J. Chem. Thermodynamics 86 (2015) 6–12

Contents lists available at ScienceDirect

J. Chem. Thermodynamics

journal homepage: www.elsevier.com/locate/jct

Thermodynamic properties of sublimation of the *ortho* and *meta* isomers of acetoxy and acetamido benzoic acids

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ARTICLE INFO

Article history:
Received 16 December 2014
Received in revised form 5 February 2015
Accepted 10 February 2015
Available online 17 February 2015

Keywords:
Acetoxybenzoic acid
Acetamidobenzoic acid
Vapour pressure
Sublimation
Thermodynamic properties
Aspirin

ABSTRACT

This paper reports vapour pressures measured at several different temperatures using the Knudsen effusion method of *ortho*-acetoxybenzoic acid (aspirin) (341.1 to 361.1) K, *meta*-acetoxybenzoic acid (344.2 to 362.2) K, *ortho*-acetamidobenzoic acid (367.2 to 389.2) K, and *meta*-acetamidobenzoic acid (423.2 to 441.1) K. The experimental results enabled the determination of the standard molar enthalpies, entropies and Gibbs energies of sublimation, at $T = 298.15$ K, of the four compounds studied. DSC experiments yield results of the temperature and enthalpy of fusion. The experimental results were compared with literature ones for the *para* isomers of the acids acetoxybenzoic and acetamidobenzoic. Correlations involving temperature of fusion, and standard molar enthalpy and Gibbs energy of sublimation of several substituted benzoic acids were proposed. Those correlation equations allow a good estimative of volatility of benzoic acid derivatives from their enthalpies of sublimation and temperatures of fusion.

1. Introduction

Experimental results of thermodynamic properties of sublimation of several substituted benzoic acids and of some of their parent methyl esters have been reported by our research group [1–12]. In this work these studies are extended to the *ortho* and *meta* isomers of acetoxy and acetamido benzoic acids enabling the comparison of the derived results with those reported before for the respective *para* isomers [7]. Moreover, we wanted to verify if a correlation relating temperatures of fusion, standard molar enthalpies and standard Gibbs energy of sublimation, derived previously for *para*-substituted benzoic acids [7], still hold for *ortho* and *meta* isomers. *Ortho*-acetoxybenzoic acid, also known as acetylsalicylic acid or aspirin, is one of the most widely used nonsteroidal anti-inflammatory drugs (NSAIDs) and its therapeutic properties have been discussed in the literature. Aspirin is often used as an antipyretic, analgesic and anti-inflammatory medication [13]. Durable use and high doses of this salicylate medication raise the risk of gastrointestinal complications; nevertheless, the ingestion of small daily doses has the potential to reduce repeated vascular events [14]. Both *ortho* and *meta* isomers of acetoxybenzoic acid are ligands of two novel organoantimony(V) and two organobismuth(V) complexes that exhibited antileishmanial and antibacterial activities [15]. The *ortho* isomer of acetamidobenzoic acid (*N*-acetylanthranilic acid) is a triboluminescent material [16,17] and presents antimicrobial activity against some plant pathogen – antifungal activity against *Fusarium avenaceum*, *Fusarium graminearum* and *Fusarium culmorum*, and also antibacterial activity against *Staphylococcus aureus* and *Escherichia coli* [18]. Further, this compound is an intermediate degradation product of quinaldine in *Arthrobacter sp.*, being metabolised to anthranilic acid [19,20]. Representations of structures of the compounds studied in this work are presented in figure 1.

2. Experimental

2.1. Materials and purity control

Table 1 reports analysis and purification details of the four compounds studied in this work: *ortho*-acetoxybenzoic acid ($C_9H_8O_4$, CASNR 50-78-2), *meta*-acetoxybenzoic acid ($C_9H_8O_4$, CASNR 6304-89-8), *ortho*-acetamidobenzoic acid ($C_9H_9NO_3$, CASNR 89-52-1) and *meta*-acetamidobenzoic acid ($C_9H_9NO_3$, CASNR 587-48-4). Prior to the experimental study, the purity of the samples was analysed by gas–liquid chromatography performed using an apparatus Agilent 4890D equipped with an HP-5 column (cross-linked, 0.05 diphenyl and 0.95 dimethylpolysiloxane by mass fraction) and a flame ionisation detector (FID), using nitrogen as the carrier gas. The samples of the two *meta* isomers were

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http://dx.doi.org/10.1016/j.jct.2015.02.010
0021-9614/

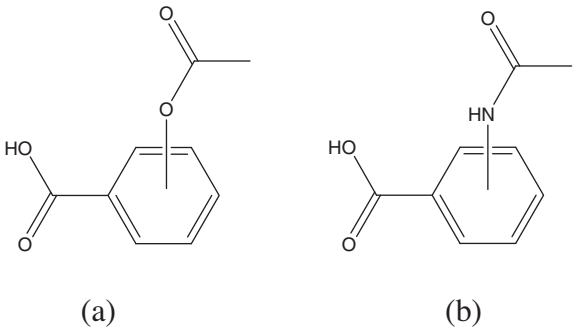

FIGURE 1. General structure of (a) *ortho* and *meta* acetoxybenzoic acids and (b) *ortho* and *meta* acetamidobenzoic acids.

further purified by sublimation under reduced pressure and their final purity was analysed again by gas–liquid chromatography.

2.2. Differential scanning calorimetry

The temperatures and the enthalpies of fusion of the samples (hermetically sealed in steel crucibles) were determined using a Setaram DSC 141 calorimeter under a heating rate of $3.3 \cdot 10^{-2}\ \mathrm{K \cdot s^{-1}}$. The calibration of the power scale of the calorimeter was performed using high-purity indium (mass fraction > 0.99999) and its temperature scale was calibrated by measuring the melting temperature of the following high purity reference materials [21]: naphthalene, benzoic acid and indium. For each compound, at least four independent runs were performed and the mean results of the onset temperatures of fusion, T_{fus}, and of the molar enthalpies of fusion, $\Delta^{l}_{cr}H^{o}_{m}(T_{fus})$, are reported in table 2 together with the results reported in literature. No phase transitions between $T = 298$ K and the melting temperature of the compounds were detected.

