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Thermal Stability and Properties of a New CRF_1 Antidepressant Compound ($C_{22}H_{28}N_4O_4$) from Low-Temperature Molar Heat Capacity

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Low-temperature heat capacities of a new CRF_1 antidepressant compound $C_{22}H_{28}N_4O_4$ were measured by a temperature modulated differential scanning calorimetry in the temperature range from T = 188 to 562 K. An obvious endothermic process took place in the temperature range of 353-372 K. The peak in the heat capacity curve was corresponding to the fusion. The experimental molar heat capacities in the temperature range of 193-353 and 372-562 K were fitted to the polynomial. 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.

Key Words: Differential scanning calorimetry, Heat capacity, Thermal decomposition, CRF_1 antidepresent.

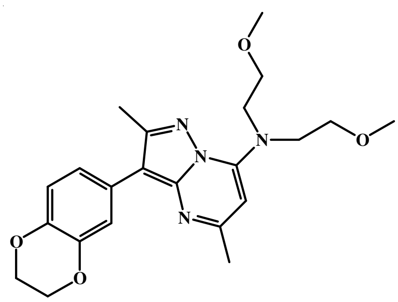
INTRODUCTION

Depression is a seriously psychological problem which affect people's health and hindered their contacts in the world[1]. The depression often cause many pain and suffering to the patient and their relatives. The cost in human suffering could not be estimated. Many methods had been developed to eliminate the sicker's pain. For example, supportive counseling helped ease the pain of depression and addressed the feelings of hopelessness that accompanied depression. However, these methods are still not effective and ideal treatment and some drugs also have some side effects[2]. Therefore, many researchers had been developed to find faster acting, safer and more effective treatments for depression. CRF_1 antigonists are regarded as a new kind of antidepressant, which show a fast action in clinical trials and animal models. The research of CRF_1 antagonists[3-5] properly helped to find new fast-action and highly effective antidepressants. Many antidepressants including $C_{22}H_{28}N_4O_4$ (3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-2,5-dimethyl-pyrazolo(1,5-a) pyrimidin-7-yl)-*bis*-(2-methoxyethyl)-amine (m.w. 412) were synthesized.

In the present work, the low-temperature heat capacity of $C_{22}H_{28}N_4O_4$ (3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-2,5-dimethyl-pyrazolo(1,5-a)pyrimidin-7-yl)-*bis*-(2-methoxyethyl)-amine has been measured over the temperature range from 188 to 562 K and its thermal properties were calculated.

EXPERIMENTAL

The sample was synthesized in our laboratory and its formula was shown in Fig. 1. Its purity was higher than 99 %. The sample mass of $C_{22}H_{28}N_4O_4$ (3-(2,3-dihydro-benzo[1,4]-dioxin-6-yl)-2,5-dimethyl-pyrazolo(1,5-a)pyrimidin-7-yl)-*bis*-(2-methoxyethyl)-amine (m.w. 412) used for heat capacity measurement was 5 mg, which was equivalent to 0.0121 mmol, based on its molar mass of 412 g mol^{-1}.



(3-(2,3-dihydro-benzo[1,4]dioxin-6-yl)-2,5-dimethyl-pyrazolo[1,5-a]pyrimidin-7-yl)-*bis*-(2-methoxyethyl)amine

Fig. 1. Molecular formula of the CRF_1 antidepressant

The heat capacity measurements were carried out by temperature modulated differential scanning calorimetry (TMDSC) on a Q1000[6] from TA Instruments under N_2 atmosphere, in a temperature range from 190 to 510 K, at a heating

TABLE-1
EXPERIMENTAL MOLAR HEAT CAPACITIES OF $C_{22}H_{28}N_4O_4$ (3-(2,3-DIHYDRO-BENZO[1,4]DIOXIN-6-YL)-2,5-DIMETHYL-PYRAZOLO(1,5-a)PYRIMIDIN-7-YL)-*BIS*-(2-METHOXY-ETHYL)-AMINE (m.w. 412)

