Thermodynamic functions of ibuprofen

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Abstract. A conformational analysis has been conducted, structures that make a significant contribution to properties are selected, and the partial thermodynamic functions of ibuprofen conformers are calculated. The temperature dependences of molar fractions and entropy of mixing are obtained. Quantum-chemical and empirical estimates of the standard enthalpy of formation are produced. The thermodynamic functions of ibuprofen in the gas phase are determined.

1. Introduction
Obtaining of the experimental gas phase physics-chemical properties for polyatomic substances requires significant efforts and resources. Therefore, computational methods of quantum chemistry have become increasingly popular and, in many cases, the only possible ones [1].

The conformational analysis (the generation of conformer structures and the search for their equilibrium geometry) is the first step in quantum chemical modeling. Moreover, for large polyatomic molecules the number of conformers grows exponentially with the number of atoms, and the number of anticipated (generated) structures is several times greater than the number of minima on the potential energy surface. Each such case requires a distinct geometry optimization.

Defining of the substance properties by theoretical methods is based on knowledge of the partial properties for each conformer as well as the dependence of the properties and mole fractions on temperature which implies a separate set of all calculations for each of them (including the determination of the translational, rotational, vibrational, and electronic contributions). In the presented work the thermodynamic functions of ibuprofen were obtained taking into account the conformational diversity.

2. Quantum chemical calculations
The generation of structures was carried out in the molecular mechanics framework using the MMFF94 force field [2], and 14 structures were initially generated. Farther, each structure has been sequentially optimized in the GAUSSIAN 09 program [3] by the HF/3-21G* and B3LYP/6-311++G(3df,3pd) 6d 10f methods and the harmonic frequencies were calculated at each local minimum. However, non-bonded intramolecular stabilizing interactions in such molecules, not captured by molecular mechanics methods, could lead to additional structures. Therefore, additional
calculations were made to determine the internal rotation potential functions for the low energy isomers, and new structures, not captured by the molmechanics method, were obtained. The search for conformers was terminated when the rotamers reached a relative total electronic energy in 20 kJ/mol (relative to the total electron energy $E_{\text{total}}$ of the most stable conformer). As a result, 17 conformers were obtained out of 32 possible hypothetical structures (formal minima on the potential energy surface) and each of them had a mirror isomer.

A complete assigned vibrational spectrum was compiled and an approximation dependence “anharmonic frequency - harmonic frequency” for fundamental transitions with a standard deviation of 20 cm$^{-1}$ was obtained based on the experimental data (IR and Raman spectra) and calculated harmonic frequencies ($\nu_{\text{harm}}$)

$$\nu_{\text{anharm}} = \frac{1}{1772736481} \left( \frac{\nu_{\text{harm}}}{17703079420} \right)$$

(1)

The harmonic frequencies were corrected for all conformers using (1) and anharmonic vibrational spectra were obtained ($\nu_{\text{anharm}}$ sets). Further, molar fractions $\chi_i(T)$, entropy of mixing $S_{\text{mix}}$ (Table 1) and partial thermodynamic functions of isomers depending on the temperature were calculated within the framework of the anharmonic approximation [4].

The total free energy has been obtained and the mole fractions (Table 1) have been computed within the interval 298.15 - 1500 K for each conformers according to the Eq. (2).

$$\chi_i(T) = \frac{e^{\frac{G_{\text{total},i}(T)}{RT}}}{\sum_{i=1}^{N} e^{\frac{G_{\text{total},i}(T)}{RT}}}$$

(2)

where $N$ is amount of conformers, $G_{\text{total},i}(T)$ is the total Gibbs free energy of the conformer $i$ equal to the sum of its total electron energy $E_{\text{total}}$, zero point vibrational energy and Gibbs free energy at temperature $T$. The entropy of mixing $S_{\text{mix}}$ has been computed based on the obtained data. In this case, the mole fractions obtained by accounting for the temperature components of the free energy produce a slightly different gradation of conformers by $\chi_i(T)$ than when comparing the total electron energies $E_{\text{total}}$. Thus, the sequence of the most stable isomers is II, IV, III, I (Table 1), and not I, II, III, IV, as follows from $E_{\text{total}}$ when taking into account the temperature.

