Low-temperature heat capacity and standard molar enthalpy of formation of crystalline (S)–(+)–Ibuprofen (C$_{13}$H$_{18}$O$_2$)(s)

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Low-temperature heat capacities of the compound, (S)–(+)–Ibuprofen (C$_{13}$H$_{18}$O$_2$), have been measured by a precision automated adiabatic calorimeter in the temperature range 78 – 348 K. The experimental molar heat capacities in the temperature range 78 – 345 K have been fitted to a polynomial equation. The smoothed heat capacities and thermodynamic functions, ($H_T - H_{298.15K}$) and ($S_T - S_{298.15K}$), of the compound have been calculated by the heat-capacity polynomial equation. The constant-volume energy of combustion of the compound, has been found to be $\Delta U_c (C_{13}H_{18}O_2, s) = - (7136.94 \pm 4.74)$ kJmol$^{-1}$ by means of a home-made oxygen-bomb combustion calorimeter at $T = 298.15 \pm 0.001$ K. The standard molar enthalpy of combustion of the sample has been calculated to be $\Delta H_m^\circ (C_{13}H_{18}O_2, s) = - (7145.62 \pm 4.74)$ kJmol$^{-1}$, from the constant-volume combustion energy. The standard molar enthalpy of formation of the compound has been derived, $\Delta f H_m^\circ (C_{13}H_{18}O_2, s) = - (542.48 \pm 5.05)$ kJmol$^{-1}$, from the combination of the data of standard molar enthalpy of combustion of the compound with other auxiliary thermodynamic quantities through a Hess thermochemical cycle.

Ibuprofen is a drug clinically used for detoxification, easing pain, anti-rheumatism and diminishing inflammation, and so on. There is a chiral carbon atom in $\alpha$ place of the carboxylic acid of the compound. This makes the drug a racemic compound composed of a pair of the enantiomer displaying optical activity clearly. It is clinically verified that the purified (S)–(+)–Ibuprofen has a higher pharmacological efficacy than that of the racemic Ibuprofen and the patients taking the purified (S)–(+)–Ibuprofen may eliminate the side effect caused from (R)–(+)–Ibuprofen without any medical function. The reported melting point of the compound is 350.15–352.15 K. Its chemical name is 2-(4-isobutylphenyl)-propanoic acid (molecular formula: C$_{13}$H$_{18}$O$_2$, CAS: 15687-27-1). Its structure is:

![Ibuprofen structure](image)

Its molar mass is 206.28 g mol$^{-1}$. The thermodynamic parameters of S (+) Ibuprofen provide significant basis for theoretically explaining its physiological activities. In view of the importance of the (S)–(+)–Ibuprofen in pharmaceutics and other fields, low-temperature heat capacity and constant-volume combustion energy of the compound have been measured by a precision automated adiabatic calorimeter in the temperature range 78 - 348 K and a oxygen-bomb combustion calorimeter at 298.15 K, respectively. The thermodynamic functions and standard molar enthalpy of formation of the compound have also been derived.

**Experimental**

Dexibuprofen (purity > 99.90 %) was supplied by Hunan Institute of Drug Detection, P.R. China. It was prepared and characterized by reported method. The crude product was recrystallized three times with AR alcohol. Finally, FTIR and NMR spectra were used to determine the structure of this compound. IR spectrum (KBr) demonstrated that there were characteristic absorption peaks at 3050, 2940, 1720, 1620, 1515, 1480, 1450, 1380, 1350, 930, 805 and 765 cm$^{-1}$. $^1$H NMR (CDCl$_3$) indicated that there were resonance absorption peaks at $\delta = 0.85 - 1.05$ (m, 6H), $\delta = 1.52$ (m, 1H), $\delta = 2.56$ (s, 3H), $\delta = 2.61$ (m, 2H), $\delta = 2.68$ (s, 1H), $\delta = 7.0 - 8.3$ (m, 4H) and $\delta = 10.55$ (s, 1H). These results are identical to the reported values.  

**Adiabatic calorimetry**

A high-precision automatic adiabatic calorimeter with a small sample size was used to measure the heat capacities of the compound in the temperature range (T) 78-348 K. The principle and design of the adiabatic calorimeter are described in detail elsewhere. Briefly, the calorimeter mainly comprised a sample cell, a platinum resistance thermometer, an electric heater, the
inner and the outer adiabatic shields, two sets of six-junctions chromel-constantan thermopiles installed between the calorimetric cell and the inner shield and between the inner and outer shields, respectively, and a vacuum can.