T (K)	Cpm ($J mol^{-1} K^{-1}$)	T (K)	Cpm ($J mol^{-1} K^{-1}$)	T (K)	Cpm ($J mol^{-1} K^{-1}$)	T (K)	Cpm ($J mol^{-1} K^{-1}$)	T (K)	Cpm ($J mol^{-1} K^{-1}$)	T (K)	Cpm ($J mol^{-1} K^{-1}$)
188	13.343	247	857.616	306	949.824	383	1268.064	444	1397.128	505	1625.200
189	88.276	248	857.344	307	952.272	384	1270.240	445	1399.168	506	1564.272
190	174.964	249	856.936	308	954.584	385	1271.328	446	1401.072	507	1656.480
191	304.191	250	856.256	309	957.576	386	1273.776	447	1409.368	508	1647.504
192	381.874	251	855.712	310	960.432	387	1275.272	448	1409.776	509	1642.336
193	426.768	252	855.984	311	962.880	388	1277.040	449	1411.136	510	1641.928
194	464.712	253	856.392	312	966.144	389	1280.032	450	1412.496	511	1642.744
195	498.984	254	856.528	313	969.952	390	1282.616	451	1414.536	512	1644.784
196	530.400	255	857.480	314	973.352	391	1284.248	452	1417.392	513	1647.232
197	558.960	256	858.024	315	976.888	392	1288.056	453	1419.976	514	1650.360
198	586.024	257	859.384	316	980.424	393	1289.552	454	1422.152	515	1655.120
199	609.688	258	859.928	317	984.096	394	1291.728	455	1424.600	516	1659.744
200	631.312	259	860.880	318	987.224	395	1293.360	456	1432.624	517	1662.328
201	651.168	260	861.152	319	990.080	396	1295.264	457	1434.120	518	1665.592
202	670.072	261	861.832	320	993.344	397	1297.576	458	1436.160	519	1669.536
203	687.344	262	862.512	321	997.016	398	1299.344	459	1438.880	522	1677.696
204	703.256	263	863.056	322	1001.096	399	1302.200	460	1442.552	523	1680.688
205	718.624	264	864.552	323	1005.992	400	1303.832	461	1445.952	524	1683.000
206	732.360	265	865.640	324	1010.616	401	1306.008	462	1449.216	525	1684.904
207	744.736	266	866.728	325	1014.424	402	1309.408	463	1452.480	526	1686.128
208	756.568	267	867.952	326	1018.504	403	1311.856	464	1456.016	527	1688.712
209	767.040	268	869.312	327	1022.720	404	1314.984	465	1464.040	528	1691.568
210	777.104	269	870.672	328	1026.256	405	1316.616	466	1465.944	529	1694.152
211	785.264	270	872.576	329	1029.792	406	1319.064	467	1468.664	530	1696.600
212	792.472	271	874.208	330	1033.056	407	1321.240	468	1471.112	531	1699.048
213	799.408	272	875.160	331	1036.184	408	1322.600	469	1473.832	532	1701.360
214	806.208	273	876.656	332	1023.400	409	1325.864	472	1485.256	533	1702.992
215	812.192	274	877.608	333	1031.424	410	1327.632	473	1487.432	534	1704.760
216	817.904	275	878.968	334	1038.224	411	1330.352	474	1489.336	535	1706.528
217	823.344	276	880.328	335	1044.208	412	1332.936	475	1494.096	536	1708.024
218	828.104	277	882.368	336	1051.416	413	1334.296	476	1495.864	537	1709.656
219	832.184	278	883.456	337	1067.464	414	1336.744	477	1496.816	538	1711.152
220	836.128	279	885.088	338	1069.368	415	1338.104	478	1441.736	539	1712.920
221	838.984	280	886.856	339	1072.632	416	1339.736	479	1520.616	540	1715.096
222	841.840	281	888.760	340	1076.712	417	1341.096	480	1516.264	541	1717.680
223	844.560	282	890.664	341	1081.744	418	1343.000	481	1517.624	542	1720.536
224	846.600	283	892.568	342	1087.048	419	1345.176	482	1520.208	543	1722.304
225	849.320	284	895.152	343	1092.488	422	1351.568	483	1521.432	544	1724.072
226	851.632	285	897.464	344	1099.832	423	1354.152	484	1482.944	545	1724.752
227	853.264	286	900.184	345	1106.632	424	1356.600	485	1530.272	546	1730.736
228	855.032	287	902.496	346	1113.840	425	1358.504	486	1562.912	547	1731.552
229	856.800	288	904.944	347	1122.544	426	1360.952	487	1578.552	548	1732.776
230	858.024	289	906.304	348	1133.288	427	1363.400	488	1556.384	549	1721.352
231	859.248	290	907.936	349	1145.120	428	1365.032	489	1534.624	550	1737.536
232	860.472	291	910.520	350	1158.720	429	1367.208	490	1495.592	551	1755.624
233	861.560	292	912.560	351	1177.624	430	1369.520	491	1575.152	552	1746.512
234	862.240	293	914.600	352	1204.280	431	1371.696	492	1547.272	553	1734.680
235	863.328	294	916.912	353	1261.128	432	1373.600	493	1522.112	554	1719.584
236	863.872	295	918.816	372	1255.416	433	1375.096	494	1582.904	555	1747.328
237	863.872	296	921.536	373	1254.192	434	1376.864	495	1592.832	556	1755.760
238	863.736	297	924.120	374	1254.464	435	1385.160	496	1604.256	557	1732.504
239	863.328	298	926.296	375	1256.096	436	1384.752	497	1623.024	558	1740.664
240	862.648	299	928.880	376	1257.320	437	1385.160	498	1593.376	559	1760.384
241	862.240	300	932.008	377	1258.408	438	1385.976	499	1541.832	560	1739.984
242	861.560	301	935.272	378	1260.448	439	1387.200	500	1616.768	561	1759.568
243	861.016	302	938.400	379	1262.216	440	1389.104	501	1629.416	562	1748.144
244	860.336	303	941.256	380	1264.392	441	1392.368	502	1643.696	–	–
245	859.384	304	944.520	381	1265.072	442	1395.904	503	1559.784	–	–
246	858.568	305	947.104	382	1266.704	443	1396.448	504	1626.832	–	–