3. Enthalpy of formation at 298 K and thermodynamic functions of ibuprofen

The enthalpy of formation ($\Delta_f H^0_{298}$) of ibuprofen cannot be correctly calculated using additive-group approach [5, 6] due to the contribution uncertainty of the C-(H)(Cd)(C)(CO) group. Assuming that the contribution of mentioned above group into $\Delta_f H^0_{298}$ is close to the same of group C-(H)(C)2(CO), then the corresponding calculation produces $\Delta_f H^0_{298} = -448.59$ kJ/mol. It appears that the contributions of these groups should be similar, however, it was not possible to correctly verify this assumption.

The calculation of $\Delta_f H^0_{298}$ using the additive-group method can also be carried out according to the program presented in NIST [7]. This calculation produces $\Delta_f H^0_{298} = -452.7$ kJ/mol (close to the experimental results, Table 2). However, an analysis of the fragments and their contributions selected by the program shows that the C-(H)(C)3 group replaced the desired C-(H)(Cd)(C)(CO) group for this task. This substitution is an even rougher assumption than the one discussed above; it also contradicts the essence of the Benson model [8], in which groups of the same structure differ depending on their closest environment. This uncertainty is exacerbated by the calculation of $\Delta_f H^0_{298}$ based on macroincremental modeling. We executed this calculation according to the following scheme:

$$\Delta_f H^0_{298} = p$-Me$_2$C$_6$H$_4$ + i-PrCH$_2$Me + s-BuCOOH - C$_2$H$_4$ - C$_3$H$_8$$

-478.5 $\leftarrow$ -17.9±1.0 -153.7±0.6 -495.4±6.6 -83.8±0.3 -104.7±0.5
The obtained value $\Delta_f H^0_{298} = -478.5 \text{ kJ/mol}$ deviates by 30 kJ/mol from the above estimate by the group contribution method. Moreover, both the model itself and the reference values adapted from [9] seem to be quite reasonable.

Using the functional B3LYP to determine the total electron energy and enthalpy of formation $\Delta_f H^0_{298}$ usually leads to significant errors (Table 2), however, the harmonic frequencies and difference energies obtained with its application can be used in conformational analysis, calculation of the vibrational contribution, and the study of internal rotation. We calculated the enthalpies of formation using the well-proven functional M06 [10, 11, 12] and composite methods G4 [13], G4MP2 [14], G2MP2 [15] (Table 2) to determine a more accurate value of $\Delta_f H^0_{298}$ in the gas phase. The value obtained by M06/6-311++G(3df,3pd) turned out to be close to the empirical value mentioned above, and $\Delta_f H^0_{298}$, computed using G4, G4MP2, G2MP2, is almost the same as the experimental estimate. Therefore, $\Delta_f H^0_{298} = -454 \text{ kJ/mol}$ was used for correcting $E_{\text{total}}$ and determining $\Delta_f H^0_T$ and $\Delta_f G^0_T$ in a wide temperature interval.

The temperature dependence of the heat capacity $C_p$ of ibuprofen is approximated by the Eq. (3):

$$C_p = a + bT + cT^2 + dT^3 + \frac{e}{T^2},$$  

(3)

with the coefficients for compound: $a = -9.043 \text{ J-K}^{-1}\text{-mol}^{-1}, b = 1.109 \text{ J-K}^{-2}\text{-mol}^{-1}, c = -6.49 \times 10^{-4} \text{ J-K}^{-3}\text{-mol}^{-1}, d = 1.46 \times 10^{-7} \text{ J-K}^{-4}\text{-mol}^{-1}$ and $e = -1.30 \times 10^{-6} \text{ J-K}-\text{mol}^{-1}$. Thermodynamic properties of the substance in the temperature range from 298.15 K to 1500 K and ideal gas state (Table 3) were calculated using partition function obtained within the "rigid rotator - anharmonic oscillator" approximation [4] by direct summation of the energies taking into account conformations.

