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Experimental Study on the Thermochemistry of Some Derivatives of Piperidinol

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Standard ($p° = 0.1$ MPa) massic energies of combustion for 1-methyl-3-piperidinol, 1-ethyl-3-piperidinol, and 1-methyl-4-piperidinol were measured at $T = 298.15$ K by static bomb calorimetry. The standard molar enthalpies of formation of the condensed phase were derived. The standard molar enthalpies of vaporization at $T = 298.15$ K of the three piperidinol derivatives studied were determined by high-temperature Calvet microcalorimetry. The respective standard molar enthalpies of formation in the gaseous phase at $T = 298.15$ K were derived.

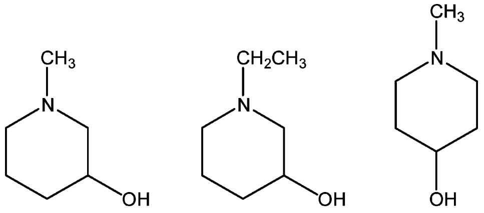
Introduction

Piperidines are nonaromatic nitrogen heterocycles that, due to their applications, have attracted the attention of many fields of research. In fact, the piperidine derivatives are largely present in natural products.[1,2] In recent years, due to their biological and potential therapeutics, much attention has been paid toward the developments of an efficient synthesis[3,4] and to the employment of these compounds in drug-like molecules with medicinal uses.[5−8]

The scientific literature already presents some thermochemical studies of some piperidine derivatives. For instance, the standard molar enthalpy of formation of piperidine itself in the gaseous phase was determined for the first time by Bedford et al.[9] with its value of $-(48.83 \pm 2.55)$ kJ·mol^{-1} and later re-determined by Good[10] as $-(47.15 \pm 0.63)$ kJ·mol^{-1}. In the later work, Good presents also the standard molar enthalpy of formation of 2-methylpiperidine, $\Delta_f H_m^\circ(g) = -(84.5 \pm 1.1)$ kJ·mol^{-1}. Procházka et al.[11] had measured by combustion calorimetry a series of N-substituted piperidines. Verevkin published several thermochemical studies where piperidine compounds are present. For example, the effect of different substituents (methyl, ethyl, propyl, etc. attached to the nitrogen atom of piperidine[12]) has been analyzed by the values of their enthalpies of formation using the results for the condensed phase previously reported by Procházka et al.[11] Verevkin determined also the standard molar enthalpies of formation in the gaseous phase of bispiperidinemethane[13] and 2,2,6,6-tetramethylpiperidine[14] using, for this later compound, the standard molar enthalpy of formation of the liquid, $\Delta_f H_m^\circ(l) = -(206.9 \pm 2.0)$ kJ·mol^{-1} given by Suradi et al.[15]

As the knowledge of the thermochemical properties was only available for a restricted number of piperidine compounds and considering the biological importance of these compounds together with our interest on the thermochemistry of heterocycles, we have carried out a series of works concerning the study of the thermochemical properties of piperidine derivatives.[16−18]

Among piperidine derivatives for which the thermochemical information has been unavailable are the derivatives of piperidinol, which can be found in a great number of natural products and belong to a kind of compounds widely applied. For example, they have been investigated as potential biologically active agents, such as a novel class of dopamine transporters (DAT) inhibitors,[19,20] cytotoxic agent compounds,[21] and analgesics.[22]



(1) **(2)** **(3)**

Figure 1. Structural formula of 1-methyl-3-piperidinol (**1**), 1-ethyl-3-piperidinol (**2**), and 1-methyl-4-piperidinol (**3**).

In this work, the standard molar enthalpies of formation in the liquid and gaseous phases at $T = 298.15$ K and the standard molar enthalpies of vaporization of the liquids 1-methyl-3-piperidinol, 1-ethyl-3-piperidinol, and 1-methyl-4-piperidinol are reported.