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 present 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.

RESULTS AND DISCUSSION

Low temperature of heat capacity: The low-temperature experimental molar heat capacities of the solid compound are plotted in Fig. 2 and listed in Table-1. The stable phase of 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 equations of heat capacities (Cp,m) against the reduced temperature by means of the least square method at temperature (188-353 K):

$$Cpm(J/(mol\cdot K)) = 875.09986 + 162.67916x + 125.90538x^2 - 446.93315x^3 + 171.51979x^4 \quad (1)$$

where X = (T-271)/83 and T is the experimental temperature, 271 is obtained from polynomial $(T_{max} + T_{min})/2$, 83 is obtained from polynomial $(T_{max} - T_{min})/2$, T_{max} is the upper limit (353 K) of the above temperature region, T_{min} is the lower limit (188 K) of the above temperature region. The correlation coefficient of the fitting, $R^2 = 0.99$. Based on eqn. 1, the heat capacity of the sample at 298.15 K is calculated to be 927.799 J mol^{-1} K^{-1}.

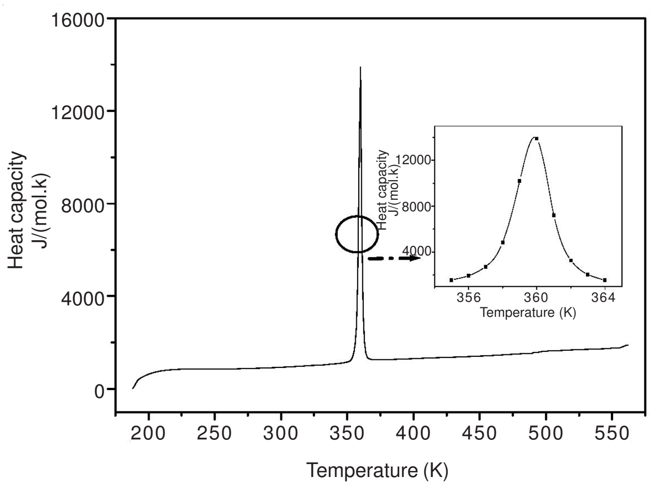


Fig. 2. Experimental molar heat capacities (Cp,m) of $C_{22}H_{28}N_4O_4$ (3-(2,3-dihydrobenzo[1,4]dioxin-6-yl)-2,5-dimethyl-pyrazolo(1,5-a)-pyrimidin-7-yl)-*bis*-2-methoxy-ethyl)-amine-5-amino-4-(3-indoly)-3-methyl pyrazole as a function of the temperature (K)

