

# Experimental and computational study on the thermochemistry of ethylpiperidines

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## Abstract

The standard ( $p^\circ = 0.1$  MPa) massic energies of combustion in oxygen of 1-ethylpiperidine and 2-ethylpiperidine, both in the liquid phase, were measured at  $T = 298.15$  K by static bomb calorimetry. These values were used to derive the standard molar enthalpies of combustion and the standard molar enthalpies of formation, in the condensed phase, for these compounds. Further, the standard molar enthalpies of vaporization, at  $T = 298.15$  K, of these two ethylpiperidine isomers were determined by Calvet microcalorimetry. The combustion calorimetry results together with those from the Calvet microcalorimetry, were used to derive the standard molar enthalpies of formation, at  $T = 298.15$  K, in the gaseous phase.

	$-\Delta_c H_m^\circ(l)/(\text{kJ} \cdot \text{mol}^{-1})$	$\Delta_l^\circ H_m^\circ/(\text{kJ} \cdot \text{mol}^{-1})$
1-Ethylpiperidine	$4776.8 \pm 1.6$	$39.44 \pm 0.65$
2-Ethylpiperidine	$4740.3 \pm 1.5$	$48.22 \pm 0.89$

In parallel, theoretical calculations have been carried out for all the ethylpiperidine isomers, enabling the estimation of gas-phase enthalpies of formation for these compounds. The comparison with the present experimental data is very good and, thus, supports the quality of the results calculated for the 3-ethyl and 4-ethylpiperidines.

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**Keywords:** Combustion calorimetry; Calvet microcalorimetry; Enthalpy of combustion; Enthalpy of sublimation; Enthalpy of formation; 1-Ethylpiperidine; 2-Ethylpiperidine; 3-Ethylpiperidine; 4-Ethylpiperidine

## 1. Introduction

The piperidine motif appears in many important natural and synthetic products with interesting therapeutical applications. Among other significant applications, piperidine derivatives are used as analgesics [1] and anti-bactericides [2] or used to treat schizophrenia, Parkinson and Alzheimer diseases [3–5]. Metal complexes with ligands containing the six-membered saturated heterocyclic ring were also found to have important catalytic or pharmacological applications [6–8] and, therefore, it is not surprising that strong

efforts are being devoted to the synthesis of new organometallic compounds containing at least a piperidine ring [9,10].

Despite the possibility of diverse interesting applications of compounds containing the piperidine ring, only a few works appear in the literature on the subject of the understanding the energetics of these molecules. Important works are those due to Good concerning the thermochemistry of piperidine and 2-methylpiperidine [11], those due to Verevkin about the thermochemistry of *N*-*R*-piperidines (*R* = methyl, ethyl, propyl, butyl, cyclopentyl, cyclohexyl and phenyl) [12,13] and 2,2,6,6-tetramethylpiperidine [14]. Procházka *et al.* have studied some of the latter compounds and a few others, namely, 1-propylpiperidine, 1-(1-propenyl)

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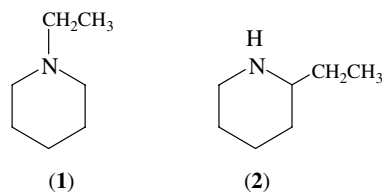


FIGURE 1. Structural formula of 1-ethylpiperidine (1) and 2-ethylpiperidine (2).

nyl)- and 1-(2-propenyl)-piperidines, 1-butylpiperidine, 1-(1-butenyl)- and 1-(2-butenyl)-piperidine, 1-cyclopentylpiperidine, 1-(1-cyclopentene-1-yl)-piperidine, 1-cyclohexylpiperidine and 1-(1-cyclohexene-1-yl)-piperidine but only in the condensed phase [15]. Further, Bedford *et al.* studied the thermochemistry of piperidine [16], Pilcher and co-workers that of 2,2,6,6-tetramethylpiperidine [17] and Matyushi *et al.* that of 1-nitropiperidine [18]. From all these works, only a set of experimental data are available in the literature concerning the ethylpiperidine derivatives. Verevkin has reported the standard molar enthalpy of formation of the 1-ethyl isomer in the condensed phase,  $\Delta_f H_m^\circ(1) = -(128.9 \pm 1.2) \text{ kJ} \cdot \text{mol}^{-1}$ , and in the gas-phase,  $\Delta_f H_m^\circ(g) = -(88.1 \pm 1.3) \text{ kJ} \cdot \text{mol}^{-1}$  [12]. In the literature, only a single computational work was found on the thermochemistry of piperidine compounds [19]. These authors have compared the accuracy of several different computational approaches on the determination of gas-phase enthalpies of formation and proton affinity of the piperidine molecule [19].

In the present work, the standard ( $p^\circ = 0.1 \text{ MPa}$ ) molar enthalpies of formation in the liquid state, at  $T = 298.15 \text{ K}$ , of 1-ethylpiperidine [CAS 766-80-6] and 2-ethylpiperidine [CAS 1484-80-6], represented in figure 1, were determined from the values of the standard molar energies of combustion. The standard molar enthalpies of vaporization, at  $T = 298.15 \text{ K}$ , were measured by Calvet microcalorimetry. From these two sets of results, the standard molar enthalpies of formation in the gaseous state, at the temperature 298.15 K, were derived.

The gas-phase values were compared with the values calculated using the group additivity scheme of Benson [20] and with results derived from G3MP2B3 calculations.