Experimental Section

Materials. All the compounds, namely, 1-methyl-3-piperidinol (CAS Registry No. 3554-74-3), 1-ethyl-3-piperidinol (CAS Registry No. 13444-24-1), and 1-methyl-4-piperidinol (CAS Registry No. 106-52-5), whose structural forms are shown in Figure 1, obtained commercially from Aldrich Chemical Co., were purified by successive fractional distillation under reduced pressure until the carbon dioxide recovery ratios were satisfactory. Since carbon dioxide determination is an excellent indication of the purity and dryness of the materials, if water or other contaminator is present in the sample, then the CO_2 recovery ratios will be lower than the predicted values. The purity criteria considered was the ratio of CO_2 higher than 0.999. In the case of 1-methyl-3-piperidinol, the lower values for the CO_2 recoveries indicated a possible presence of water, as confirmed by Karl Fischer titration. The small amount of water present in this compound is expected to have an insignificant effect on the value of the energy of combustion when the amount of compound really used in each combustion experiment is calculated from the mass of CO_2 produced in the particular combustion experiment.

The absence of other impurities, like isomeric impurities that would not be shown by the CO_2 analysis, was checked by GLC.

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Table 1. Physical Properties of the Compounds

compound	formula	M $g \cdot mol^{-1}$	% CO_2 recovery[a]	ρ^b $kg \cdot m^{-3}$
1-methyl-3-piperidinol	$C_6H_{13}NO$	115.174	99.642 ± 0.029	0.999
1-ethyl-3-piperidinol	$C_7H_{15}NO$	129.200	99.943 ± 0.007	0.98
1-methyl-4-piperidinol	$C_6H_{13}NO$	115.174	100.079 ± 0.007	0.97

[a] Mean and standard deviation of the mean. [b] www.sigmaaldrich.com.

After purification, all the liquid samples were stored and handled under nitrogen atmosphere. Table 1 registers the values of the CO_2 recovery ratios of the combustion experiments together with the standard deviations of the mean.

Combustion Measurements. The apparatus and procedures used to determine the standard ($p° = 0.1$ MPa) massic energies of combustion by static bomb calorimetry have been previously described.[23,24] The calorimeter and bomb used in the experiments were calibrated with NBS Thermochemical Standard benzoic acid. The certified value of National Bureau of Standards for the benzoic acid used, sample 39j, was $\Delta_c u = -(26434 \pm 3)$ $J \cdot g^{-1}$ for the combustion under bomb conditions.[25] The energy equivalent (ϵ_{cal}) of the calorimeter and bomb was determined as $\epsilon_{cal} = (15905.72 \pm 0.96)$ $J \cdot K^{-1}$ from six independent experiments using the same procedure as described previously.[26] The energy equivalent was corrected to the average mass of water added to the calorimeter (3119.6 g), and the uncertainty associated to ϵ_{cal} is the standard deviation of the mean.

Combustion experiments were made in oxygen at $p = 3.04$ MPa with 1.00 cm^3 of water added to the bomb, a twin-valve combustion bomb, type 1105 (Parr Instruments Company), made of stainless steel with an internal volume of 0.340 cm^3.

The samples were burnt sealed in polyester bags, made by Melinex film with 0.025 mm thickness. The mass of Melinex used in each experiment was corrected for the mass fraction of water (0.0032), and the mass of CO_2 produced was calculated using the factor reported in the literature.[27] The ignition was made at $T = (298.150 \pm 0.001)$ K by discharge of a 1400 μF capacitor through the platinum ignition wire. A cotton thread of empirical formula $CH_{1.686}O_{0.843}$ was used as the fuse.[26] All temperature readings were made with a quartz crystal thermometer (Hewlett-Packard HP 2804 A) interfaced to a PC. At least 100 readings at time intervals of 10 s were taken for the initial, main, and final periods of the combustion experiments.

At the end of the experiment, the CO_2 produced in combustion was recovered in order to determine the amount of compound used in each experiment. In all experiments, no carbon residue resulting from incomplete combustions was observed.

