were amplitude AT of 0.5 K and a period of 40 s. Liquid nitrogen was used as the cooling medium. Prior to the heat capacity measurement of the sample, the reliability of the calorimetric apparatus was verified by heat capacity measurements of the standard reference material-Al_2O_3 (NBS SRM-720). The results showed that the deviation of our calibration data over the whole temperature range was within ± 3 %. The heat capacity measurements were continuously and automatically carried out by the standard procedure of intermittently heating the sample and alternately measuring the temperature.

A thermogravimetric analyzer (Model:Setsys 16/18, Setaram Co., France) was used for DTA-TG measurement of this sample under nitrogen atmosphere (99.999 %). The heating rate was 10 K min^{-1} and the flow rate of nitrogen was 30 mL min^{-1}. The mass of the sample was 7.9 mg. Two Al_2O_3 crucibles were used (capacity: 100 mmL). The reference crucible was filled with α-Al_2O_3. The TG equipment was calibrated by the $CaC_2O_4 \cdot H_2O$ (99.9 %).

RESULTS AND DISCUSSION

Low temperature of heat capacity: The low-temperature experimental molar heat capacities of the solid compound are presented in Fig. 1. The stable phase of

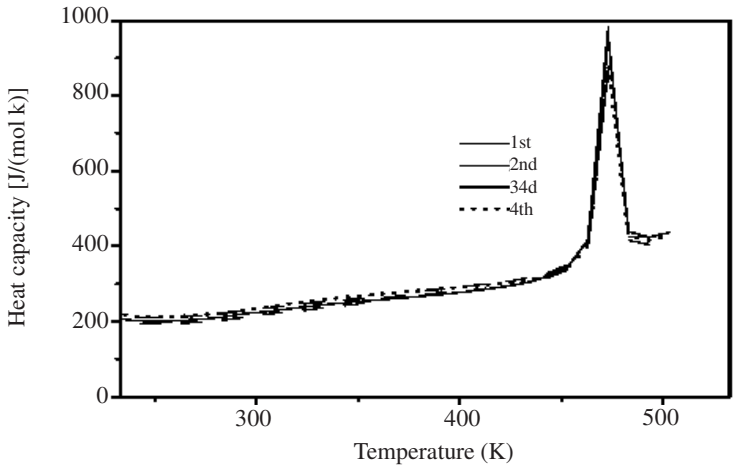

Fig. 1. Experimental molar heat capacities (C_{pm}) of 5-amino-4-(3-indoly)-3-methyl pyrazole as a function of the temperature (K)

solid and the solid-liquid transition occurred in the heat capacity curves. The molar heat capacities of the sample are fitted to the following polynomial equation of heat capacities (C_{pm}) against the reduced temperature by means of the least square method at temperature 243-443 K):

$$C_{pm}\ [J/(mol\ k)] = 268.4247 + 54.7556X - 22.001X^2 + 16.2830X^3 + 27.0074X^4 - 7.9732X^5 + 6.1297X^6 \quad (1)$$

where X = (T-343)/100 and T is the experimental temperature, 343 is obtained from polynomial $(T_{max} + T_{min})/2$, 100 is obtained from polynomial $(T_{max} - T_{min})/2$, T_{max} is the upper limit (443 K) of the above temperature region, T_{min} is the lower limit (243 K) of the above temperature region. The correlation coefficient of the fitting, $R^2 = 0.9999$. Based on eqn. 1, the heat capacity of the sample at 298.15 K is calculated to be 239.1512 J mol^{-1} K^{-1}.

From Fig. 1, it can be seen that the heat capacity of the sample increases with increasing temperature in a smooth and continuous manner in the temperature range from 243-503 K. In this temperature range, only phase transition is observed, which shows that this sample is stable in the above temperature range (Table-1).