## 2. Experimental

### 2.1. Compounds and purity control

The 1-ethylpiperidine and 2-ethylpiperidine were obtained commercially from Aldrich Chemical Co. The liquid compounds were purified by repeated distillation at atmospheric pressure and stored under nitrogen atmosphere, until the recoveries of the carbon dioxide resulted from combustions were satisfactory. The 1-ethylpiperidine is a hygroscopic compound, absorbing a small amount of water when it was handled during the experiments, as shown by the  $\text{CO}_2$  recovers from combustion and con-

firmed by Karl Fischer titration. The average ratios of the mass of carbon dioxide recovered from combustion to that calculated from the mass of sample were: for 1-ethylpiperidine ( $0.99811 \pm 0.00035$ ), for 2-ethylpiperidine ( $1.00017 \pm 0.00036$ ), where the uncertainties are twice the standard deviation of the mean. The absence of other impurities than water was checked by g.l.c.

### 2.2. Combustion calorimetry

The bomb calorimeter, subsidiary apparatus and technique have been described previously in the literature [21,22].

The energy equivalent of the calorimeter was determined by combustion of Thermochemical Standard benzoic acid. For 1-ethylpiperidine, the energy equivalent of the calorimeter was derived as  $\varepsilon_{\text{cal}} = (15905.72 \pm 0.96) \text{ J} \cdot \text{K}^{-1}$ , as the average of six combustion experiments with benzoic acid, sample NBS 39j, with  $\Delta_c u = -(26,434 \pm 3) \text{ J} \cdot \text{g}^{-1}$  [23]. For 2-ethylpiperidine, the energy equivalent of the calorimeter was determined as  $\varepsilon_{\text{cal}} = (15908.78 \pm 0.77) \text{ J} \cdot \text{K}^{-1}$ , from the combustion of six samples of benzoic acid, sample BAS 693976/01, with massic energy of combustion, under bomb conditions, of  $\Delta_c u = -(26435.1 \pm 3.5) \text{ J} \cdot \text{g}^{-1}$  [24]. The calibration procedure was the same as previously described [25], and the results from the calibration were corrected to give the energy equivalents,  $\varepsilon_{\text{cal}}$ , corresponding to 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,  $1.00 \text{ cm}^3$  of water was introduced into the bomb, a twin-valve combustion bomb Type 1105, Parr Instrument Company, made of Carpenter 20Cb3 stainless steel, with an internal volume of  $0.340 \text{ cm}^3$ . The bomb was purged twice to remove air, before being charged with 3.04 MPa of oxygen.

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 ignition of the samples was made at  $T = (298.150 \pm 0.001) \text{ K}$ , at least 100 readings, at time intervals of 10 s, after the start of the experiment, by the discharge of a  $1400 \mu\text{F}$  capacitor through the platinum ignition wire. After ignition, 100 readings were taken for the main and after periods.

The liquid samples were contained in sealed polyester bags made of Melinex<sup>®</sup> (0.025 mm of thickness) with massic energy of combustion  $\Delta_c u^\circ = -(22902 \pm 5) \text{ J} \cdot \text{g}^{-1}$  [26]. The mass of Melinex<sup>®</sup> 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 [26]. For the cotton thread fuse, with empirical formula  $\text{CH}_{1.686}\text{O}_{0.843}$ , the massic energy of combustion was assigned to  $-\Delta_c u^\circ = 16250 \text{ J} \cdot \text{g}^{-1}$  [25]. The massic energies of combustion of Melinex<sup>®</sup> and of the cotton thread fuse have been confirmed in our laboratory.

The corrections for nitric acid formation were based on  $-59.7 \text{ kJ} \cdot \text{mol}^{-1}$ , for the molar energy of formation of  $0.1 \text{ mol} \cdot \text{dm}^{-3} \text{ HNO}_3(\text{aq})$ , from  $\text{N}_2(\text{g})$ ,  $\text{O}_2(\text{g})$ , and  $\text{H}_2\text{O}(\text{l})$  [27]. In the experiments with carbon residue soot formation during the combustion, the necessary energetic correction for its formation was based on  $\Delta_c u^\circ = -33 \text{ kJ} \cdot \text{g}^{-1}$  [28]. This value was confirmed in our laboratory. All the necessary weighing was made in a Mettler Toledo 240 balance, sensitivity  $\pm(1 \cdot 10^{-5}) \text{ g}$ , and corrections from apparent mass to true mass were made. For each compound an estimated pressure coefficient of massic energy,  $(\partial u / \partial p)_T$ , at  $T = 298.15 \text{ K}$ , was assumed to be  $-0.2 \text{ J} \cdot \text{g}^{-1} \cdot \text{MPa}^{-1}$ , a typical value for most organic compounds [29]. For each compound  $\Delta_c u^\circ$  was calculated by the procedure of Hubbard *et al.* [30]. The amount of substance used in each experiment, and on which the energy of combustion was based, was determined from the mass of  $\text{CO}_2$  Mettler Toledo AT 201 balance, sensitivity  $\pm(1 \cdot 10^{-4}) \text{ g}$ , produced during the experiments taking into account that formed from the combustion of the cotton-thread fuse, of the Melinex<sup>®</sup> and that lost due to carbon formation.

The small amount of water present in the compound 1-ethylpiperidine is expected to have a negligible effect on the energy of combustion when based on the  $\text{CO}_2$  formed.