Calvet Microcalorimetric Measurements. The standard molar enthalpies of vaporization were measured using the same method described by Skinner and co-workers[28] for sublimation of solids, the “vacuum sublimation drop microcalorimetric method”, and tested for liquid vaporization in our laboratory.[29] Apparatus and technique have been already described in the literature.[30] Samples of about 4−5 mg of each compound, contained in thin glass capillary tubes sealed at one end, were dropped from room temperature into the hot reaction vessel in the Calvet high-temperature microcalorimeter (Setaram HT 100D) held at a predefined temperature (T) and then removed from the hot zone by vacuum vaporization. For 1-methyl-3-piperidinol and 1-methyl-4-piperidinol, the calorimeter was held at $T = 358$ K; for 1-ethyl-3-piperidinol, the calorimeter was held at $T = 339$ K. The thermal correction for the glass capillary was made by dropping tubes of nearly equal masses into each of the twin cells.

For each temperature, *n*-undecane was used to calibrate, in situ, the calorimeter using its reported standard molar enthalpy of vaporization at $T = 298.15$ K, $\Delta_l^g H_m^\circ = (56.580 \pm 0.566)$ $kJ \cdot mol^{-1}$.[31] The calibration procedure was the same as for the samples. The calibration constant of the calorimeter (k_{cal}) was obtained as the average of six independent experiments: at $T = 358$ K, $k_{cal} = (1.0167 \pm 0.0021)$; at $T = 339$ K, $k_{cal} = (0.9794 \pm 0.0020)$.

Calorimetric Calculations and Results

Typical combustion experiments for each of the three compounds are summarized in Table 2. The mass of compound, m(cpd), used in each experiment was determined from the total mass of CO_2 produced in each combustion, $m(CO_2$, total), taking into account the amount of CO_2 produced by the combustion of the fuse and the of Melinex film.

The internal energy for the isothermal bomb process, ΔU(IPB), was calculated according to $\Delta U(\text{IPB}) = -\{\epsilon_{cal} + \Delta m(H_2O)c_p(H_2O, l) + \epsilon_f\}\Delta T_{ad}$, where $\Delta m(H_2O)$ is the deviation of the mass of water added to the calorimeter from the average mass (3119.6 g) assigned to ϵ_{cal}; $c_p(H_2O, l)$ is the heat capacity of liquid water; ϵ_f is the energy of bomb contents after ignition; and ΔT_{ad} is the adiabatic temperature change corrected for the heat exchange and the work of stirring. The energies of combustion of the Melinex and of the cotton-thread fuse were calculated from the respective massic energies of combustion: $\Delta_c u^0(\text{Melinex}) = -(22902 \pm 5)$ $J \cdot g^{-1}$ [27] and $\Delta_c u^0(\text{fuse}) = -16250$ $J \cdot g^{-1}$.[26] The correction for nitric acid formation, $\Delta U(HNO_3)$, was based on − 59.7 $kJ \cdot mol^{-1}$,[32] for the molar energy of formation of 0.1 $kJ \cdot mol^{-1}$ HNO_3(aq) from N_2(g), O_2(g), and H_2O(l).

The electrical energy for ignition, ΔU(ign), was determined from the change in potential difference across a capacitor when discharged through the platinum wire. For all compounds, the corrections to standard state (ΔU_Σ) and the calculation of $\Delta_c u^0$ were made as described by Hubbard et al.[33] For each compound,

Table 2. Typical Combustion Experiments, at $T = 298.15$ K, for Each of the Compounds

experiment	1-methyl-3-piperidinol	1-ethyl-3-piperidinol	1-methyl-4-piperidinol
$m(CO_2$, total)/g	1.78718	1.50255	1.77381
m(cpd)/g	0.73835	0.58377	0.71889
m(Melinex)/g	0.03932	0.04628	0.05313
m(fuse)/g	0.00268	0.00284	0.00245
ΔT_{ad}/K	1.64368	1.36912	1.61774
$\epsilon_f/(J \cdot K^{-1})$	17.26	16.55	17.23
$\Delta m(H_2O)$/g	+ 0.1	0	0
$-\Delta U$(IBP)/J	26172.94	21799.47	25759.32
ΔU(Melinex)/J	900.54	1060.00	1216.71
ΔU(fuse)/J	43.52	46.12	39.79
$\Delta U(HNO_3)$/J	52.00	37.85	44.94
ΔU (ign)/J	1.07	0.87	1.12
$-\Delta U$(carbon)/J	0	0	0
ΔU_Σ/J	10.87	8.65	10.55
$-\Delta_c u°/J \cdot g^{-1}$	34082.67	35366.63	34005.49

