



Experimental and computational study of the energetics of 5- and 6-aminoindazole

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ABSTRACT

This work aims to study the influence of the amino group in positions 5 and 6 of the benzene ring of indazole. For that purpose, the standard ($p^\circ = 0.1$ MPa) molar enthalpies of formation of 5- and 6-aminoindazole, in the gaseous phase, at $T = 298.15$ K were determined. These values were calculated from the standard massic energies of combustion, measured by combustion calorimetry, and from the standard molar enthalpies of sublimation, computed from the variation with the temperature of the vapour pressures of each compound, measured by the Knudsen effusion technique.

Compound	$\Delta_c u^\circ / (\text{J} \cdot \text{g}^{-1})$	$\Delta_{\text{cr}}^\circ H_m^\circ / (\text{kJ} \cdot \text{mol}^{-1})$	$\Delta_f H_m^\circ (\text{g}) / (\text{kJ} \cdot \text{mol}^{-1})$
5-Aminoindazole (cr)	-29299.4 ± 3.7	118.34 ± 0.69	265.1 ± 1.8
6-Aminoindazole (cr)	-29255.9 ± 3.9	121.95 ± 0.63	263.0 ± 1.7

The final results for the enthalpies of formation in the gaseous phase are discussed in terms of structural contributions of the amino group.

The theoretically estimated gas-phase enthalpies of formation were calculated from high-level *ab initio* molecular orbital calculations at the G3(MP2)//B3LYP level of theory. The computed values compare very well with the experimental results obtained in this work and show that the 6-aminoindazole is the most stable isomer from the thermodynamic point of view. Furthermore, this composite approach was also used to obtain information about the gas-phase acidities, gas-phase basicities, proton and electron affinities, adiabatic ionization enthalpies and, finally, N–H bond dissociation enthalpies.

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1. Introduction

The interest in indazoles is associated with the crucial importance of this class of compounds. Although indazoles are rare in nature [1], they play an important role in biological and pharmaceutical areas. Due to the relevance of these compounds, the determination of physical and chemical properties of indazole derivatives has been the object of many studies in order to contribute for the elucidation of reaction mechanisms, for example in the development of new pharmaceuticals [2]. Numerous studies are published regarding the properties of the aminoindazoles. For example, 3-aminoindazole derivatives are reported as having anti-inflammatory, analgesic, and antipyretic properties [3]. Studies with 5-aminoindazole prove that it is potentially active in reproductive systems, having antispermatic and antifertility properties [4]. The compound 6-aminoindazole reduces the gastric acid secretion in rats [5].

The study of the influence of different groups in the benzene ring of the indazole molecule has recently been started in our Research

Group. The results for 5- and 6-nitroindazole were already published and it was concluded that the introduction of the nitro group has a stabilization effect in the indazole molecule and that this effect is similar, whether the nitro group is in position 5 or 6 [6].

In the present work, we intend to study the influence of the amino groups in the indazole molecule. Combustion experiments with a static bomb calorimeter were carried out with 5-aminoindazole and 6-aminoindazole to determine the respective standard massic energies of combustion and, consequently, the standard molar enthalpies of formation in the solid phase. The vapour pressures on the temperature ranges of (358 to 380) K for 5-aminoindazole and, (366 to 388) K for 6-aminoindazole, were measured by the Knudsen effusion technique. From the vapour pressures, the respective standard molar enthalpies of sublimation were computed applying the Clausius–Clapeyron equation. The results obtained by these two techniques enabled us to calculate the standard molar enthalpies of formation, at $T = 298.15$ K, in the gaseous phase.

Additionally, the gas-phase standard molar enthalpies of formation of these compounds were estimated computationally as well as the gas-phase acidities, gas-phase basicities, proton and electron affinities, adiabatic ionization enthalpies, and N–H bond dissociation enthalpies.

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2. Experimental

2.1. Compounds and purity control

In this work, the compounds 5-aminoindazole [CAS 19335-11-6] and 6-aminoindazole [CAS 6967-12-0] whose structural formulae are depicted in figure 1 were supplied by Aldrich Chemical Co., with initial mass fraction purity of 0.97 and 0.98, respectively. Both compounds were purified by sublimation.

The purity of the compounds was determined recovering the carbon dioxide produced in the combustion experiments and it was confirmed by glc. The average ratios of the mass of carbon dioxide recovered after combustion experiments to that calculated from the mass of sample were: 5-aminoindazole (99.945 ± 0.022) and 6-aminoindazole (100.016 ± 0.021), where the uncertainties are the standard deviations of the means. The densities of each compound were estimated from the mass and the dimensions of pellets made in vacuum, with an applied pressure of $10^5 \text{ kg} \cdot \text{cm}^{-2}$, as $(1.40 \text{ and } 1.45) \text{ g} \cdot \text{cm}^{-3}$ for 5-aminoindazole and 6-aminoindazole, respectively. The relative atomic masses used were those recommended by the IUPAC Commission in 2005 [7].

2.2. Combustion calorimetry

The standard massic energies of combustion of 5- and 6-aminoindazole were determined by static bomb calorimetry, using an isoperibol system with a twin valve combustion bomb, model 1105 (Parr Instrument, Illinois, USA), with an internal volume of 0.340 cm^3 . The bomb calorimeter, subsidiary apparatus, and working technique have been described previously in the literature [8,9].