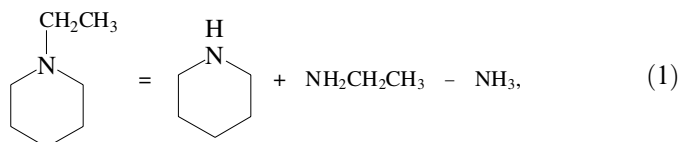
Finally, the relative atomic masses used were those recommended by the IUPAC Commission in 2001 [31] yielding the molar mass of the ethyl piperidine isomers  $113.201 \text{ g} \cdot \text{mol}^{-1}$ .

### 2.3. Microcalorimetry Calvet

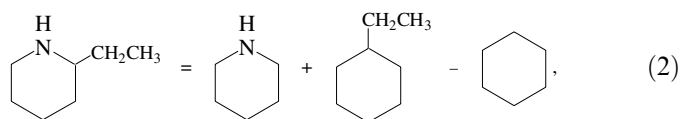
The standard molar enthalpies of vaporization of 1-ethylpiperidine and 2-ethylpiperidine were measured using a method similar to that used for the sublimation of solids, the “vacuum sublimation drop microcalorimetric method”, described by Skinner *et al.* [32]. The apparatus and technique have been recently described [33].

Samples of about 5 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  $T = 334.3 \text{ K}$ , and then removed from the hot zone by vacuum vaporization. The thermal corrections for the glass capillaries were made by dropping tubes of nearly equal mass into each of the twin cells.

The observed standard molar enthalpies of vaporization, at  $T = 334.3 \text{ K}$ , were corrected to  $T = 298.15 \text{ K}$  using  $\Delta_{298.15 \text{ K}}^{334.3 \text{ K}} H_m^\circ(\text{g})$  estimated by a group method based on the values of Messerly *et al.* [34] and Stull *et al.* [35]. The scheme applied for 1-ethylpiperidine was:



while for 2-ethylpiperidine another scheme was used:



yielding the following corrections: for 1-ethylpiperidine,  $\Delta_{298.15 \text{ K}}^{334.1 \text{ K}} H_m^\circ(\text{g})$  is  $5.57 \text{ kJ} \cdot \text{mol}^{-1}$ , while for 2-ethylpiperidine it is  $6.17 \text{ kJ} \cdot \text{mol}^{-1}$ .

The calorimeter was calibrated *in situ* with *n*-undecane, using the same experimental procedure used for the ethylpiperidine compounds, and using the value of  $\Delta_1^g H_m^\circ = (56.58 \pm 0.57) \text{ kJ} \cdot \text{mol}^{-1}$  [36] as the standard molar enthalpy of vaporization for *n*-undecane at  $T = 298.15 \text{ K}$ . The calibration constants of the calorimeter,  $k_{\text{cal}}$ , were obtained as the average of six independent experiments at  $T = 334 \text{ K}$ :  $k_{\text{cal}} = 1.0134 \pm 0.0075$ .

### 2.4. Theoretical calculations

The composite G3MP2B3 method [37] was used to calculate the absolute enthalpies of 1-, 2-, 3-, and 4-ethylpiperidine compounds and of H, C, and N gaseous atoms, at  $T = 298.15 \text{ K}$ . This composite method combines a series of separately performed standard *ab initio* calculations intended to introduce successively corrections to the enthalpy initially calculated using a less expensive computational approach. In a first step, the B3LYP/6-31G(d) approach is used for the full-optimization and the calculation of the frequencies of the atom/molecule. Then, keeping the B3LYP/6-31G(d) geometry frozen, single-point calculations are performed at higher levels of theory (QCISD(T)/6-31G(d) and MP2/GTMP2Large) with the aim of diminishing errors of the initial B3LYP/6-31G(d) energy, correcting correlation and basis set deficiencies. This energy at  $T = 0 \text{ K}$  is corrected for  $T = 298.15 \text{ K}$  by introducing the vibrational, translational, rotational and the  $pV$  terms computed at the B3LYP/6-31G(d) level. The enthalpies of formation for the ethylpiperidines in the gas-phase were estimated by considering their atomization reactions as used with standard Gaussian-N theories. The following atomic experimental gas-phase enthalpies of formation were used: hydrogen,  $218.00 \text{ kJ} \cdot \text{mol}^{-1}$ ; carbon,  $716.67 \text{ kJ} \cdot \text{mol}^{-1}$ ; and nitrogen,  $472.68 \text{ kJ} \cdot \text{mol}^{-1}$  [38]. Further, for comparison purposes, group substitution type working reactions were also used to estimate the enthalpies of formation of all ethylpiperidines. All calculations have been performed with the Gaussian-98 package [39].

## 3. Results and discussion

### 3.1. Condensed phase and phase transition

Table 1 lists detailed results for a typical combustion experiment of each compound, where  $\Delta m(\text{H}_2\text{O})$  is the deviation of the mass of water added to the calorimeter from 3119.6 g,  $\Delta U(\text{IPB})$  is the energy change for the isothermal