Table 3. Individual Values of the Massic Energy of Combustion, $\Delta_c u^\circ$, for the Compounds, at $T = 298.15$ K

1-methyl-3-piperidinol	1-ethyl-3-piperidinol	1-methyl-4-piperidinol
	$-\Delta_c u^\circ/(\mathrm{J \cdot g^{-1}})$	
34082.67	35385.57	33998.83
34086.76	35392.81	34000.16
34072.03	35393.47	34005.49
34066.73	35378.82	33978.33
34064.55	35366.63	33984.60
34060.09	35372.96	33990.18
	35388.60	
	$-\langle \Delta_c u^\circ \rangle/(\mathrm{J \cdot g^{-1}})$	
34072.1 ± 4.3	35382.7 ± 3.9	33992.9 ± 4.2

Table 4. Condensed Phase Standard ($p^\circ = 0.1$ MPa) Molar Thermochemical Functions at $T = 298.15$ K

compound	$-\Delta_c U_m^\circ$(l) kJ·mol^{-1}	$-\Delta_c H_m^\circ$(l) kJ·mol^{-1}	$\Delta_f H_m^\circ$(l) kJ·mol^{-1}
1-methyl-3-piperidinol	3924.2 ± 1.5	3929.8 ± 1.5	289.2 ± 1.7
1-ethyl-3-piperidinol	4571.4 ± 1.6	4578.2 ± 1.6	320.1 ± 1.9
1-methyl-4-piperidinol	3915.1 ± 1.4	3920.7 ± 1.4	298.3 ± 1.7

it was assumed that $(\partial u/\partial T)_T = -0.2$ J·g^{-1} MPa^{-1} at $T = 298.15$ K, a typical value for organic compounds.[34]

The molar masses used for the elements were those recommended by the IUPAC Commission.[35] Table 3 gives the individual values of $\Delta_c u^0$ for all compounds together with the mean value and its standard deviation.

Table 4 lists, for each compound, the derived standard molar values for the energy ($\Delta_c U_m^\circ$) and enthalpy ($\Delta_c H_m^\circ$) of the combustion reactions according to eq 1 for 1-methyl-3-piperidinol and 1-methyl-4-piperidinol and according to eq 2 for 1-ethyl-3-piperidinol. In this table, the standard molar enthalpy of formation, $\Delta_f H_m^\circ$, in the liquid phase is also presented:

$$C_6H_{13}NO(l) + \frac{35}{4}O_2(g) \rightarrow 6CO_2(g) + \frac{13}{2}H_2O(l) + \frac{1}{2}N_2(g) \quad (1)$$

$$C_7H_{15}NO(l) + \frac{41}{4}O_2(g) \rightarrow 7CO_2(g) + \frac{15}{2}H_2O(l) + \frac{1}{2}N_2(g) \quad (2)$$

In accordance with the normal thermochemical practice, the uncertainties assigned to the standard molar enthalpies of combustion are, in each case, twice the overall standard deviation of the mean and include the uncertainties in calibration[36,37] and in the values of the auxiliary quantities. The values of the standard molar enthalpies of formation in the liquid phase, $\Delta_f H_m^\circ$(l), were derived from $\Delta_c H_m^\circ$ using the values at $T = 298.15$ K of the standard molar enthalpies of formation of liquid water and gaseous carbon dioxide respectively as $\Delta_f H_m^\circ(H_2O, l) = -(285.830 \pm 0.042)$ kJ·mol^{-1} [38] and $\Delta_f H_m^\circ(CO_2, g) = -(393.51 \pm 0.13)$ kJ·mol^{-1}.[38]

