



# Calorimetric and computational studies for three nitroimidazole isomers



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## ABSTRACT

In the present work, a combined experimental and computational thermochemical study of nitroimidazole isomers was carried out. The standard ( $p^\circ = 0.1$  MPa) molar enthalpy of combustion, in the crystalline phase, for 4-nitroimidazole was determined, at the temperature of 298.15 K, using a static bomb combustion calorimeter. Calvet microcalorimetry experiments were performed to measure its standard molar enthalpy of sublimation. The standard molar enthalpy of formation of 4-nitroimidazole, in the gaseous phase, at  $T = 298.15$  K,  $(116.9 \pm 2.9)$  kJ·mol<sup>-1</sup>, has been derived from the corresponding standard molar enthalpy of formation in the crystalline phase and the standard molar enthalpy of sublimation.

Computational studies for 4-nitroimidazole were performed to complement the experimental work. These were also extended to the 2- and 5-nitroimidazole isomers. The gas-phase enthalpies of formation were estimated from high level *ab initio* molecular orbital calculations, at the G3 level. Also investigated were the tautomeric equilibrium of 4(5)-nitroimidazole in the gaseous phase and it was concluded that the two tautomers are equally stable.

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## 1. Introduction

Nitroimidazoles have been investigated extensively mainly due to their biological activity [1–3], in particular, their antibacterial properties [4,5]. Since one of the many applications of this kind of compounds is to cure the infections induced by bacteria and to kill pathogenic protozoan parasites in human body [6], their toxicity and metabolism have been characterized [7]. Moreover they are promising candidates for high energy materials since they have favourable insensitivity and performance [8–10].

Also several studies [11–19] about tautomerism of these compounds have been carried out. For instance, the migration of the hydrogen atom to the nitrogen atoms in the imidazole ring can lead to the tautomeric forms. According to these studies, the 4-nitro isomer was found to predominate both in the crystal phase [12,16] and in aqueous solution [11,18]. Favouring the 4-nitro tautomer observed in the latter case seems to be principally a solvation phenomenon associated with its dipole moment which is much higher than that of the alternative tautomer. For the gaseous phase, the relative stability of both, 4- and 5-nitroimidazole

is quite confusing; some results show that both tautomers are of similar energy [11,19] while other results favour the tautomer 4 or 5 depending on the theoretical method used for calculating the energy [9,17–19].

Knowledge of the energetic properties of the imidazole derivatives is important for the evaluation of their reactivity, therefore studies about the energy and structure of these compounds have been made [10,17–22].

In this work, we report the standard molar ( $p^\circ = 0.1$  MPa) enthalpy of formation of 4-nitroimidazole, in the gaseous phase, at  $T = 298.15$  K, derived from measurements of the standard molar enthalpy of combustion by static bomb combustion calorimetry and from the standard molar enthalpy of sublimation as measured by Calvet microcalorimetry.

Additionally, standard *ab initio* molecular calculations, at the G3 level, were performed and the standard enthalpies of formation of 2-, 4- and 5-nitroimidazole were estimated. Estimates of the enthalpies of formation, obtained by using appropriate working reactions, were calculated and compared with the experimental data. The good agreement verified between computational and experimental results allows reliable estimates of the enthalpies of formation of the compounds which were not studied experimentally. The stability of the tautomeric forms, in the gaseous phase, has also been studied.

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## 2. Experimental

### 2.1. Compound and purity control

The compound was commercially obtained from TCI, with certified mole fraction purity of 1.000, and was purified by sublimation under reduced pressure. The purity of the sample was also checked by the amount of carbon dioxide recovered after the combustion experiments. The average ratio of the mass of carbon dioxide recovered to that calculated from the mass of sample was  $(0.9997 \pm 0.0005)$ , where the uncertainty is the standard deviation of the mean. Details of the origin and purification of the sample are presented in Table 1.

### 2.2. Combustion calorimetry

The combustion experiments were performed with an isoperibol calorimetric system. The bomb calorimeter, subsidiary apparatus, and technique have been previously described in the literature [23–25]. Combustion of certificated benzoic acid (calorimetric standard – Standard Reference Material 39j) was used for calibration of the bomb. Its massic energy of combustion,  $\Delta_c u^\circ$ , is  $-(26,434 \pm 3) \text{ J} \cdot \text{g}^{-1}$  under certificate conditions [26]. The calibration results were corrected to give the energy equivalent of the calorimeter,  $\varepsilon_{\text{cal}}$ , corresponding to the average mass of 2900.0 g of water added to the calorimeter. From six independent calibration experiments performed,  $\varepsilon_{\text{cal}} = (15551.2 \pm 1.6) \text{ J} \cdot \text{K}^{-1}$ , where the uncertainty quoted is the standard deviation of the mean.