TABLE 1  
Results of a typical combustion experiment at  $T = 298.15$  K

Experiment	1-Ethylpiperidine	2-Ethylpiperidine
$m(\text{CO}_2, \text{total})/\text{g}$	1.68927	1.78932
$m(\text{cpd})/\text{g}$	0.57035	0.61657
$m(\text{melinex})/\text{g}$	0.05790	0.04791
$m(\text{fuse})/\text{g}$	0.00278	0.00368
$\Delta T_{\text{ad}}/\text{K}$	1.59810	1.69193
$\varepsilon_{\text{f}}/(\text{J} \cdot \text{K}^{-1})$	17.01	16.99
$\Delta m(\text{H}_2\text{O})/\text{g}$	0	+0.1
$-\Delta U(\text{IBP})^a/\text{J}$	25445.07	26944.83
$\Delta U(\text{melinex})/\text{J}$	1326.14	1097.23
$\Delta U(\text{fuse})/\text{J}$	45.15	59.76
$\Delta U(\text{HNO}_3)/\text{J}$	42.51	42.33
$\Delta U(\text{ign})/\text{J}$	1.01	1.20
$-\Delta U(\text{carbon})/\text{J}$	0	38.61
$\Delta U_{\Sigma}/\text{J}$	8.95	9.51
$-\Delta_c u^\circ/\text{J} \cdot \text{g}^{-1}$	42118.56	41803.22

$m(\text{CO}_2, \text{total})$  is the total mass of carbon dioxide recovered in the combustion;  $m(\text{cpd})$  is the mass of compound burnt in each experiment;  $m(\text{melinex})$  is the mass of Melinex<sup>®</sup> used to enclose the liquid compounds;  $m(\text{fuse})$  is the mass of the cotton thread fuse;  $\Delta T_{\text{ad}}$  is the adiabatic temperature rise;  $\varepsilon_{\text{f}}$  is the energy equivalent of the calorimeter including the contents of the bomb in the final state;  $\Delta m(\text{H}_2\text{O})$  is the deviation of the mass of water added to the calorimeter from 3119.6 g;  $\Delta U(\text{IBP})$  is the energy change for isothermal combustion reaction under actual bomb conditions;  $\Delta U(\text{melinex})$  is the energy of combustion of the Melinex<sup>®</sup> used in each experiment;  $\Delta U(\text{fuse})$  is the energy of combustion of the fuse (cotton);  $\Delta U(\text{HNO}_3)$  is the energy correction for the nitric acid formation;  $\Delta U(\text{ign})$  is the electrical energy supplied for ignition,  $\Delta U(\text{carbon})$  is the energy correction for the carbon residue soot formation;  $\Delta U_{\Sigma}$  is the standard state correction;  $\Delta_c u^\circ$  is the massic energy of combustion of the compound.

<sup>a</sup>  $\Delta U(\text{IBP})$  already includes  $\Delta U(\text{ign})$ .

TABLE 2  
Individual values of the massic energy of combustion,  $\Delta_c u^\circ$ , for the compounds, at  $T = 298.15$  K

1-Ethylpiperidine	2-Ethylpiperidine
$-\Delta_c u^\circ/(\text{J} \cdot \text{g}^{-1})$	
42114.06	41811.57
42126.21	41810.91
42121.63	41792.47
42138.37	41803.22
42135.70	41801.78
42118.56	41814.87
	41796.13
	41794.30
$-\langle \Delta_c u^\circ \rangle/(\text{J} \cdot \text{g}^{-1})$	
42125.8 $\pm$ 4.5	41803.2 $\pm$ 3.0

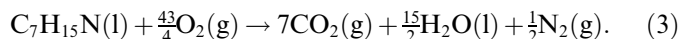
combustion reaction under bomb conditions and  $\Delta U_{\Sigma}$  is the correction to the standard state calculated by the procedure of Hubbard *et al.* [30]; the remaining quantities are as

TABLE 3  
Derived standard ( $p^\circ = 0.1$  MPa) molar energies of combustion,  $\Delta_c U_{\text{m}}^\circ$ , standard molar enthalpies of combustion,  $\Delta_c H_{\text{m}}^\circ$ , and the standard molar enthalpies of formation for the compounds in the liquid phase,  $\Delta_f H_{\text{m}}^\circ(\text{l})$ , at  $T = 298.15$  K

Compound	$\Delta_c U_{\text{m}}^\circ(\text{l})/(\text{kJ} \cdot \text{mol}^{-1})$	$\Delta_c H_{\text{m}}^\circ(\text{l})/(\text{kJ} \cdot \text{mol}^{-1})$	$\Delta_f H_{\text{m}}^\circ(\text{l})/(\text{kJ} \cdot \text{mol}^{-1})$
1-Ethylpiperidine	$-4768.7 \pm 1.6$	$-4776.8 \pm 1.6$	$-121.5 \pm 1.9$
2-Ethylpiperidine	$-4732.2 \pm 1.5$	$-4740.3 \pm 1.5$	$-158.0 \pm 1.7$

previously described [30]. As the samples were ignited at  $T = (298.150 \pm 0.001)$  K, with  $\Delta U(\text{IPB}) = -\{\varepsilon_{\text{cal}} + \Delta m(\text{H}_2\text{O})c_{\text{p}}(\text{H}_2\text{O}, \text{l}) + \varepsilon_{\text{f}}\}\Delta T_{\text{ad}} + \Delta U(\text{ign})$ . The massic energies of combustion,  $\Delta_c u^\circ$ , for all the combustion experiments, together with the mean values and their standard deviation are registered, for each compound, in table 2.

Table 3 lists, for each compound, the derived standard molar values for the energy ( $\Delta_c U_{\text{m}}^\circ$ ) and enthalpy ( $\Delta_c H_{\text{m}}^\circ$ ) of the combustion reactions according to equation (3) and the standard molar enthalpy of formation,  $\Delta_f H_{\text{m}}^\circ$ , in the liquid phase.



