



The thermodynamic stability of the three isomers of methoxybenzamide: An experimental and computational study



Ana R.R.P. Almeida^a, Manuel J.S. Monte^{a,*}, M. Agostinha R. Matos^a, Victor M.F. Morais^{a,b}

^a Centro de Investigação em Química, Departamento de Química e Bioquímica, Faculdade de Ciências da Universidade do Porto, Rua do Campo Alegre, 687, P-4169-007 Porto, Portugal

^b Instituto de Ciências Biomédicas Abel Salazar da, Universidade do Porto, Rua de Jorge Viterbo Ferreira n.º 228, 4050-313 Porto, Portugal

ARTICLE INFO

Article history:

Available online 12 July 2013

This article is dedicated to the memory of Prof. Manuel A.V. Ribeiro da Silva

Keywords:

Methoxybenzamide
Enthalpy of sublimation
Enthalpy of combustion
Enthalpy of formation
Enthalpy of fusion
Vapour pressures
Gibbs energy of formation
Quantum chemical calculations
G3
G4

ABSTRACT

Thermodynamic properties of *ortho*, *meta* and *para* methoxybenzamides were determined using the Knudsen effusion method and calorimetric experiments as well as computational approaches. The vapour pressure of the crystalline phase of the three isomers was measured and values of the standard ($p^\circ = 0.1$ MPa) molar enthalpy, Gibbs energy and entropy of sublimation, at $T = 298.15$ K, were derived. Static bomb combustion calorimetry was used to measure the standard molar enthalpies of combustion from which the standard molar enthalpies of formation in the crystalline state, at $T = 298.15$ K, were derived. Together with the standard molar enthalpies of sublimation, these results yielded the standard molar enthalpies of formation in gaseous phase of the three isomers. The standard Gibbs energies of formation in crystalline and gaseous phases were also derived and used to differentiate the thermodynamic stability of the three isomers. Moreover, differential scanning calorimetry analysis enabled determination of the temperature and molar enthalpies of fusion of the studied compounds. Gas-phase enthalpies of formation of the three compounds were estimated computationally at the G3 and G4 levels of theory and compared with the experimental results.

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1. Introduction

With the purpose to understand better the influence of different substituents in the thermodynamic properties of several substituted benzenes, we extended our previous work on volatility [1–5] and relative stability [6–8] of those compounds to the study of the three methoxybenzamide isomers (structural formula of 2-methoxy isomer is represented in figure 1) that are known to have interesting biological activity. Substituted 2-methoxybenzamide drugs are a group of dopamine receptor antagonists [9] that exhibit anti-emetic, neuroleptic, and anti-psychotic properties [10], as well as anti-dyspeptic and anti-depressant activity [11]. The compound 3-methoxybenzamide, which is known to be an inhibitor of ADP-ribosyltransferase, inhibits cell division in *Bacillus subtilis*, leading to filamentation and eventually lysis of cells [12]. This isomer has an analgesic action in rats since it produces a dose-related elevation of the threshold for response to a painful stimulus [13]. Small molecule ligands of sigma receptors, such as 4-methoxybenzamide (*p*-anisamide), have achieved considerable importance as tumor imag-

ing agents and in targeted therapy. Sigma receptors are overexpressed in a variety of human tumors including non-small cell lung carcinoma (NSCLC), prostate cancer, melanoma, and breast cancer [14–16] and it was demonstrated the targeted delivery of oligodeoxynucleotides and siRNA to lung cancer and melanoma using 4-methoxybenzamide-decorated nanoparticles [17–19].