Meanwhile, according to the same method, the molar heat capacities (Table-1) of the sample are fitted to the following polynomial equations of heat capacities (Cp,m) against the reduced temperature by means of the least square method at temperature (372-562 K):

$$Cpm (J/(mol\cdot k)) = 1476.0487 + 321.29162x + 89.46436x^2 - 42.07566x^3 + 319x^4 \quad (2)$$

where X = (T-467)/95 and T is the experimental temperature, 467 is obtained from polynomial $(T_{max} + T_{min})/2$, 95 is obtained from polynomial $(T_{max} - T_{min})/2$, T_{max} is the upper limit (562 K) of the above temperature region, T_{min} is the lower limit (372 K) of the above temperature region. The correlation coefficient of the fitting, $R^2 = 0.99$.

From Fig. 2, 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 188 to 562 K. In this temperature range, only phase transition was observed, which shows that this sample is stable in the above temperature range.

Thermodynamic functions of the compound: Enthalpy and entropy of substances are basic thermodynamic functions. Through the polynomial representing heat capacity and the relationship between thermodynamic functions and heat

TABLE-2
THERMODYNAMIC FUNCTIONS OF (3-(2,3-DIHYDRO-BENZO[1,4]DIOXIN-6-YL)-2,5-DIMETHYL-PYRAZOLO-(1,5-a)PYRIMIDIN-7-YL)-*BIS*-(2-METHOXY-ETHYL)-AMINE-5-AMINO-4-(3-INDOLY)-3-METHYL PYRAZOLE

T (K)	Cpm ($J mol^{-1} K^{-1}$)	H_T-$H_{298.15}$ ($KJ mol^{-1} k^{-1}$)	S_T-$H_{298.18}$ ($J mol^{-1} K^{-1}$)
188	13.343	-1.469730	-6.15312
198	586.024	-58.690300	-239.87700
208	756.568	-68.204600	-272.41000
218	828.104	-66.372500	-259.27900
228	856.800	-60.104500	-229.83700
238	863.736	-51.953700	-194.62600
248	857.344	-42.995800	-157.89700
258	859.928	-34.526100	-124.38000
268	869.312	-26.209800	-92.67740
278	883.456	-17.801600	-61.82430
288	904.944	-9.185180	-31.34730
298	926.296	-0.138940	-0.46614
308	954.584	9.402652	31.02398
318	987.224	19.596400	63.62659
328	1026.256	30.633740	97.92535
338	1069.368	42.614310	134.15220
348	1133.288	56.494410	175.21770
353	1261.128	69.172870	212.96670
362	Melting temperature		
372	1255.416	92.712470	277.82360
382	1266.704	106.213100	313.91460
392	1288.056	120.884100	352.50230
402	1309.408	135.982000	391.32970
412	1332.936	151.754800	431.11150
422	1351.568	167.391700	469.54820
432	1373.600	183.856400	509.37210
442	1395.904	200.800800	549.58140
452	1417.392	218.065800	589.76260
462	1449.216	237.454000	634.71310
472	1485.256	258.211800	682.29690
482	1520.208	279.490200	730.23190
492	1547.272	299.938700	774.99760
502	1643.696	335.067400	856.36560
512	1644.784	351.737100	889.38410
522	1677.696	375.552200	939.62720
532	1701.360	397.863000	985.17250
542	1720.536	419.552700	1028.31300
552	1746.512	443.352100	1075.76400

capacity, the thermodynamic functions relative to the reference temperature of 298.15 K were calculated in the temperature ranges from 188 to 552 K with an interval of 10 K. The thermodynamic relationships are as follows:

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

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

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

Conclusion

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

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