Fig. 2 gives the plot of relative deviations of the experimental heat capacity values of the sample, C_{pm} (exp), from the fitting heat capacity values, C_{pm} (fit), *versus* the absolute temperature (T). It can be seen from Fig. 2 that relative deviations of all the experimental points from the fitting heat capacity values are within ± 3 %.

Thermodynamic functions of the compound: Enthalpy and entropy of substances are basic thermodynamic functions. Though the polynomial representing heat capacity and the relationship between thermodynamic functions and heat capacity, the thermodynamic functions relative to the reference temperature of 298.15 K are calculated in the temperature ranges from 243-443 K with an interval of 10 K. The thermodynamic relationships are as follows:

TABLE-1
EXPERIMENTAL MOLAR HEAT CAPACITIES OF
5-AMINO-4-(3-INDOLY)-3-METHYL PYRAZOLE (212 g mol^{-1})

T (K)	Heat capacity J mol^{-1} k^{-1}	T (K)	Heat capacity J mol^{-1} k^{-1}
193.15	226.204	353.15	273.904
203.15	287.260	363.15	277.720
213.15	281.960	373.15	283.232
223.15	245.496	383.15	288.532
233.15	222.600	393.15	294.044
243.15	216.240	403.15	300.192
253.15	215.604	413.15	307.824
263.15	217.724	423.15	316.728
273.15	221.964	433.15	327.116
283.15	227.476	443.15	343.016
293.15	236.804	453.15	371.212
303.15	242.528	463.15	448.804
313.15	249.524	473.15	1026.08
323.15	256.308	483.15	472.760
333.15	263.092	493.15	456.012
343.15	269.028	503.15	469.792

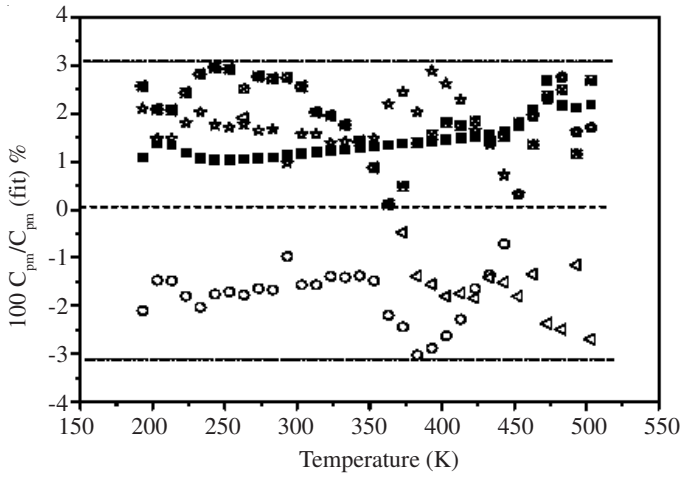

Fig. 2. Plot of relative deviations of the experimental heat capacity values [C_{pm} (exp)] from the fitting heat capacity values [C_{pm} (fit)] *versus* the absolute temperature (T). C_{pm} = [C_{pm} (exp) - C_{pm} (fit)]

$$H_T - H_{298.15} = \int_{298.15}^{T} C_{pm} dT \tag{2}$$

$$S_T - S_{298.15} = \int_{298.15}^{T} \frac{C_{pm} dT}{T} \tag{3}$$

The polynomial fitted values of the molar heat capacities and fundamental thermo-dynamic functions of the sample relative to the standard reference temperature 298.15 K. The values of thermodynamic function $H_T - H_{298.15}$, $S_T - S_{298.15}$ are listed in Table-2 with the interval of 10 K.