2. Experimental

2.1. Materials and purity control

All the compounds are commercial products and were purified by repeated sublimation under reduced pressure before experimental studies. An Agilent 4890D chromatograph, equipped with a flame ionisation detector and an HP-5 column, (cross-linked, 0.05 diphenyl and 0.95 dimethylpolysiloxane by mass fraction), was used to check the final purities of the three isomers. The purity of the samples was also confirmed through the carbon dioxide recovered in combustion calorimetric experiments. The average ratios, together with the standard deviation of the mean, of the mass of carbon dioxide recovered to that calculated from the mass of sample used in each experiment were: (1.00034 ± 0.00006) for 2-methoxybenzamide, (1.00048 ± 0.00011) for 3-methoxybenzamide, and (1.00055 ± 0.00015) for 4-methoxybenzamide. Table 1 lists the

* Corresponding author. Tel.: +351 22 0402 516; fax: +351 22 0402 659.

E-mail addresses: ana.figueira@fc.up.pt (A.R.R.P. Almeida), mjmonte@fc.up.pt (M.J.S. Monte), marmatos@fc.up.pt (M. Agostinha R. Matos), vmmorais@icbas.up.pt (V.M.F. Morais).

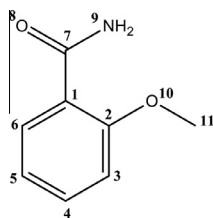


FIGURE 1. Structural formula of the *o*-methoxybenzamide isomer.

original purity of the three isomers, presented in certificate of analysis of the supplier, and the final one related to the purified samples of each isomer. The specific density of the 4-methoxybenzamide was taken from literature [20] as $\rho = 1.143 \text{ g} \cdot \text{cm}^{-3}$ and the same value was assumed for *ortho*- and *meta*- isomers. The atomic weights of the elements used were those recommended by the IUPAC commission in 2009 [21].

2.2. Differential scanning calorimetry

A power compensated differential scanning calorimeter (Setaram 141) was used to detect possible phase transitions in the crystalline phase and to determine the temperatures and enthalpies of fusion of the purified compounds. Six fresh samples of each compound, sealed in aluminium pans, were heated at $(3.3 \cdot 10^{-2}) \text{ K} \cdot \text{s}^{-1}$. The calibration of the power scale of the calorimeter was performed using high purity indium (mass fraction > 0.99999) and the temperature scale was calibrated measuring the temperature of fusion of the following high purity reference materials: benzoic acid, naphthalene, tin and indium [22]. The recorded thermograms (under a nitrogen flow) did not show any phase transition between $T = 298 \text{ K}$ and the melting temperature of the compounds studied. The onset temperatures of fusion as well as the molar enthalpy of fusion related to the three compounds are presented in table 2.

2.3. Vapour pressures measurements

The Knudsen effusion apparatus used to measure the vapour pressures of the three isomers of methoxybenzamide was previously described in detail [23]. This apparatus enables the simultaneous operation of nine effusion cells, contained in cylindrical holes inside three temperature-controlled aluminium blocks. During an effusion experiment, each aluminium block, containing three effusion cells, is kept at a constant temperature, different from the other two blocks. Three different groups of effusion cells according to their different areas of effusion orifices were used: one “small” ($A_0 \approx 0.5 \text{ mm}^2$: series A), one “medium” ($A_0 \approx 0.8 \text{ mm}^2$: series B) and one “large” ($A_0 \approx 1.1 \text{ mm}^2$: series C). The temperature of each block is measured using a platinum resistance thermometer Pt100 class 1/10 (in a four wire connection) previously calibrated by comparison with an SPRT (25 X; Tinsley, 5187 A). The exact areas and transmission probability factors of each used effusion orifice, made in platinum foil of 0.0125 mm thickness, are presented in the supporting information, table S1. In each effusion experiment, the mass loss

TABLE 2

Temperature and enthalpy of fusion for the compounds studied.^a

Compound	T_{fus}/K	$\Delta_{\text{cr}}^{\text{l}}H_{\text{m}}^{\circ}(T_{\text{fus}})/\text{kJ} \cdot \text{mol}^{-1}$
<i>o</i> -Methoxybenzamide	401.66 ± 0.18	27.21 ± 0.25
<i>m</i> -Methoxybenzamide	407.15 ± 0.16	28.60 ± 0.21
<i>p</i> -Methoxybenzamide	440.64 ± 0.14	29.04 ± 0.25