The uncertainties assigned to the standard molar enthalpies of combustion, in accordance with the normal thermochemical practice are, in each case, twice the overall standard deviation of the mean and include the uncertainties in calibration [40,41] and in the values of auxiliary quantities. The values of the standard molar enthalpies of formation in the liquid phase,  $\Delta_f H_{\text{m}}^\circ(\text{l})$ , were derived from  $\Delta_c H_{\text{m}}^\circ$ , using the values, at  $T = 298.15$  K, of the standard molar enthalpies of formation of liquid water and gaseous carbon dioxide, respectively, as  $\Delta_f H_{\text{m}}^\circ(\text{H}_2\text{O}, \text{l}) = -(285.830 \pm 0.042)$  kJ  $\cdot$  mol<sup>-1</sup> [28] and  $\Delta_f H_{\text{m}}^\circ(\text{CO}_2, \text{g}) = -(393.51 \pm 0.13)$  kJ  $\cdot$  mol<sup>-1</sup> [28].

Results of the microcalorimetric determination of the enthalpies of vaporization are given in table 4, with uncertainties, as twice the standard deviation of the mean. The values determined show that the intermolecular interactions are weaker for 1-ethylpiperidine isomer.

For 1-ethylpiperidine, the present enthalpy of vaporization,  $(39.44 \pm 0.65)$  kJ  $\cdot$  mol<sup>-1</sup>, is identical to that measured by Verevkin [12] if uncertainty intervals are considered,  $(40.83 \pm 0.89)$  kJ  $\cdot$  mol<sup>-1</sup>, but a significant difference is noticed between the standard molar enthalpy of formation in the liquid-phase reported in this work,  $-(121.5 \pm 1.9)$  kJ  $\cdot$  mol<sup>-1</sup>, and that given in the study of Verevkin,  $-(128.9 \pm 1.2)$  kJ  $\cdot$  mol<sup>-1</sup> [12].

### 3.2. Gas-phase

The results given in the two sub-sections above, regarding the derived standard molar enthalpies of formation in the liquid state (last column of table 3) and the standard molar enthalpies of vaporization (last column of table 4), allowed us to obtain the gaseous state standard molar enthalpies of formation of the two ethylpiperidine isomers studied at  $T = 298.15$  K. The latter results are summarized in table 5. The difference between the two  $\Delta_f H_{\text{m}}^\circ(\text{g})$  values is 27.7 kJ  $\cdot$  mol<sup>-1</sup>, the 1-ethylpiperidine compound being the



TABLE 4

Microcalorimetric standard ( $p^\circ = 0.1\text{ MPa}$ ) molar enthalpies of vaporization, at  $T = 298.15\text{ K}$ 

Compound	Number of experiments	$T/\text{K}$	$\Delta_{\text{f},298.15\text{ K}}^{334.3\text{ K}} H_{\text{m}}^\circ/(\text{kJ} \cdot \text{mol}^{-1})$	$\Delta_{298.15\text{ K}}^{334.3\text{ K}} H_{\text{m}}^\circ(\text{g})/(\text{kJ} \cdot \text{mol}^{-1})$	$\Delta_{\text{f}}^{\text{g}} H_{\text{m}}^\circ(T = 298.15\text{ K})/(\text{kJ} \cdot \text{mol}^{-1})$
1-Ethylpiperidine	5	334.3	$45.01 \pm 0.16$	5.57	$39.44 \pm 0.65$
2-Ethylpiperidine	5	334.3	$54.39 \pm 0.30$	6.17	$48.22 \pm 0.89$

TABLE 5

Experimental gas-phase molar enthalpies of formation,  $\Delta_{\text{f}} H_{\text{m}}^\circ$ , at  $T = 298.15\text{ K}$ , for 1-ethylpiperidine and 2-ethylpiperidine isomers

Compound	$\Delta_{\text{f}} H_{\text{m}}^\circ(\text{g})/(\text{kJ} \cdot \text{mol}^{-1})$		
	Experimental	Benson's Group	G3MP2B3
1-Ethylpiperidine	$-82.1 \pm 2.0$	-81.1	$-79.9^a$ ( $-83.8^b$ )
2-Ethylpiperidine	$-109.8 \pm 1.9$	-105.9	$-101.0^a$ ( $-108.0^c$ )
3-Ethylpiperidine		-99.1	$-94.0^a$ ( $-101.0^c$ )
4-Ethylpiperidine		-99.1	$-94.9^a$ ( $-101.9^c$ )

These values are compared with results estimated by the Benson's Group Method or from composite theoretical calculations.

<sup>a</sup> Values estimated from atomization reaction (4).

<sup>b</sup> Value estimated from working reaction (5).

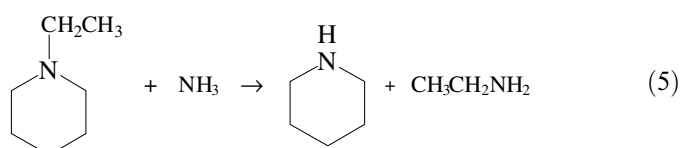
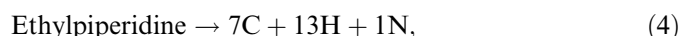
<sup>c</sup> Values estimated from working reaction (6).

less stable as expected due to the presence of the bulky  $-\text{CH}_2\text{CH}_3$  ligand near the nitrogen's lone pair. This destabilizing interaction is weaker or absent in the case of the 2-ethylpiperidine isomer. Due to the difference between ours and Verevkin's value for the standard molar enthalpy of formation in the liquid-phase [12], there is also a significant difference between ours and Verevkin's values in the gas-phase: our value registered in table 5,  $-(82.1 \pm 2.0)\text{ kJ} \cdot \text{mol}^{-1}$ , differs by  $6.0\text{ kJ} \cdot \text{mol}^{-1}$  from that reported in the work of Verevkin,  $-(88.1 \pm 1.3)\text{ kJ} \cdot \text{mol}^{-1}$  [12]. Since this is not a negligible difference, we have tried other strategies to understand which value will be more accurate. These strategies are based on Benson's Group Method or on first-principles calculations and are explained below.

