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# Combined experimental and computational study of the energetics of methylindoles

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ABSTRACT

In order to understand the influence of the methyl group in the stability of the indole unit, the standard ($p^\circ = 0.1$ MPa) molar enthalpies of formation of 1-, 2-, and 3-methylindoles, in the gaseous phase, were determined at $T = 298.15$ K. For that, combustion calorimetry was used to determine the massic energies of combustion and consequently the standard molar enthalpies of formation in the condensed phase, and Calvet microcalorimetry was employed to measure the standard molar enthalpy of phase transition (vaporization for the liquid 1-methylindole and sublimation for the other two solid compounds). The G3(MP2)//B3LYP composite approach was used to calculate the gas-phase enthalpies of formation, at $T = 298.15$ K, of all possible single methylated indoles using four different working reactions. The enthalpies calculated for the 1-, 2-, and 3-methylindoles are in excellent agreement with the values derived from the experimental work.



## 1. Introduction

The indole molecule is a common sub-unit of a great variety of important chemicals. Due to their importance, they have attracted the attention of many fields of research, from biology to industry or environment. The indole motif is the building block of some significant biologically active molecules, such as the amino-acid tryptophan, serotonin, and melatonin [1]. Tryptophan fluorescence is widely used for characterizing the structure and dynamics of the surrounding protein environment. So, it is of great interest the electronic structure of indole and methylindoles, once the indole ring is a chromophore of the tryptophan. 3-Methylindole is of particular interest, since the methyl group has nearly the same effect on the indole ring as the alanyl group, and the absorption spectrum of 3-methylindole in solution is very similar to that of tryptophan [2].

The methylindole derivatives are found in wastes of many industrial processes such as petroleum refinery, pharmaceuticals, pesticides, and dyestuffs [3], and because of their structure they are easily transported in sediment and groundwater, causing several environmental damages [4]. Depending on concentration, 3-methylindole could have a positive aroma profile, as during ripening of cheese [5] and as additive in some perfumes [4]. It can also have an unpleasant odor, which constitutes a primary problem in livestock management, especially in swine production [6], and it was confirmed to be one of the responsible constituents for the fecal off-odour frequently detected in white pepper [7]. This compound, a pneumotoxin, formed by the bacterial degradation of tryptophan, shows high toxicity and it is recognized as a possible agent involved in the schizophrenia acute bovine pulmonary edema and emphysema. It is responsible for the boar taint given off from pig meat on cooking which is unpleasant to consumers and which has harmful consequences for the beef and pork industries [8]. Humans are exposed to methylindoles from cigarette smoke [9] and from colonic degradation of tryptophan, however the potential risk is still unclear [10].

In the present work, the standard ($p^\circ = 0.1$ MPa) massic energies of combustion of 1-, 2-, and 3-methylindole (figure 1) were measured by static bomb calorimetry. The standard molar enthalpies of phase transition (vaporization of 1-methylindole and sublimation of 2- and 3-methylindole) were determined by Calvet microcalorimetry. Combining the results obtained by these two techniques, the standard molar enthalpies of formation, at $T = 298.15$ K, in gaseous phase, were derived. Additionally, standard molar enthalpies of formation of these three compounds were estimated computationally.

## 2. Experimental

All the compounds were obtained commercially from Aldrich Chemical Co. The liquid compound, 1-methylindole [CAS 603-76-9], was twice distilled while the solid compounds, namely,

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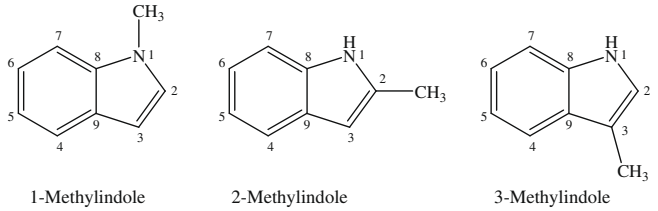


**FIGURE 1.** Structural formula of 1-, 2-, and 3-methylindole.

2-methylindole [CAS 92-20-5] and 3-methylindole [CAS 83-34-1], were purified by sublimation under reduced pressure.

The purity of the compounds was determined by recovering the carbon dioxide produced in the combustion experiments and confirmed by glc. The final purity of each isomer was checked by gas chromatography, performed on an Agilent 4890D Gas Chromatograph equipped with an HP-5 column, cross-linked, 5% diphenyl and 95% dimethylpolysiloxane (15 m × 0.530 mm i.d. × 1.5 μm film thickness), and with nitrogen as the carrier gas. The temperature of the injector was set at 470 K and the oven temperature was programmed as follows: 320 K (1 min), ramp at 10 K · min$^{-1}$, 470 K (10 min). No impurities greater than $10^{-3}$ in mass fraction could be detected in the samples used in the thermochemical determinations. The average ratios of the mass of carbon dioxide recovered after combustion experiments to that calculated from the mass of sample were: 1-methylindole (99.945 ± 0.022); 2-methylindole (100.016 ± 0.021); and 3-methylindole (100.039 ± 0.020), where the uncertainties are the standard deviation of the mean. It was assumed that the densities of the compounds are: for 1-methylindole, $\rho$ = 1.051 g · cm$^{-1}$ [11], for 2-methylindole, $\rho$ = 1.07 g · cm$^{-1}$ [12], and for 3-metylindole, its density was assumed to be identical with 2-methylindole. The relative atomic masses used were those recommended by the IUPAC Commission in 2005 [13].