2.3. Vapour pressures measurements

The vapour pressures of the crystalline phase of *ortho*-acetoxybenzoic acid and of *ortho* and *meta* acetamidobenzoic acids were measured over the range (0.1 to 1) Pa, using a Knudsen effusion apparatus allowing the simultaneous operation of nine effusion cells – the experimental set-up and procedure have been tested and described before [22]. The experiments related to the *ortho*-acetoxybenzoic acid and to the *meta*-acetamidobenzoic acid were performed using six effusion cells with different effusion circular orifices made in platinum discs of 0.0125 mm thickness – three of the series A ($A_o \approx 0.5\ \mathrm{mm^2}$) and three of the series B ($A_o \approx 0.8\ \mathrm{mm^2}$). Later, all platinum discs of the effusion cells were substituted for new ones [23] that were used for the vapour pressure measurements of *ortho*-acetamidobenzoic acid. The new effusion orifices also made in platinum discs of (0.0125 ± 0.001) mm thickness were acquired from Goodfellow Cambridge Ltd as

TABLE 2
Temperatures, and molar enthalpies and entropies of fusion of the three isomers of acetoxy and acetamido benzoic acids.

Compound	T_{fus}/K	$\Delta^{l}_{cr}H^{o}_{m}(T_{fus})$/ kJ · mol^{-1}	$\Delta^{l}_{cr}S^{o}_{m}(T_{fus})$/ J · K^{-1} · mol^{-1}
o-Acetoxybenzoic acid	407.38 ± 0.16[a] 405 ± 10[c] [26] 414 [27] 412.7 [28] 409.2 [29]	33.85 ± 0.07[a] 29.8 [27] 31.01 [28] 29.17 [29]	83.1 ± 0.2[b]
m-Acetoxybenzoic acid	404.76 ± 0.16[a] 400 [30]	26.27 ± 0.30[a]	64.9 ± 0.7[b]
p-Acetoxybenzoic acid	464.8 ± 0.2 [7]	30.5 ± 0.1 [7]	
o-Acetamidobenzoic acid	455.11 ± 0.21[a] 458.4 ± 0.2 [31]	29.32 ± 0.23[a] 49.4 ± 0.2 [31]	64.4 ± 0.5[b]
m-Acetamidobenzoic acid	522.19 ± 0.16[a] 518.2 ± 0.2 [31]	42.28 ± 0.54[a] 39.4 ± 0.2 [31]	81.0 ± 1.0[b]
p-Acetamidobenzoic acid	531.7 ± 0.2 [7] 535.3 ± 0.2 [31]	42.4 ± 0.1 [7] 34.2 ± 0.2 [31]	

[a] This work. The uncertainties assigned are expanded uncertainties ($k = 2$).
[b] Uncertainties calculated through the RSS method.
[c] Average of 103 values.

the previous ones. Their diameters were precisely measured by this company with an assigned uncertainty of 0.005 mm, leading to the resulting areas and Clausing factors: C_1, C_2, C_3, $A_o = (0.636 \pm 0.004)\ \mathrm{mm^2}$ and $w_o = 0.986$; D_1, D_2, D_3, $A_o = (0.785 \pm 0.004)\ \mathrm{mm^2}$ and $w_o = 0.988$; E_1, E_2, E_3, $A_o = (0.985 \pm 0.004)\ \mathrm{mm^2}$ and $w_o = 0.989$.

Since the amount of the purified sample of *meta*-acetoxybenzoic acid was not enough to use more than three effusion cells, the crystalline vapour pressures of this compound were measured at different temperatures using another mass-loss Knudsen-effusion apparatus that enables the simultaneous operation of three effusion cells, with three different effusion orifices made in platinum foil. A complete description of this apparatus, procedure and the results obtained with test substances has been reported before [24], although some minor changes have been introduced to the original apparatus including the use of thin (0.0125 mm) platinum discs for the effusion orifices (F, G and H). The good performance of both effusion apparatus has been periodically tested. The areas and Clausing factors of orifices A, B, F, G, and H are gather together in table S1 in supplementary information.

The mass loss of each sample during the effusion process was determined by weighing the effusion cells, before and after the effusion period, with an estimated uncertainty of $1 \cdot 10^{-5}$ g. At the temperature T, the vapour pressure p of the crystalline sample contained in each cell was calculated using equation (1),

$$p = \frac{m}{A_o w_o t}\left(\frac{2\pi RT}{M}\right)^{0.5}, \qquad (1)$$

where m is the sublimed mass, t is the effusion time period, M is the molar mass of the effusing vapour (assumed monomeric), and R is

TABLE 1
Provenance, purification and analysis details of the compounds studied.

Chemical name	Source	Initial purity	Purification method	Final mass fraction purity	Analysis method[a]
o-Acetoxybenzoic acid	Sigma–Aldrich	0.999[b]		0.9990	GC
m-Acetoxybenzoic acid	Sigma–Aldrich	0.991[b]	Sublimation[c]	0.9957	GC
o-Acetamidobenzoic acid	Sigma–Aldrich	0.996[b]		0.9960	GC
m-Acetamidobenzoic acid	Fluka	0.98	Sublimation[c]	0.9978	GC

[a] Gas–liquid chromatography (FID).
[b] As stated in the certificate of analysis of the manufacturer.
[c] Under reduced pressure ($p = 1$ Pa).