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Vapour pressures of 1-methyl derivatives of benzimidazole, pyrazole and indole. The energy of the intermolecular hydrogen bond N—H···N

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ABSTRACT

The vapour pressures of the liquid phase of 1-methylpyrazole, 1-methylbenzimidazole and 1-methylindole were measured over the temperature ranges (253.9 to 293.3) K, (303.2 to 372.5) K, and (268.6 to 341.9) K, respectively, using a static method. The vapour pressures of the crystalline phase of the two latter compounds were also measured at temperatures between (301.2 to 328.9) K and (267.6 to 275.5) K, respectively. The results obtained enabled the determination of the standard molar enthalpies and entropies of sublimation and of vaporisation at the mean temperatures of the measurements and at $T = 298.15$ K. The temperatures and molar enthalpies of fusion were determined using differential scanning calorimetry. The enthalpies of the intermolecular hydrogen bonds N—H···N in the crystalline phase of benzimidazole and pyrazole were determined and compared with the result previously determined for the energy of the intermolecular hydrogen bond in crystalline imidazole.

1. Introduction

In previous work [1], the energies of the intermolecular hydrogen bonds N—H···N formed in the crystals of imidazole and of its 4,5-dichloro and dicyano derivatives were estimated from experimental vapour pressure measurements. In this work, we planned to follow a similar approach to determine the energy of analogous bonds existing in crystalline benzimidazole and pyrazole, by measuring the vapour pressures of their 1-methyl derivatives, and of 1-methylindole, and comparing the derived enthalpies of sublimation with the ones published in the literature for the parent compounds.

Nitrogen heterocyclic compounds present diverse biological and pharmacological applications, mainly due to structural resemblances with several natural and synthetic molecules with biological activity [2]. Benzimidazole interacts easily with biopolymers of living systems, since it is structurally similar to naturally occurring nucleotides [3]. This characteristic is responsible for its several biological activities (antihelminthic [4], antifungal [5,6], anti-allergic [7], anti-microbial [8], anti-viral [8] and anti-neoplasic properties [9]). Owing to its ability to establish hydrogen bonds and π–π stacking interactions with the imidazole ring of histidine residue of some metalloproteases, this compound has been used as a structural component and part of the central scaffold in several inhibitors of these enzymes [3,10]. Pyrazole is a prevalent frame in drug discovery programs and its derivatives possess pharmacological effects on humans [11]. Pyrazoles are classified as alkaloids and have been used as herbicides, drugs in agrochemical and pharmaceutical industries; the ones containing pharmacoactive agents are used in medicinal chemistry. Due to their potential biological activities, the pyrazole derivatives exhibit different pharmacological properties including antitumor, antimicrobial, anti-inflammatory, antiviral, anticonvulsant and antidepressant behaviour [11]. Finally, the indole ring system is the most widely heterocycle

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found in nature [12], being a common component of several fragrances and the precursor of many pharmaceuticals [13]; the essential amino acid tryptophan, the neurotransmitter serotonin, and numerous groups of significant alkaloids have such a core in their structures [2].

The substitution of the hydrogen atom attached to nitrogen by a methyl group inhibits the possibility of establishing intermolecular hydrogen bonds that are formed in crystalline imidazole, benzimidazole, and pyrazole, and increases significantly their volatility. 1-Methylindole shows higher toxicity than the parent compound and the 1-methylindole derivatives are found in wastes of various industrial processes (petroleum refining, pharmaceuticals, pesticides, disinfectants, and dyestuff) [14]; 1-methylpyrazole is a common core of several pesticides frequently found in foodstuff that induce DNA damage in human cells [15]; some derivatives of 1-methylbenzimidazol are active ingredients of fungicides [16].

2. Experimental

2.1. Materials and purity control

The source, purification methods, and the purities of the samples of the compounds studied in this work – 1-methylbenzimidazole ($C_8H_8N_2$, CASRN 1632-83-3), 1-methylpyrazole ($C_4H_6N_2$, CASRN 930-36-9) and 1-methylindole (C_9H_9N, CASRN 603-76-9) – are summarised in table 1. This table presents the initial and final purities of the purified samples of these compounds; the mass fractions of the purified samples were evaluated by gas chromatography performed using an Agilent 4890D gas chromatograph equipped with an HP-5 column (cross-linked, 0.05 diphenyl and 0.95 dimethylpolysiloxane, by mass fraction), and a flame ionisation detector, using nitrogen as the carrier gas.

2.2. Differential scanning calorimetry

Differential scanning calorimetry (Setaram DSC 141) was used to determine the temperatures and enthalpies of fusion of the purified samples of the compounds studied and to identify possible phase transitions in their crystalline phase. The calibration of the power scale of the calorimeter was accomplished using high-purity indium (mass fraction > 0.99999) and its temperature scale was calibrated by measuring the fusion temperature of high purity reference materials (naphthalene, benzoic acid, tin and indium [17]). Under nitrogen atmosphere, six samples (sealed in aluminium pans) of each compound were independently scanned from $T = 298$ K (1-methylbenzimidazole), or from $T = 193$ K (1-methylpyrazole and 1-methylindole) to a temperature *ca.* 20 K above the melting point, using a heating rate of $3.3 \cdot 10^{-2}\ \mathrm{K \cdot s^{-1}}$. No solid-solid phase transitions were detected between the initial temperature and the melting temperature of the three compounds. Their onset temperatures of fusion, T_{fus}, and the enthalpies of fusion, $\Delta_{\mathrm{cr}}^{\mathrm{l}}H_{\mathrm{m}}^{\mathrm{o}}$ (T_{fus}), were computed from the DSC thermograms and are presented in table 4, where the uncertainties assigned are expanded uncertainties ($k = 2$).