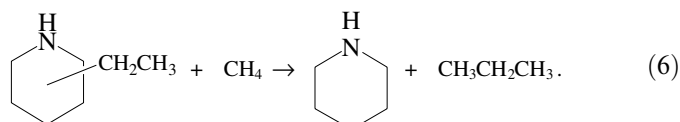
In order to estimate, by the Benson's Group Method [20], the values of  $\Delta_{\text{f}} H_{\text{m}}^\circ(\text{g})$  of the gaseous ethylpiperidine isomers, the following literature [42] group contributions have been used:  $[\text{N}-(\text{C})_3] = 102.09\text{ kJ} \cdot \text{mol}^{-1}$ ;  $[\text{N}-(\text{C})_2(\text{H})] = 64.43\text{ kJ} \cdot \text{mol}^{-1}$ ;  $[\text{C}-(\text{N})(\text{C})_2(\text{H})] = -21.76\text{ kJ} \cdot \text{mol}^{-1}$ ;  $[\text{C}-(\text{N})(\text{C})(\text{H})_2] = -27.61\text{ kJ} \cdot \text{mol}^{-1}$ ;  $[\text{C}-(\text{H})_2(\text{C})_2] = -20.63\text{ kJ} \cdot \text{mol}^{-1}$ ;  $[\text{C}-(\text{H})_3(\text{C})] = -42.68\text{ kJ} \cdot \text{mol}^{-1}$ ; **ring correction for piperidine**  $= 4.18\text{ kJ} \cdot \text{mol}^{-1}$ . The enthalpies of formation estimated by the Benson's Group Method are also reported in table 5. Results obtained with this approximated method are in fair agreement with the experimental values with the largest difference, being only  $3.9\text{ kJ} \cdot \text{mol}^{-1}$ , calculated for the 2-ethylpiperidine isomer.

A second approach was used to estimate the enthalpies of formation of the two ethylpiperidines studied experimentally and further extended to the other ethylpiperidine isomers. For that purpose, the G3MP2B3 approach has been used. Several different initial geometries have been used due to the possibility of inter-conversion between chair and boat conformations. The computed most stable structures found are depicted in figure 2. Then, in order

to convert absolute enthalpies into relative enthalpies, the selected gas-phase reactions shown below have been used. The reactions considered are that of atomization (4) and those considering group substitutions, such as reactions (5) and (6).



and



Combining the enthalpy of reaction (4) for each of the four ethylpiperidines with the gas-phase enthalpies of formation of the component atoms given above, it was possible to estimate the enthalpies of formation of the ethylpiperidines. These results are also reported in table 5. The estimated enthalpy of formation for 1-ethylpiperidine from the atomization reaction is  $-79.9\text{ kJ} \cdot \text{mol}^{-1}$ ,  $2.2\text{ kJ} \cdot \text{mol}^{-1}$  less negative than our experimental result, while a much more significant deviation appears for the 2-ethylpiperidine compound,  $\Delta = 8.8\text{ kJ} \cdot \text{mol}^{-1}$ . When using the group substitution reactions and the experimental gas-phase enthalpies of methane,  $-(74.4 \pm 0.4)\text{ kJ} \cdot \text{mol}^{-1}$  [43], ammonia,  $-(45.94 \pm 0.35)\text{ kJ} \cdot \text{mol}^{-1}$  [28], ethylamine,  $-(47.5 \pm 0.6)\text{ kJ} \cdot \text{mol}^{-1}$  [43], propane,  $-(104.7 \pm 0.5)\text{ kJ} \cdot \text{mol}^{-1}$  [43] and piperidine  $-(47.15 \pm 0.63)\text{ kJ} \cdot \text{mol}^{-1}$  [11], this larger deviation vanishes, meaning that some errors on the correct description of the energetics of these substances are cancelled due to the presence of similar species on both sides of the reactions. The newly calculated enthalpies of formation almost match experimental results, with deviations smaller than the uncertainty intervals associated with the experimental values,  $-1.7\text{ kJ} \cdot \text{mol}^{-1}$  for 1-ethylpiperidine and  $+1.8\text{ kJ} \cdot \text{mol}^{-1}$  for 2-ethylpiperidine. These results strongly support the experimental results here presented and give support to the quality of the calculated values for the other two ethylpiperidine compounds for which experimental determinations were not possible. In principle and taking into account the previous words, the suggested gas-phase enthalpies of formation for 3-ethylpiperidine and 4-ethylpiperidine are those estimated from the group substitution reaction (6), *i.e.*,  $-101.0\text{ kJ} \cdot \text{mol}^{-1}$  and  $-101.9\text{ kJ} \cdot \text{mol}^{-1}$ , respectively.