The individual values for the standard molar enthalpies of vaporization at the experimental temperature for 1-methyl-3-piperidinol, 1-ethyl-3-piperidinol, and 1-methyl-4-piperidinol are given in Table 5. In this table, the mean and the correspondent standard deviation are also included. These values were corrected to $T = 298.15$ K, using $\Delta^T_{298K}H_m^\circ(g)$ estimated by a group scheme based on values of Messerly et al.[39] and Stull et al.[40] The schemes applied for 1-methyl-3-piperidinol and 1-methyl-4-piperidinol were

1-methyl-3(or 4)-piperidinol = piperidine + cyclohexanol − cyclohexane + methylamine − ammonia

and for 1-ethyl-4-piperidinol was

1-ethyl-4-piperidinol = piperidine + cyclohexanol − cyclohexane + ethylamine − ammonia

Table 5. Individual Values of the Standard Molar Enthalpy of Vaporization, for the Compounds, at the Experimental Temperatures[a]

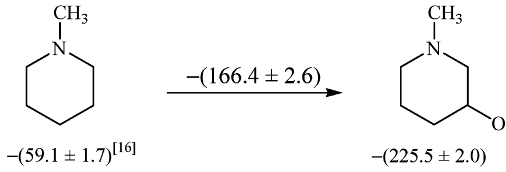
1-methyl-3-piperidinol	1-ethyl-3-piperidinol	1-methyl-4-piperidinol
	$\Delta^{g,T}_{l,298.15K}H_m^\circ/(\mathrm{kJ \cdot mol^{-1}})$	
72.31	74.79	80.03
71.21	76.96	81.19
74.24	77.15	81.11
74.04	75.88	79.76
73.17	76.16	81.71
	74.48	
	74.67	
	$\langle \Delta^{g,T}_{l,298.15K}H_m^\circ \rangle/(\mathrm{kJ \cdot mol^{-1}})$	
72.99 ± 0.56	75.73 ± 0.42	80.76 ± 0.37

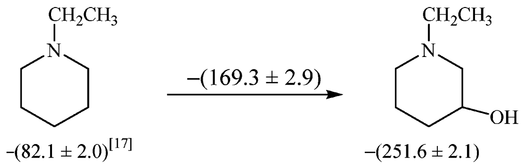
[a] For 1-methyl-3-piperidinol, $T = 358.0$ K; for 1-ethyl-3-piperidinol, $T = 339.1$ K; and for 1-methyl-4-piperidinol, $T = 357.9$ K.

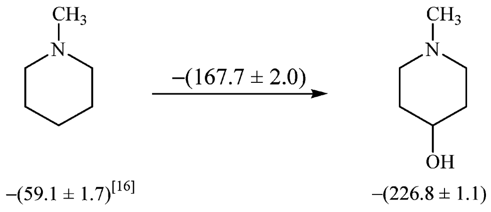
which yielded for 1-methyl-3-piperidinol, at $T = 358.0$ K, $\Delta^{358.0K}_{298.15K}H_m^\circ(g) = 9.31$ kJ·mol^{-1}; for 1-ethyl-3-piperidinol, at $T = 339.1$ K, $\Delta^{339.1K}_{298.15K}H_m^\circ(g) = 7.25$ kJ·mol^{-1}; and for 1-methyl-4-piperidinol, at $T = 357.9$ K, $\Delta^{357.9K}_{298.15K}H_m^\circ(g) = 9.28$ kJ·mol^{-1}. The standard molar enthalpies of vaporization at $T = 298.15$ K for each compound are registered in Table 6, where the uncertainties are twice the overall standard deviation of the mean and include the uncertainties in calibration. The derived standard molar enthalpies of formation in liquid and gaseous phase at $T = 298.15$ K are also summarized in Table 6.