TABLE-2
THERMODYNAMIC FUNCTIONS OF
5-AMINO-4-(3-INDOLY)-3-METHYL PYRAZOLE

T(K)	C_{pm} J mol^{-1} k^{-1}	$H_T - H_{298.15}$ KJ mol^{-1} k^{-1}	$S_T - S_{298.15}$ J mol^{-1} k^{-1}
243.15	216.4954	-11.939700	-3.936280
253.15	215.1388	-9.713520	-4.780860
263.15	217.4844	-7.644580	-6.213840
273.15	222.2759	-5.590230	-8.891040
283.15	228.5400	-3.462380	-15.236000
293.15	235.5441	-1.213050	-47.108800
303.15	242.7583	1.177378	48.551660
313.15	249.8208	3.709838	16.654720
323.15	256.5094	6.811862	10.964770
333.15	262.7156	9.664695	7.923505
343.15	268.4247	12.674470	6.279929
353.15	273.6991	15.814140	5.242112
363.15	278.6670	19.133770	4.539180
373.15	283.5147	22.491800	4.006555
383.15	288.4837	26.114500	3.620853
393.15	293.8722	30.024100	3.332031
403.15	300.0409	34.280850	3.113822
413.15	307.4237	39.344160	2.978869
423.15	316.5419	46.318590	2.967951
433.15	328.0233	60.689080	3.333695
443.15	342.6262	148.458800	7.068372

TG-DTA results: The DTA curve of the compound in Fig. 3 exhibits two sharp endothermic peaks in the temperature range of 401-700 K. Based on the TG-DTA

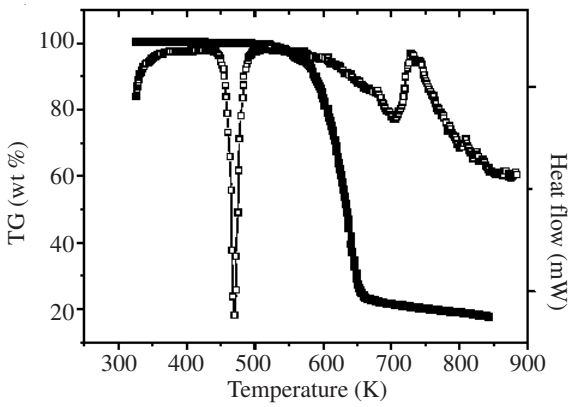

Fig. 4. TG-DTG curve of 5-amino-4-(3-indoly)-3-methyl pyrazole

curve, the first endothermic peak is a phase transition and the second endothermic peak exhibits the decomposition. Above 400 K, the first significant sharp endothermic peak starts at 401 K and ends at 481 K with the peak temperature at 443 K. Next to the first peak, the decomposition temperature begin at 500 K, with the peak temperature at 678 K. TG analysis of the compound shows that the two- step mass loss occurrs in the temperature range above 500 K and the majority of the mass loss in the first step in the temperature range of 500-700 K.The results show that the sample is stable at 500 K.

Conclusion

The low-temperature heat capacities and thermal stability are measured by a temperature modulated differential scanning calorimetry and a thermogravimetric analyzer. From the experimental results, the thermodynamic parameters of phase transition, thermodynamic functions and decomposition process of the compound are further analyzed.

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REFERENCES

1. R.A. Hodgson, G.A. Higgins, D.H. Guthrie, S.X. Lu and A.J. Pond, *Pharm. Biochem. Behavior*, **431**, 440 (2007).
2. P.E. Holtzheimer and C.B. Nemeroff, *NeuroRx*, **3**, 42 (2006).
3. G. Gentile, R.D. Fabio, F. Pavone, F.M. Sabbatini and S.D. Yves, *Biorg. Med. Chem. Lett*., **17**, 5218 (2007).
4. S.R.J. Hoare, B.T. Brown, M.A. Santos, S. Malany, S.F. Betz and D.E. Grigoriadis, *Biochem. Pharm*., **72**, 244 (2006).
5. G. Gentile, R.D. Fabio, F. Pavone, F.M. Sabbatini and S.D. Yves, *Biorg. Med. Chem. Lett*., **17**, 5218 (2007).
6. D.G. Archer, *J. Phys. Chem. Ref. Data*, **22**, 1441 (1992).

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