To verify the accuracy of the calorimeter, the heat-capacity measurements of the reference standard material, \( \alpha\text{-Al}_2\text{O}_3 \), were made in the temperature range 78-350 K. The sample mass used was 1.6382 g, which was equivalent to 0.0161 mol based on its molar mass, \( M(\text{Al}_2\text{O}_3) = 101.9613 \text{ g mol}^{-1} \). The results indicated that deviations of the experimental data from those of the former National Bureau of Standards were 
± 0.5 %.

Heat-capacity measurements were continuously and automatically carried out by means of the standard method of intermittently heating the sample and alternately measuring the temperature. The heating rate and temperature increments were generally controlled at 0.1-0.4 K min\(^{-1} \) and 1-3 K. The heating duration was 10 min, and the temperature drift rates of the sample cell measured in an equilibrium period were always kept within \( 10^{-3} \) to \( 10^{-4} \) K min\(^{-1} \) during the acquisition of all heat-capacity data. In order to obtain good adiabatic conditions between the calorimetric cell and its surroundings, the temperature difference between the calorimetric cell and the inner shield was automatically kept within 1 mK. The data of heat capacities and corresponding equilibrium temperature have been corrected for heat exchange of the sample cell with its surroundings\(^3,4 \). The sample mass used for the calorimetric measurements was 3.2972 g, which was equivalent to 0.01598 mol in terms of molar mass of the sample, \((S)\quad(+)\quad\text{Ibuprofen} \quad (C_{13}H_{18}O_2)(s), M = 206.28 \text{ g mol}^{-1}\).

**Oxygen-bomb combustion calorimetry**

The constant-volume energy of combustion of the sample was measured by means of a homemade precision oxygen-bomb combustion calorimeter. The structure and principle of the calorimeter have been described earlier in detail\(^6 \). It consists of a static oxygen bomb, inner calorimetric vessel, outer thermostatic bath, platinum resistance thermometer, precision temperature controller, ignition system and temperature measurement system.

Measurements show that the precision of controlling the temperature for the thermostatic system is \( \pm 0.001 \text{ K} \).

The correction of the temperature rise (\( \zeta \)) was carried out as already reported\(^9 \). The standard energy of combustion of the nickel fuse for ignition has been determined previously to be
\[ \Delta cU^\circ \quad(\text{in J cm}^{-1}) = 2.929. \]

The real energy of combustion of the nickel fuse \( (Q_N) \) was calculated from the formula,
\[ Q_N \quad(J) = 2.929 \times \Delta L, \]
in which \( \Delta L \quad(\text{cm}) \) was the length of the combusted nickel wire. The correction for the energy of formation of aqueous nitric acid, produced by oxidation of a trace of nitrogen contained in the oxygen bomb, was determined by the neutral titration with a 0.1000 mol dm\(^{-3} \) of sodium hydroxide solution by using the methyl orange as the indicator. The heat of formation of the aqueous nitric acid \( (Q_N) \) in the oxygen bomb can be derived from the equation,
\[ Q_N \quad(\text{in J}) = 59.8 NV, \]
in which \( N \quad(\text{in mol dm}^{-3}) \) is the concentration of the sodium hydroxide solution and \( V \quad(\text{in cm}^3) \) is the volume of the consumed sodium hydroxide solution, based on the molar energy of formation of \( \text{HNO}_3(aq) \) from \( \text{N}_2(g), \text{O}_2(g) \) and \( \text{H}_2\text{O}(l) \),
\[ n_{\text{HNO}_3} = 59.8 \text{ kJ mol}^{-1} \quad(\text{refs 7-9}), \]
for 0.1 mol dm\(^{-3} \) of \( \text{HNO}_3(aq) \).

After each run, the combustion products were analyzed mainly for carbon dioxide by the Rossini method. No soot was observed in the sample crucible after each of combustion experiments for the \((S)\quad(+)\quad\text{Ibuprofen} \quad (C_{13}H_{18}O_2). \] Qualitative tests for CO with indicator tubes were negative within the limits of their sensitivity \{mole fraction \( x \quad(\text{CO}) < 1 \times 10^{-6} \} \.

The energy equivalent, \( \varepsilon_{\text{calor}} \), of the calorimeter has been determined from 10 combustion experiments using about 0.7 g of NIST 39i benzoic acid with a certified constant-volume energy of combustion under experimental conditions of \( \Delta cU = -(26434 \pm 3) \text{ J g}^{-1} \) to be:
\[ \varepsilon_{\text{calor}} = 13572.22 \pm 0.98 \text{ JK}^{-1}. \]

The uncertainty of the results was the standard deviation of the mean value from the respective measurements.

**Results and discussion**

**Low-temperature heat capacities**

Experimental heat capacities of the crystalline \((S)\quad(+)\quad\text{Ibuprofen} \quad (C_{13}H_{18}O_2) \quad(s) \) are listed in Table 1. Figure 1 shows that the structure of the compound is stable over the temperature range \( T = 78 - 348 \text{ K} \). Thus, no phase change, association or thermal decomposition occurs.