The energy equivalent of the calorimeter was determined by combustion of Thermochemical Standard benzoic acid, sample NBS 39j, with $\Delta_c u = -(26434 \pm 3) \text{ J} \cdot \text{g}^{-1}$ [10] under bomb conditions, adopting the same procedure described by Coops *et al.* [11]. For 5-aminoindazole, the energy equivalent of the calorimeter used was found to be $\varepsilon_{\text{cal}} = (15906.6 \pm 1.9) \text{ J} \cdot \text{K}^{-1}$ and for 6-aminoindazole, $\varepsilon_{\text{cal}} = (15917.4 \pm 1.4) \text{ J} \cdot \text{K}^{-1}$, since the calorimeter undergone some small changes. The results from the calibration were corrected to give the energy equivalents, $\varepsilon_{\text{corr}}$, 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.

Both compounds were burnt in pellet form; however, it was necessary to use paraffin oil (Aldrich Gold Label, mass fraction >0.999) as combustion auxiliary with 6-aminoindazole, since during the preliminary combustion experiments of this compound, a significant amount of carbon soot was found. The standard massic energy of combustion of this oil was measured in our laboratory resulting the value of $\Delta_c u^\circ = -(47193.3 \pm 3.3) \text{ J} \cdot \text{g}^{-1}$. For all experiments, the calorimeter temperatures were measured to $\pm(1 \cdot 10^{-4}) \text{ K}$, at time intervals of 10 s , with a quartz crystal thermometer (Hewlett Packard HP 2804A), interfaced to a PC. The igni-

tion of the samples was made at $T = (298.150 \pm 0.001) \text{ K}$ by the discharge of a $1400 \mu\text{F}$ capacitor through the platinum ignition wire. At least 100 readings were taken for the initial and for the main periods and 200 readings for the after period.

For the cotton-thread fuse, with empirical formula $\text{CH}_{1.686}\text{O}_{0.843}$, the massic energy of combustion was assigned to $-\Delta_c u^\circ = 16250 \text{ J} \cdot \text{g}^{-1}$ [11], a value that was previously confirmed in our laboratory.

The amount of substance used in each experiment, on which the energy of combustion was 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 paraffin oil, in the experiments with 6-aminoindazole.

The amount of HNO_3 produced during the experiment was quantified by titration of the aqueous solution resulting from the washing inside of the bomb. Corrections for carbon soot formation were based on the standard massic energy of combustion of carbon, $\Delta_c u^\circ = -33 \text{ kJ} \cdot \text{g}^{-1}$ [11].

2.3. Knudsen effusion technique

For the crystalline 5-aminoindazole and 6-aminoindazole, the vapour pressures were measured using a Knudsen mass-loss effusion apparatus, enabling the simultaneous operation of nine effusion cells at three different temperatures. The experimental temperatures were chosen in order to obtain pressures between $(0.1 \text{ and } 1.0) \text{ Pa}$. The temperature ranges used in the experiments with 5-aminoindazole was $(358 \text{ to } 380) \text{ K}$ and for 6-aminoindazole $(366 \text{ to } 388) \text{ K}$. The detailed description of the apparatus, procedure, and the technique was previously done [12].

In each effusion experiment, the loss of the mass of the sample, Δm , during the effusion period t , is determined by weighing the effusion cells before and after the effusion time, in a system evacuated to a pressure near $1 \cdot 10^{-4} \text{ Pa}$. At the temperature T of the experiment, the vapour pressure p is calculated by equation (1),

$$p = \left(\frac{\Delta m}{A_0 w_0 t} \right) \sqrt{\frac{2\pi RT}{M}}, \quad (1)$$

where M is the molar mass of the effusing vapour, R is the gas constant, A_0 is the area of the effusion orifice, and w_0 is the respective Clausing factor calculated by equation (2), where l is the thickness of effusion orifice and r its radius:

$$w_0 = \left\{ 1 + \left(\frac{3l}{8r} \right) \right\}^{-1}. \quad (2)$$

The thickness of the effusion holes was 0.0125 mm and their areas and Clausing factors of effusion orifices are present in the supporting information, table S1.

2.4. Computational methods

Standard *ab initio* molecular orbital calculations were performed with the Gaussian 03 series of programs [13]. The G3MP2B3 composite method was used throughout this work [14]. This is a variation of the G3MP2 theory [15] which uses the B3LYP density functional method [16,17] for geometries and zero-point energies. The B3LYP functional uses a combination of the hybrid three-parameter Becke's functional, first proposed by Becke [16], together with the Lee–Yang–Parr non-local correlation functional [18].

The computations carried out with the G3MP2B3 composite approach use the B3LYP method and the 6-31G(d) basis set for both the optimization of geometry and calculation of frequencies. Introduction of high-order corrections to the B3LYP/6-31G(d) enthalpy is done in a manner that follows the Gaussian-3 philosophy, albeit

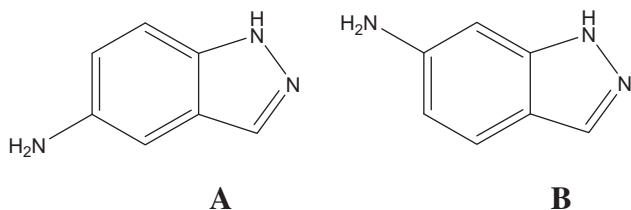


FIGURE 1. Structural formula of 5-aminoindazole (A) and 6-aminoindazole (B).

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