Discussion

The experimental thermochemical results presented in this work enable one to establish the enthalpic effect due to introduction of the −OH group directly in piperidine group. Taking into consideration the values of $\Delta_f H_m^\circ$(g) for 1-methylpiperidine and 1-ethylpiperidine previously reported, $\Delta_f H_m^\circ$(g, 1-methylpiperidine) = −(59.1 ± 1.7) kJ·mol^{-1},[16] and $\Delta_f H_m^\circ$(g, 1-ethylpiperidine) = −(82.1 ± 2.0) kJ·mol^{-1},[17] the enthalpic increment due to the introduction of the −OH group directly into the piperidine ring is −(166.4 ± 2.6) kJ·mol^{-1} for 1-methyl-3-piperidinol, −(169.3 ± 2.9) kJ·mol^{-1} for 1-ethyl-3-piperidinol, and −(167.7 ± 2.0) kJ·mol^{-1} for 1-methyl-4-piperidinol, as illustrated in following schemes (all the values in kJ·mol^{-1}):





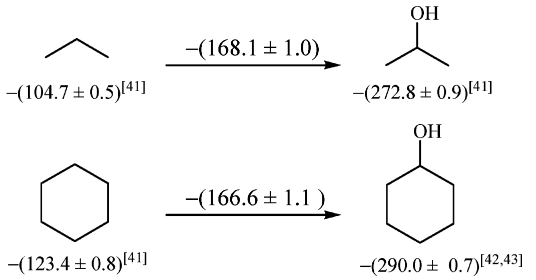


The derived value for the enthalpic increment due to the introduction of a −OH group into the piperidine ring averages

Table 6. Derived Standard ($p^\circ = 0.1$ MPa) Molar Enthalpies of Formation, $\Delta_f H^\circ_m$, and of Vaporization, $\Delta_l^g H^\circ_m$, at $T = 298.15$ K

compound	$-\Delta_f H^\circ_m(l)$ kJ·mol^{-1}	$\Delta_l^g H^\circ_m$ kJ·mol^{-1}	$-\Delta_f H^\circ_m(g)$ kJ·mol^{-1}
1-methyl-3-piperidinol	289.2 ± 1.7	63.7 ± 1.0	225.5 ± 2.0
1-ethyl-3-piperidinol	320.1 ± 1.9	68.48 ± 0.81	251.6 ± 2.0
1-methyl-4-piperidinol	298.3 ± 1.7	71.48 ± 0.72	226.8 ± 1.8

−(167.8 ± 2.5)kJ·mol^{-1}, which is similar, within the experimental uncertainties, to the increments for the conversion of propane[41] into 2-propanol,[41] −(168.1 ± 1.0)kJ·mol^{-1}, and for the conversion of cyclohexane[41] to cyclohexanol,[42,43] −(166.6 ± 1.1)kJ·mol^{-1}, as shown below:



The experimental values determined in this work for the standard molar enthalpies of formation of the three alkyl piperidinols in the gaseous phase can be compared with the values of the same property estimated by one modern bond energy scheme, such as the Benson's Group Method.[44] This method is known to yield reliable results for a large number of compounds, and it is easy to apply. To do that, the following literature[45] group contributions have been used: [**N**−(C)$_3$] = 102.09 kJ·mol^{-1}; [**C**−(N)(H)$_3$] = −42.17 kJ·mol^{-1}; [**C**−(N)(C)(H)$_2$] = −27.61 kJ·mol^{-1}; [**C**−(H)$_2$(C)$_2$] = −20.63 kJ·mol^{-1}; [**C**−(H)$_3$(C)] = −42.68 kJ·mol^{-1}; [**C**−(H)(O)(C)$_2$] = −30.12 kJ·mol^{-1}; [**O**−(H)(C)] = −158.57 kJ·mol^{-1}; and the **correction for the piperidine ring system** = 4.18 kJ·mol^{-1}.

The enthalpies of formation estimated with this method are as follows: for 1-methyl-3-piperidinol, −221.08 kJ·mol^{-1}; for 1-ethyl-3-piperidinol, −249.20 kJ·mol^{-1}; and for 1-methyl-4-piperidinol, −221.08 kJ·mol^{-1}, which differ from our experimental results by −4.4 kJ·mol^{-1}, −2.4 kJ·mol^{-1}, and −5.7 kJ·mol^{-1}, respectively. So the results obtained with this approximated method are in fair agreement with the experimental values, with the largest difference being only −5.7 kJ·mol^{-1}.

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