4. Conclusion

The thermodynamic functions of ibuprofen in the gas phase are presented in Tables 1-3. The calculated values in Table 3 are rounded to integer values, so the calculation error (taking into account the experimental correction) is at least 2 kJ/mol.

| Table 1. Temperature dependence of the molar fractions $\chi_i(T)$ of ibuprofen conformers (I - XVII) for the temperature range 298.15 - 1000 K and entropy of mixing $S_{\text{mix}}$, J mol$^{-1}$ K$^{-1}$ |  |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $T$, K | I | II | III | IV | V | VI | VII | VIII | IX |  |
| 298.15 | 0.140 | 0.247 | 0.192 | 0.223 | 0.035 | 0.026 | 0.033 | 0.036 | 0.034 |  |
| 300 | 0.139 | 0.246 | 0.193 | 0.222 | 0.035 | 0.026 | 0.034 | 0.036 | 0.035 |  |
| 400 | 0.125 | 0.218 | 0.172 | 0.199 | 0.048 | 0.037 | 0.046 | 0.049 | 0.047 |  |
| 500 | 0.113 | 0.197 | 0.156 | 0.180 | 0.056 | 0.044 | 0.054 | 0.058 | 0.056 |  |
| 1000 | 0.083 | 0.144 | 0.115 | 0.132 | 0.068 | 0.055 | 0.066 | 0.071 | 0.069 |  |
| $T$, K | X | XI | XII | XIII | XIV | XV | XVI | XVII | $S_{\text{mix}}$ |  |
| 298.15 | 0.014 | 0.016 | 0.001 | 0.001 | 0.001 | 0.001 | 0.000 | 0.000 | 22 |  |
| 300 | 0.014 | 0.016 | 0.001 | 0.001 | 0.001 | 0.001 | 0.000 | 0.000 | 22 |  |
| 400 | 0.022 | 0.025 | 0.003 | 0.003 | 0.003 | 0.003 | 0.000 | 0.000 | 24 |  |
| 500 | 0.029 | 0.031 | 0.007 | 0.006 | 0.006 | 0.006 | 0.001 | 0.001 | 25 |  |
| 800 | 0.038 | 0.042 | 0.019 | 0.017 | 0.018 | 0.017 | 0.004 | 0.005 | 27 |  |
| 900 | 0.040 | 0.043 | 0.023 | 0.020 | 0.022 | 0.021 | 0.006 | 0.006 | 27 |  |
| 1000 | 0.041 | 0.044 | 0.026 | 0.023 | 0.025 | 0.024 | 0.007 | 0.008 | 27 |  |

* mole fractions are given for only one mirror isomer
Table 2. Enthalpy of formation of ibuprofen in the gas phase $\Delta_f H^0_{298}$, obtained by various methods, kJ/mol.

| Method          | G4     | G4MP2   | G3MP2   | M06/6-311++G(3df,3pd) | B3LYP/6-311++G(3df,3pd) | exp     |
|-----------------|--------|---------|---------|----------------------|-------------------------|---------|
|                 | -453.0 (I) | -453.5 (I) | -455.5 (I) | -476.4 (I) | -310.9 (I) | -454.6±3.3 |
|                 | -453.6 (II) | -455.4 (II) | -476.3 (II) | -311.3 (II) | -311.0 (III) | -453.9±3.5 |
|                 |         |         |         | -311.3 (IV) |         | -457.1±3.5 |
|                 |         |         |         | -304.8 (V) |         |         |
|                 |         |         |         | -304.6 (VI) |         |         |
|                 |         |         |         | -306.7 (VII) |         |         |
|                 |         |         |         | -306.2 (VIII) |         |         |
|                 |         |         |         | -306.1 (IX) |         |         |

Table 3. Thermodynamic functions of ibuprofen in the ideal gas state for the temperature range 298.15 - 1000 K.

| $T$, K | $\Delta_f H^0_T$ | $\Delta_f G^0_T$ | $H^0_T - H^0_0$ | $S^0$ | $G^0_T - H^0_0$ | $C^0_p$ |
|--------|-----------------|-----------------|-----------------|------|-----------------|--------|
| 298.15 | -454            | -238            | 44              | 565  | -125            | 256    |
| 300    | -454            | -236            | 44              | 567  | -126            | 331    |
| 400    | -467            | -166            | 74              | 652  | -187            | 397    |
| 500    | -477            | -93             | 110             | 734  | -257            | 451    |
| 600    | -484            | -19             | 153             | 812  | -335            | 497    |
| 700    | -488            | 56              | 200             | 886  | -420            | 535    |
| 800    | -491            | 131             | 252             | 955  | -512            | 567    |
| 900    | -492            | 207             | 307             | 1021 | -612            | 595    |
| 1000   | -492            | 282             | 365             | 1082 | -717            | 618    |

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