### 2.1. Combustion calorimetry

The standard massic energies of combustion of 1-methylindole, 2-methylindole, and 3-methylindole were measured by static bomb calorimetry, using an isoperibol system with a twin valve bomb combustion, model 1105 (Parr Instrument, Illinois, USA), with an internal volume of 0.340 cm$^3$. The bomb calorimeter, subsidiary apparatus, and technique have been described previously in the literature [14,15].

The energy equivalent of the calorimeter was determined by combustion of Thermochemical Standard benzoic acid, sample NBS 39j, with $\Delta_c u$ = − (26434 ± 3) J · g$^{-1}$ [16] under bomb conditions. For 1- and 3-methylindole, the energy equivalent of the calorimeter was derived as $\varepsilon_{cal}$ = (15917.4 ± 1.4) J · K$^{-1}$ and for 2-methylindole, measured some months later, the energy equivalent of the calorimeter was determined as $\varepsilon_{cal}$ = (15907.1 ± 0.7) J · K$^{-1}$. The calibration procedure was the same as previously described [17], and the results from the calibration were corrected to give the energy equivalents, $\varepsilon_{cal}$, corresponding to the average mass of water added to the calorimeter: 3119.6 g; the uncertainties quoted are the standard deviations of the mean.

In all combustion experiments, 1.00 cm$^3$ of water was introduced into the bomb, and the bomb was purged twice, to remove air, before being charged with 3.04 MPa of oxygen.

The liquid samples of 1-methylindole were contained in sealed polyester bags made of melinex (0.025 mm of thickness), with massic energy of combustion $\Delta_c u^\circ = -(22902 \pm 5)$ J · g$^{-1}$ [18], a value previously confirmed in our Laboratory. Samples of 2-methylindole and 3-methylindole were burnt in pellet form, for which however it was found to be necessary to enclose the pellets in melinex bags, due to the high volatility of these compounds. The mass of melinex used in each experiment was corrected for the mass fraction of water ($w$ = 0.0032) and the mass of carbon dioxide produced from its combustion was calculated using the factor previously reported [18].

For all experiments, the calorimeter temperatures were measured to ±(1 · 10$^{-4}$) K, at time intervals of 10 s, with a quartz crystal thermometer (Hewlett Packard HP 2804A), interfaced to a PC. The ignition of the samples was made at $T$ = (298.150 ± 0.001) K, by the discharge of a 1400 μF capacitor through the platinum ignition wire, after at least one hundred readings were recorded. After ignition, 100 readings were taken both for the main and the after periods.

For the cotton-thread fuse, with empirical formula $CH_{1.686}O_{0.843}$, the massic energy of combustion was assigned to $-\Delta_c u^\circ$ = 16250 J · g$^{-1}$ [17], a value which was confirmed in our Laboratory.

The amount of substance used in each experiment, and on which the massic energy of combustion values were based, was determined from the mass of $CO_2$ produced during the experiments, taking into account that formed from the combustion of the cotton-thread fuse and of the melinex. The amount of $HNO_3$ produced during the experiment was quantified by titration of the aqueous solution resulting from the washing of the interior of the bomb.

### 2.2. Calvet Microcalorimetry

The standard molar enthalpy of vaporization of 1-methylindole and the standard molar enthalpies of sublimation of 2- and 3-methylindole were measured by Calvet microcalorimetry, using the "vacuum sublimation drop microcalorimetric method", described by Ribeiro da Silva *et al.* [19] and by Skinner *et al.* [20], respectively for enthalpies of vaporization and enthalpies of sublimation. The apparatus and technique have been described in detail [21].

Samples of about (4 to 6) mg of each compound, contained in a thin glass capillary tube sealed at one end, were dropped from room temperature into the hot zone of the calorimeter, a Calvet High Temperature Microcalorimeter (Setaram, HT 1000D), held at a pre-defined temperature, and then removed from the hot zone by vacuum vaporization or sublimation. In this work, the temperature was defined as $T$ = 334.3 K for 1-methylindole, $T$ = 360.1 K for 2-methylindole, and $T$ = 349.9 K for 3-methylindole.

The thermal corrections for the glass capillaries were made by dropping tubes of nearly equal mass into each of the twin cells.

The calorimeter was calibrated *in situ* with *n*-undecane, for the work with 1-methylindole and with naphthalene for the study of 2- and 3-methylindole, using the same experimental procedure used with the compounds. The calibration constants of the calorimeter, $k_{cal}$, were obtained as the average of six independent experiments: for 1-methylindole $k_{cal}$ ($T$ = 334.3 K) = 0.9987 ± 0.0066; for 2-methylindole $k_{cal}$ ($T$ = 360.1 K) = 0.9964 ± 0.0046 and for 3-methylindole $k_{cal}$ ($T$ = 349.9 K) = 1.0244 ± 0.0061, using the values of $\Delta_l^g H_m^\circ$(*n*-undecane) = (56.58 ± 0.57) kJ · mol$^{-1}$ [22] and $\Delta_{cr}^g H_m^\circ$(naphthalene) = (72.60 ± 0.60) kJ · mol$^{-1}$ [22] as the standard molar enthalpies of vaporization of *n*-undecane and of sublimation of naphthalene, respectively, both at $T$ = 298.15 K.

### 2.3. Computational details

The composite G3(MP2)//B3LYP approach [23], as included in the Gaussian 03 code [24] was used in all the calculations. The G3(MP2)//B3LYP approach uses the B3LYP/6-31G(d) method in both geometry optimization and calculation of frequencies. The final absolute G3(MP2)//B3LYP enthalpy is obtained by including the thermal corrections obtained at the B3LYP/6-31G(d) level of theory and the energies from single-point calculations at the QCISD(T)/6-