^a Derived from six DSC independent runs; quoted uncertainties are twice the standard deviation of the mean of the individual results.

of the crystalline sample, Δm , was measured by weighing the cells with samples, within $\pm 0.01 \text{ mg}$, before and after a convenient effusion time period, t , in a system evacuated to a pressure near $1 \cdot 10^{-4} \text{ Pa}$. For the temperature T , measured with an accuracy of $\pm 0.01 \text{ K}$, the vapour pressure p of the crystalline sample contained in each effusion cell is calculated by equation (1) where M is the molar mass of the effusing vapour, R is the gas constant, A_0 represents the area of the effusion orifice and w_0 is the respective transmission probability factor. The accuracy of the measured pressures is estimated to be better than $\pm 0.01 \text{ Pa}$.

$$p = (\Delta m / A_0 w_0 t) (2\pi RT / M)^{1/2}. \quad (1)$$

2.4. Combustion calorimetry

The combustion experiments were performed with an isoperibol static bomb calorimeter [24,25], made of stainless steel and with an internal volume of 0.342 dm^3 . Benzoic acid (NIST Thermochemical Standard 39j) was used for the calibration of the bomb. Its massic energy of combustion is $\Delta_{\text{c}}u = -(26434 \pm 3) \text{ J} \cdot \text{g}^{-1}$ [26], under certificate conditions. The calibration experiments were made following the procedure described by Coops *et al.* [27] and the calibration results were corrected to give the energy equivalent ε_{cal} corresponding to the average mass of water added to the calorimeter, 3119.6 g . From six calibration experiments performed $\varepsilon_{\text{cal}} = (15995.3 \pm 2.0) \text{ J} \cdot \text{K}^{-1}$, where the uncertainty quoted refers to the standard deviation of the mean. The samples of the crystalline compounds were burnt in pellet form, and 1.00 cm^3 of deionized water was introduced into the bomb, which was purged twice with oxygen to remove air, before being filled with 3.04 MPa of oxygen. The calorimeter temperatures were measured to $(1 \cdot 10^{-4}) \text{ K}$, at intervals of 10 s , with a quartz crystal thermometer (Hewlett–Packard HP 2804 A), interfaced to a PC. The ignition of the samples was made at $T = 298.15 \text{ K}$, at least 100 readings after the start of the experiment, by the discharge of a $1400 \mu\text{F}$ capacitor through a platinum ignition wire of diameter 0.05 mm . After ignition, another 100 readings were taken for each the main and the after periods. Data acquisition, control of the calorimeter temperature, and the calculation of the adiabatic temperature change were performed using the program LABTERMO [28].

For the cotton-thread used as a fuse in all the experiments, the empirical formula and the massic energy of combustion are, respectively, $\text{CH}_{1.686}\text{O}_{0.843}$ and $\Delta u = -16240 \text{ J} \cdot \text{g}^{-1}$ [29]. This value has been previously confirmed in our laboratory. The corrections for nitric acid formation ΔU (HNO_3) were based on

TABLE 1

Source, purification and analysis details of the three methoxybenzamide isomers.

Chemical name	CAS register no.	Source	Initial purity ^a	Purification method	Final mass fraction purity	Analysis method
<i>o</i> -Methoxybenzamide	2439-77-2	Alfa Aesar	0.999	Sublimation	0.9992	GC ^b
<i>m</i> -Methoxybenzamide	5813-86-5	Sigma–Aldrich	0.997	Sublimation	0.9996	GC ^b
<i>p</i> -Methoxybenzamide	3424-93-9	Sigma–Aldrich	0.996	Sublimation	0.9990	GC ^b

^a Certificate of analysis.

^b Gas chromatography.

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