The 106 experimental points in the temperature region \((T) \quad 78 - 348 \text{ K} \) were fitted by means of the least squares method, and a polynomial of experimental
The correlation coefficient for the fitting $R^2$ equals 0.99996.

**Thermodynamic functions of the compound**

The smoothed molar heat capacities and thermodynamic functions of the compound were calculated based on the fitted polynomial equation of the heat capacities as a function of the reduced temperature ($X$) according to the following thermodynamic equations:

\[
C_{p,m} = 222.242 + 143.576X + 30.114X^2 + 3.444X^3 - 4.190X^4 + 10.989X^5
\]

Here, $X = (T - 213)/135$. The relative deviations of experimental molar heat capacities from the smoothed heat capacities calculated by the polynomial equation were within ± 0.5% except for several points around the lower temperature limit.
\[
(H_T - H_{298.15}) = \int_{298.15}^{T} C_p \, dT \quad \ldots \quad (1)
\]
\[
(S_T - S_{298.15}) = \int_{298.15}^{T} C_p \, T^{-1} \, dT \quad \ldots \quad (2)
\]

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 are given in Table 2 with the interval 5 K.

**Constant-volume combustion energy**

The method for determining the constant-volume combustion energy of the sample was the same as that used in the calibration of the calorimeter with benzoic acid. The constant-volume combustion energy, \( \Delta_c U^o \) (in J mol\(^{-1}\)), of the substance can be calculated from\(^9\):

\[
\Delta_c U^o = (\varepsilon_{\text{calor}} \Delta T - Q_{\text{Ni}} - Q_{\text{N}}) \cdot M/W \quad \ldots \quad (3)
\]

in which \( \varepsilon_{\text{calor}} \) (J K\(^{-1}\)) is the energy equivalent of the oxygen-bomb calorimeter, \( \Delta T \) (K) the corrected temperature rise, \( M \) (g mol\(^{-1}\)) the molar mass of the sample, and \( W \) (g) the mass of the sample.

The calculated results of the constant-volume combustion energy of the (S)-(+)–Ibuprofen from the six combustion tests are shown in Table 3. The average value obtained from six tests is

\[
\Delta_c U^o_{\text{C}_13\text{H}_{18}\text{O}_2, \text{s}} = - (7136.94 \pm 4.74) \text{ kJ mol}^{-1},
\]

taking into account the standard deviation of mean value from respective results.

**Standard molar enthalpy of combustion and standard molar enthalpy of formation of the compound**

The standard molar enthalpy of combustion of the (S)-(+)–Ibuprofen, \( \Delta_c H^o_{\text{m}} \) (C\(_{13}\text{H}_{18}\text{O}_2, \text{s}) \), was the combustion enthalpy change of the following chemical reaction at \( T = 298.15 \) K and \( P = 100 \) kPa:

\[
\text{C}_{13}\text{H}_{18}\text{O}_2(s) + 33/2\text{O}_2(g) = 13\text{CO}_2(g) + 9\text{H}_2\text{O}(l) \quad \ldots \quad (4)
\]

The standard molar enthalpy of combustion of the compound can be derived from the constant-volume combustion energy by:

\[
\Delta_c H^o_{\text{m}} = \Delta_c U^o_{\text{m}} + \Delta n \cdot RT \quad \ldots \quad (5)
\]

\[\Delta n = \Sigma n_i(\text{products}, \text{g}) - \Sigma n_i(\text{reactants}, \text{g})\]
Table 3 — Experimental results of the constant-volume energy of combustion of (S)–(+)-Ibuprofen obtained from oxygen-bomb combustion calorimeter at $T = 298.15 \, \text{K}$.

<table>
<thead>
<tr>
<th>No.</th>
<th>$W (g)$</th>
<th>$Q_{\text{n}} (J)$</th>
<th>$Q_{\text{N}} (J)$</th>
<th>$\Delta T (\text{K})$</th>
<th>$-\Delta U_c (\text{kJ mol}^{-1})$</th>
</tr>
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<tr>
<td>1</td>
<td>0.8685</td>
<td>43.6391</td>
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<tr>
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<td>7145.53</td>
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<tr>
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<td>7151.35</td>
</tr>
<tr>
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<td>44.2249</td>
<td>151.2579</td>
<td>2.2797</td>
<td>7138.48</td>
</tr>
</tbody>
</table>

$W (g)$: mass of the sample; $Q_{\text{n}} (J)$: combustion heat of nickel wire; $Q_{\text{N}} (J)$: molar enthalpy of formation of nitric acid; $\Delta T (\text{K})$: corrected temperature rise; $-\Delta U_c (\text{kJ mol}^{-1})$: constant–volume combustion energy.

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References