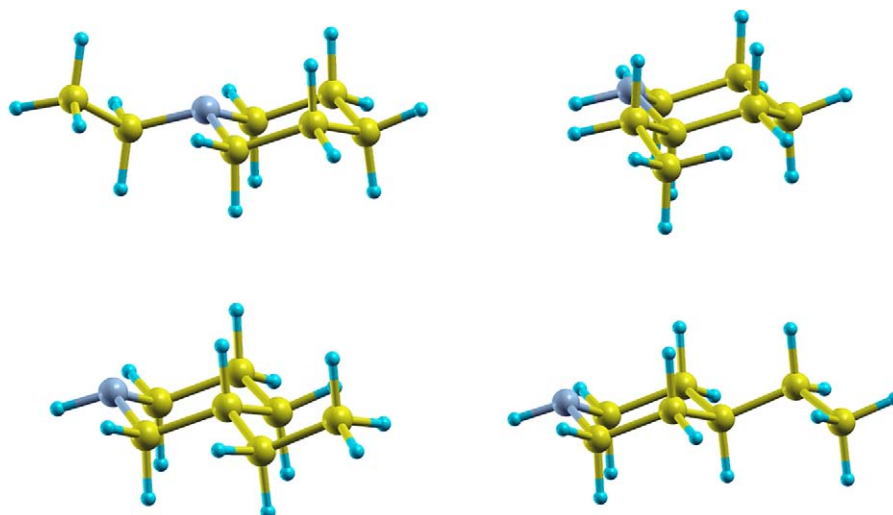


FIGURE 2. B3LYP/6-31G(d) optimized most stable conformations for the ethylpiperidine derivatives.

Finally, the comparison between experimental and calculated values shows that the estimates based on G3M-P2B3 enthalpies, together with working reactions (5) and (6) almost match the experimental results herewith presented. However, it should be pointed out that the Benson's Group Method is capable to predict very good results for this class of compounds and may be a cheap choice to test the quality of experimentally determined enthalpies of formation. Further, the estimates from the atomization reaction scheme are in agreement with experimental values but differences as large as  $\sim 9 \text{ kJ} \cdot \text{mol}^{-1}$  may appear. Therefore, when dealing with other piperidine derivatives, this strategy should be avoided if one can use appropriate group substitution working reactions. Finally, all calculated values are closer to the present experimental enthalpy of formation of the 1-ethylpiperidine than that reported previously by Verevkin [12] supporting the quality of our experimental results.

#### 4. Conclusions

A combined experimental and computational study has been carried out to obtain the standard molar enthalpies of formation, in the gas-phase and at  $T = 298.15 \text{ K}$ , for the four different ethylpiperidine isomers. From the experimental side and for 1-ethylpiperidine and 2-ethylpiperidine compounds, combustion calorimetry and Calvet microcalorimetry experiments have been performed, and the standard molar enthalpies of formation, in the condensed phase, and also the standard molar enthalpies of vaporization, have been derived at  $T = 298.15 \text{ K}$ . Combining these two quantities, the standard molar enthalpies of formation in the gas-phase, at  $T = 298.15 \text{ K}$ , have been obtained. The final values are  $-(82.1 \pm 2.0) \text{ kJ} \cdot \text{mol}^{-1}$  and  $-(102.8 \pm 1.9) \text{ kJ} \cdot \text{mol}^{-1}$  for 1-ethyl and 2-ethylpiperidine, respectively.

Two different approximate approaches have been also used to extract the standard molar enthalpies of formation

in the gas-phase and at  $T = 298.15 \text{ K}$  for the 1-ethyl and 2-ethylpiperidines, namely the Benson's Group Method and the much more sophisticated first-principles approach. It was found that both methods yielded results which are in excellent agreement with experimental data. The G3M-P2B3 calculations have been extended to the other two ethylpiperidine isomers and the following values are suggested as the best estimates for the standard molar enthalpies of formation of gaseous 3-ethylpiperidine,  $-101.0 \text{ kJ} \cdot \text{mol}^{-1}$  and 4-ethylpiperidine,  $-101.9 \text{ kJ} \cdot \text{mol}^{-1}$ .

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#### References

- [1] A. Ranise, S. Schenone, O. Bruno, F. Bondavalli, W. Filippelli, G. Falcone, B. Rivaldi, *Il Farmaco* 56 (2001) 647–657.
- [2] G.G. Baikenova, G.A. Abdulina, A.M. Gazaliev, S.D. Fazylov, S.Z. Kudaibergenova, *Pharmaceut. Chem. J.* 38 (2004) 19–20.
- [3] T. Klockgether, U. Wüllner, J.P. Steinbach, V. Petersen, L. Turski, P.A. Löschmann, *Eur. J. Pharmacol.* 301 (1996) 67–73.
- [4] P.S. Watson, B. Jiang, B. Scott, *Org. Lett.* 21 (2000) 3679–3681.
- [5] M.G. Bursavich, C.W. West, D.H. Rich, *Org. Lett.* 3 (2001) 2317–2320.
- [6] J. Kasparkova, O. Novakova, V. Marini, Y. Najajreh, D. Gibson, J.M. Perez, V. Brabec, *J. Biol. Chem.* 278 (2003) 47516–47525.
- [7] J. Kasparkova, V. Marini, Y. Najajreh, D. Gibson, V. Brabec, *Biochemistry* 42 (2003) 6321–6332.
- [8] Y. Najajreh, D. Prilutski, Y. Ardelli-Tzaraf, J.M. Perez, E. Khazanov, Y. Barenholz, J. Kasparkova, V. Brabec, D. Gibson, *Angew. Chem. Int. Ed.* 44 (2005) 2885–2887.