2.3. Vapour pressure measurements

The vapour pressures of the three compounds were measured at different temperatures using an experimental set-up based on a static method that has been described in detail [18,19]. This apparatus includes two Baratron diaphragm capacitance gauges that operate at self-controlled temperatures. Baratron 631A01TBEH (gauge I, $T = 423$ K), for pressures in the range (0.3 to 130) Pa and for sample temperatures within the interval (253 to 413) K; Baratron 631A11TBFP (gauge II, $T = 473$ K) for pressures in the range (3 to 1330) Pa and for sample temperatures in the interval $T = (253$ to $463)$ K. The temperature of the condensed samples was measured using a Pt100 PRT (platinum resistance thermometer) class 1/10 DIN in a four-wire connection, that was calibrated by comparison with a standard PRT (25 Ω; Tinsley 5187A). To prevent condensation, the temperature of the tubing between the condensed sample and the pressure gauge was kept at a temperature slightly higher than the temperature of the sample. The uncertainties in the vapour pressure measurements, using gauges I and II, may be described by the expressions $u(p/\mathrm{Pa}) = 0.01 + 0.0025(p/\mathrm{Pa})$ and $u(p/\mathrm{Pa}) = 0.1 + 0.0025(p/\mathrm{Pa})$, respectively. The uncertainty in the temperature measurements is estimated to be $u(T/\mathrm{K}) = 0.01$.

3. Results and discussion

3.1. Vapour pressures and enthalpies and entropies of phase transitions

Table 2 presents the vapour pressures of the crystalline and liquid (both stable and super-cooled) phases of 1-methylbenzimidazole and 1-methylindole and also the vapour pressures of liquid 1-methylpyrazole. These results are also shown through graphic representations in figures 1 to 3. The experimental solid and liquid vapour pressures were independently fitted by the truncated form of the Clarke and Glew equation (1) [20].

$$R\ln\left(\frac{p}{p^{\mathrm{o}}}\right) = -\frac{\Delta_{\mathrm{cd}}^{\mathrm{g}}G_{\mathrm{m}}^{\mathrm{o}}(\theta)}{\theta} + \Delta_{\mathrm{cd}}^{\mathrm{g}}H_{\mathrm{m}}^{\mathrm{o}}(\theta)\left(\frac{1}{\theta}-\frac{1}{T}\right) + \Delta_{\mathrm{cd}}^{\mathrm{g}}C_{p,\mathrm{m}}^{\mathrm{o}}(\theta)\left[\left(\frac{\theta}{T}\right) - 1 + \ln\left(\frac{T}{\theta}\right)\right]. \tag{1}$$

In this equation, p is the vapour pressure at the temperature T, p^{o} is a selected reference pressure ($p^{\mathrm{o}} = 10^5$ Pa, in this work), θ represents selected reference temperatures and R is the gas constant ($8.3144621\ \mathrm{J \cdot K^{-1} \cdot mol^{-1}}$ [21]). Table 3 presents the values of the adjustable thermodynamic parameters of sublimation and vaporisation of the condensed phases, $\Delta_{\mathrm{cd}}^{\mathrm{g}}G_{\mathrm{m}}^{\mathrm{o}}(\theta)$ and $\Delta_{\mathrm{cd}}^{\mathrm{g}}H_{\mathrm{m}}^{\mathrm{o}}(\theta)$, for three different temperatures (298.15 K, the mean temperature of the experiments, and also the triple point temperatures for the two compounds studied in both condensed phases, 1-methylbenzimidazole and 1-methylindole). The quoted uncertainties are standard deviations of the least squares regressions. This table also presents the standard molar entropies of those phase transitions that were calculated as $\Delta_{\mathrm{cd}}^{\mathrm{g}}S_{\mathrm{m}}^{\mathrm{o}}(\theta) = \{[\Delta_{\mathrm{cd}}^{\mathrm{g}}H_{\mathrm{m}}^{\mathrm{o}}(\theta) - \Delta_{\mathrm{cd}}^{\mathrm{g}}G_{\mathrm{m}}^{\mathrm{o}}(\theta)]/\theta\}$. The results for $\Delta_{\mathrm{l}}^{\mathrm{g}}C_{p,\mathrm{m}}^{\mathrm{o}}$, at $T = 298.15$ K, presented in this table, were derived

TABLE 1
Source, purification and analysis details of the samples of the three compounds studied.

Chemical name	Source	Initial purity[a]	Purification method	Final mass fraction purity	Analysis method[b]
1-Methylbenzimidazole	Sigma–Aldrich	0.995	Sublimation[c]	0.997	GC
1-Methylpyrazole	Sigma–Aldrich	1.000	None		
1-Methylindole	Sigma–Aldrich	0.978	Fractional distillation[c]	0.992	GC

[a] Fraction of the GC area, as stated in the certificates of analysis of the manufacturer.
[b] Gas-liquid chromatography (FID).
[c] Under reduced pressure ($p = 1$ Pa).