In all combustion experiments, 1.00 cm<sup>3</sup> of deionised water was introduced into the bomb, a twin valve static bomb, with an internal volume of 0.290 dm<sup>3</sup>. The bomb was purged twice to remove air, before being charged with 3.04 MPa of oxygen. Also, in all combustion experiments, the crystalline compound was burnt in pellet form. The ignition of the samples was made at  $T = (298.150 \pm 0.001) \text{ K}$  and the electrical energy for ignition was determined from the change in potential difference across a 1400  $\mu\text{F}$  condenser when discharged through the platinum ignition wire. For the cotton thread fuse used, empirical formula  $\text{CH}_{1.686}\text{O}_{0.843}$ ,  $\Delta_c u^\circ = -16,240 \text{ J} \cdot \text{g}^{-1}$  [27]; this value has been previously confirmed in our laboratory. *n*-Hexadecane (Aldrich, mass fraction > 0.999), stored under nitrogen was used as auxiliary combustion. The massic energy of combustion of the particular sample used, was determined in our laboratory as  $\Delta_c u^\circ = -(47136.7 \pm 2.3) \text{ J} \cdot \text{g}^{-1}$ . The calorimeter temperatures were measured to  $\pm(1 \cdot 10^{-4}) \text{ K}$ , at time intervals of 10 s, with a S10 four wire calibrated ultra-stable thermistor probe (Thermometrics, Standard Serial No. 1030) and recorded by a high sensitivity nanovolt/microohm meter (Agilent 34420A) interfaced to a computer. Data acquisition and control of the calorimeter were performed using the program LAB-TERMO [28,29]. At least 100 readings were taken for the period before the ignition and 100 readings for each the main and the after periods. The corrections for nitric acid formation were based on  $-59.7 \text{ kJ} \cdot \text{mol}^{-1}$  [30] for the molar energy of formation of 0.1 mol·dm<sup>-3</sup>  $\text{HNO}_3(\text{aq})$  from  $\text{N}_2(\text{g})$ ,  $\text{O}_2(\text{g})$ , and  $\text{H}_2\text{O}(\text{l})$ . All the necessary weighings were made in a Mettler AE 240 balance and corrections from apparent mass to true mass were made using density  $1.4858 \text{ g} \cdot \text{dm}^{-3}$  [31]. An estimated pressure coefficient of specific energy,  $(\partial u / \partial p)_T = -0.2 \text{ J} \cdot \text{g}^{-1} \cdot \text{MPa}^{-1}$  at  $T = 298.15 \text{ K}$ , a typical value

for most organic compounds [32], was assumed. For each compound, the massic energy of combustion,  $\Delta_c u^\circ$ , was calculated by the procedure given by Hubbard et al. [33].

At the end of each combustion experiment, the amount of compound burnt in that experiment was determined from the total mass of  $\text{CO}_2$  produced taking into account that formed from the cotton-thread fuse and from *n*-hexadecane. The amount of  $\text{HNO}_3$  formed was determined by titration of the aqueous solution resulting from washing the inside of the bomb.

The molecular mass of the compound was calculated by the conventional procedure using the averaged atomic masses of elements derived from data recommended by the IUPAC Commission in 2013 [34].

### 2.3. High temperature Calvet microcalorimetry

The standard molar enthalpy of sublimation of 4-nitroimidazole was measured in a high temperature Calvet microcalorimeter (Setaram, model HT 1000), using the technique described by Skinner et al. [35]. The details of the apparatus and the technique have been previously described [36].

For each one of the sublimation experiments, the samples of about 4–6 mg of the compound were introduced in thin glass capillary tubes sealed at one end. The two thin glass capillary tubes, one containing the crystalline sample and the other being the reference tube were simultaneously dropped into the hot reaction vessel, held at a suitable predefined temperature,  $T$ , and then removed from the hot zone by vacuum sublimation. The thermal corrections for the glass capillary tubes were determined in separate experiments, and were minimized by dropping tubes of nearly equal mass, to within  $\pm 10 \mu\text{g}$ , into each of the twin calorimetric cells [36].

The microcalorimeter was calibrated *in situ* at the experimental temperature  $T = 487.6 \text{ K}$ , performing sublimation experiments with anthracene, in the same experimental conditions, using the reported standard molar enthalpy of sublimation  $(101.9 \pm 1.3) \text{ kJ} \cdot \text{mol}^{-1}$  [37]. The calibration constant determined for 4-nitroimidazole sublimation study was  $k_{\text{cal}}(487.6 \text{ K}) = (1.0486 \pm 0.0105)$ , obtained as the average of six independent experiments, with the quoted uncertainty being the standard deviation of the mean.

### 2.4. Computational details

In the present work the absolute enthalpies, at  $T = 298.15 \text{ K}$ , of 2-, 4-, 5-nitroimidazole and all the auxiliary species considered were calculated using the composite G3 approach [38]. This protocol involves an initial geometry optimization at the Hartree-Fock (HF) level with the 6-31G(d) basis [39] and the subsequent determination of the harmonic frequencies, which are then scaled by a factor of 0.8929 to take account of known deficiencies at this level [40]. These frequencies are used to evaluate the zero-point energy (E(ZPE)) and thermal effects. The equilibrium geometry is further refined at the MP2(full)/6-31G(d) level, using all electrons for the calculation of correlation energy. Finally, a series of single point energy calculations, including MP4 and QCISD(T) (quadratic configuration interaction including single and double excitations with triple excitations being taken into account perturbatively) using the 6-31G(d) basis set, is then performed and the results properly

**Table 1**  
Purification details of the 4-nitroimidazole.

Chemical name	CAS	Provenance	Initial mass fraction purity <sup>a</sup>	Purification method	Final mass fraction purity	Analysis method
4-Nitroimidazole	3034-38-6	TCI	1.000	Sublimation	0.9997	$\text{CO}_2$ recovery

<sup>a</sup> Commercial information.

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