- [9] H. Kurosaki, H. Koike, S. Omori, Y. Okuno, Y. Ogata, Y. Yamaguchi, *Inorg. Chem. Commun.* 8 (2005) 437–439.
- [10] M.A. El-Sayed, T.S. Kassem, H.A. Abo-Eldahab, A.E. El-Kholy, *Inorg. Chim. Acta* 358 (2005) 22–28.
- [11] W. Good, *J. Chem. Eng. Data* 17 (1972) 28–31.
- [12] S.P. Verevkin, *Struct. Chem.* 9 (1998) 113–119.
- [13] S.P. Verevkin, *J. Chem. Thermodyn.* 34 (2002) 263–275.
- [14] S.P. Verevkin, *J. Chem. Thermodyn.* 29 (1997) 891–899.
- [15] M. Procházka, V. Krestanova, M. Palecek, K. Pecka, *Coll. Czech. Chem. Commun.* 35 (1970) 3813–3817.
- [16] A.F. Bedford, A.E. Beezer, C.T. Mortimer, *J. Chem. Soc.* (1963) 2039–2043.
- [17] S. Suradi, J.M. Hacking, G. Pilcher, I. Gümrük, M.F. Lappert, *J. Chem. Thermodyn.* 13 (1981) 857–861.
- [18] Y.N. Matyushi, I.B. V'yunova, V.I. Pepekin, A.Y. Apin, *Bull. Acad. Sci. URSS, Div. Chem. Sci.* (1971) 2320–2323. Available from: <http://webbook.nist.gov/>.
- [19] E. Vayner, D.W. Ball, *J. Mol. Struct. (Theochem)* 496 (2000) 175–183.
- [20] S.W. Benson, J.H. Buss, *J. Chem. Phys.* 29 (1958) 546–572.
- [21] M.A.V. Ribeiro da Silva, M.D.M.C. Ribeiro da Silva, G. Pilcher, *Rev. Por. Quím.* 26 (1984) 163–172.
- [22] M.A.V. Ribeiro da Silva, M.D.M.C. Ribeiro da Silva, G. Pilcher, *J. Chem. Thermodyn.* 16 (1984) 1149–1155.
- [23] Certificate of Analysis Standard Reference Material 39j Benzoic Acid Calorimetric Standard. NBS, Washington, 1995.
- [24] G. Pilcher, Personal Communication, University of Manchester, 1995.
- [25] J. Copps, R.S. Jessup, K. Van Nes, in: F.D. Rossini (Ed.), *Experimental Thermochemistry*, vol. 1, Interscience, New York, 1956 (Chapter 3).
- [26] H.A. Skinner, A. Snelson, *Trans. Faraday Soc.* 56 (1960) 1776–1783.
- [27] D.D. Wagman, W.H. Evans, V.B. Parker, R.H. Shum, F. Halow, S.M. Bailey, K.L. Churney, R.L. Nuttall, *J. Phys. Chem. Ref. Data* 11 (Suppl. 2) (1982).
- [28] J.D. Cox, D.D. Wagman, V.A. Medvedev, CODATA Key Values for Thermodynamics, Hemisphere, New York, 1989.
- [29] E.N. Washburn, *J. Res. Natl. Bur. Stand. (U.S)* 10 (1933) 525–558.
- [30] W.N. Hubbard, D.W. Scott, G. Waddington, in: F.D. Rossini (Ed.), *Experimental Thermochemistry*, vol. 1, Interscience, New York, 1956 (Chapter 5).
- [31] R.D. Loss, *Pure Appl. Chem.* 35 (2003) 1107–1122.
- [32] F.A. Adedeji, D.L.S. Brown, J.A. Connor, M. Leung, M.I. Paz-Andrade, H.A. Skinner, *J. Organomet. Chem.* 97 (1975) 221–228.
- [33] L.M.N.B.F. Santos, B. Schröder, O.O.P. Fernandes, M.A.V. Ribeiro da Silva, *Thermochim. Acta* 415 (2004) 15–20.
- [34] J.F. Messerly, S.S. Todd, H.L. Fink, W.D. Good, B.E. Gammon, *J. Chem. Thermodyn.* 20 (1988) 209–224.
- [35] R.D. Stull, E.F. Westrum, G.C. Sinke, *The Chemical Thermodynamics of Organic Compounds*, Wiley, New York, 1969.
- [36] R. Sabbah, A. Xu-wu, J.D. Chickos, M.L. Planas Leitão, M.V. Roux, L.A. Torres, *Thermochim. Acta* 331 (1999) 93–204.
- [37] L.A. Curtiss, K. Raghavachari, J.A. Pople, *J. Chem. Phys.* 110 (1999) 7650.
- [38] M.W. Chase Jr., *J. Phys. Chem. Ref. Data Monograph* 9 (1998) 1.
- [39] M.J. Frisch et al., *Gaussian-98, Revision A.9*, Gaussian, Inc., Pittsburgh, PA, 1998.
- [40] F.D. Rossini, in: F.D. Rossini (Ed.), *Experimental Thermochemistry*, vol. 1, Interscience, New York, 1956 (Chapter 14).
- [41] G. Olofsson, in: S. Sunner, M. Månsson (Eds.), *Combustion Calorimetry*, Pergamon Press, Oxford, 1979 (Chapter 6).
- [42] S.W. Benson, *Thermochemical Kinetics*, second ed., Wiley, New York, 1976.
- [43] B. Pedley, *Thermochemical Data and Structures of Organic Compounds*, vol. 1, TRC Data Series, College Station, TX, 1994.

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