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Thermochemical Insights on the Conformational Energetics of Azepan and Azepan-1-ylacetonitrile

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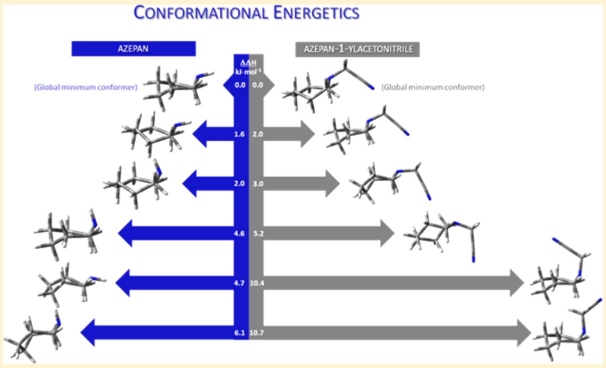
Supporting Information

ABSTRACT: This paper is concerned with computational and experimental thermochemical studies of azepan and azepan-1-ylacetonitrile, molecules whose flexible ring structure provides several conformational forms with low energy barriers among them. The computational study describes the energetic analysis of the six most stable conformers on the potential energy surfaces and the determination of their gas-phase standard enthalpy of formation at the reference temperature of 298.15 K. The same gas-phase enthalpic parameters are also derived from the enthalpies of formation in the liquid phase and the enthalpies of vaporization, at $T = 298.15$ K, determined experimentally using the combustion calorimetry and the Calvet microcalorimetry techniques, respectively. The experimental data reported in this work for the two titled compounds together with other available in the literature for related molecules enabled the establishment of an increments scheme, providing a reliable approach on the prevision of gas-phase enthalpy of formation of cyclic/acyclic hydrocarbons and amines. Complementary, natural bond orbital (NBO) calculations were also performed, allowing an advance on the analysis of the structural and reactivity behavior of these type of compounds.



1. INTRODUCTION

Azepan (also known by homopiperidine, azacycloheptane, hexahydroazepine, and hexamethylenimine) is a seven-member alicyclic molecule containing a secondary amine in the ring system, as shown in Figure 1. This molecule has a flexible ring structure with several conformations that can interconvert with relatively low energy barriers. The multiplicity of forms that may occur makes the study of the structural forms of these type of compounds challenging. Computational conformational analysis can be used to predict and explain the mechanism, rates of reaction, and product selectivity. For example, in many systems ligand−receptor interactions frequently require conformational changes, and such conformational "induced fits" give specificity in molecular recognition in selecting a particular reaction or binding outcome.[1] The study of the conformational energetics on azepan together with azepan-1-ylacetonitrile, a derivative of azepan with the acetonitrile fragment attached to the nitrogen of the amine group, is the subject of this paper. These two compounds make up the core of several interesting molecules, with particular relevance to the pharmacological field due to their remarkable biological activities.[2−8] New ionic liquids based on azepan derivatives have been also synthesized, exhibiting remarkable properties, as bioactive epitotes.[1,9,10]

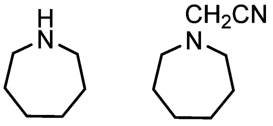

(1) (2)

Figure 1. Structural formula of azepan (1) and azepan-1-ylacetonitrile (2).

This paper reports a combined experimental and computational thermochemical study on the conformational energetics of the two titled compounds. The experimental studies of azepan and azepan-1-ylacetonitrile were performed using two calorimetric techniques (static bomb calorimetry and drop-microcalorimetry) that enabled the standard ($p° = 0.1$ MPa) molar enthalpy of formation, in the liquid phase, $\Delta_{\mathrm{f}}H_{\mathrm{m}}^{\mathrm{o}}(\mathrm{l})$, and the standard molar enthalpy of vaporization, $\Delta_{\mathrm{l}}^{\mathrm{g}}H_{\mathrm{m}}^{\mathrm{o}}$, at $T = 298.15$ K, respectively, to be derived. The combination of the two experimental techniques allows the determination of the standard molar enthalpy of formation, in the gaseous phase, $\Delta_{\mathrm{f}}H_{\mathrm{m}}^{\mathrm{o}}(\mathrm{g})$, at the reference temperature, 298.15 K.

Previous energetic studies of azepan have been already reported by An et al.,[11] in a context of a bond energy study of

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Table 1. Standard ($p° = 0.1$ MPa) Molar Enthalpies of Vaporization for Azepan (1) and Azepan-1-ylacetonitrile (2), at $T = 298.15$ K, Determined by Calvet Microcalorimetry

	T/K	$\Delta_{\mathrm{l},298.15\mathrm{K}}^{\mathrm{g},T}H_{\mathrm{m}}^{\circ}/\mathrm{kJ\cdot mol^{-1}}$	$\Delta_{298.15\mathrm{K}}^{T}H_{\mathrm{m}}^{\circ}(\mathrm{g})/\mathrm{kJ\cdot mol^{-1}}$	$\Delta_{\mathrm{l}}^{\mathrm{g}}H_{\mathrm{m}}^{\circ}/\mathrm{kJ\cdot mol^{-1}}$
(1)	334.6	51.5 ± 0.3[a]	4.8372 ± 0.0003[a,b]	46.7 ± 0.6[c]
(2)	334.4	68.7 ± 0.1[a]	6.488 ± 0.004[a,b]	62.2 ± 0.5[c]

[a] Uncertainties correspond to standard deviation of the mean. [b] Uncertainties of the computational method and scaling factor are not included. [c] Uncertainty associated is twice the standard deviation of the mean and includes the uncertainties associated with the calibration procedure and the molar heat capacity of the compound in the gaseous state.

Table 2. Derived Standard ($p° = 0.1$ MPa) Molar Values of Azepan (1) and Azepan-1-ylacetonitrile (2) in Liquid and Gas Phases, at $T = 298.15$ K

	$\Delta_{\mathrm{c}}U_{\mathrm{m}}^{\circ}(\mathrm{l})/\mathrm{kJ\cdot mol^{-1}}$	$\Delta_{\mathrm{c}}H_{\mathrm{m}}^{\circ}(\mathrm{l})/\mathrm{kJ\cdot mol^{-1}}$	$\Delta_{\mathrm{f}}H_{\mathrm{m}}^{\circ}(\mathrm{l})/\mathrm{kJ\cdot mol^{-1}}$	$\Delta_{\mathrm{f}}H_{\mathrm{m}}^{\circ}(\mathrm{g})/\mathrm{kJ\cdot mol^{-1}}$
(1)	−4118.1 ± 2.2	−4124.9 ± 2.2	−94.1 ± 2.3	−47.4 ± 2.4
(2)	−5160.2 ± 1.7	−5166.4 ± 1.7	17.5 ± 2.2	79.7 ± 2.3

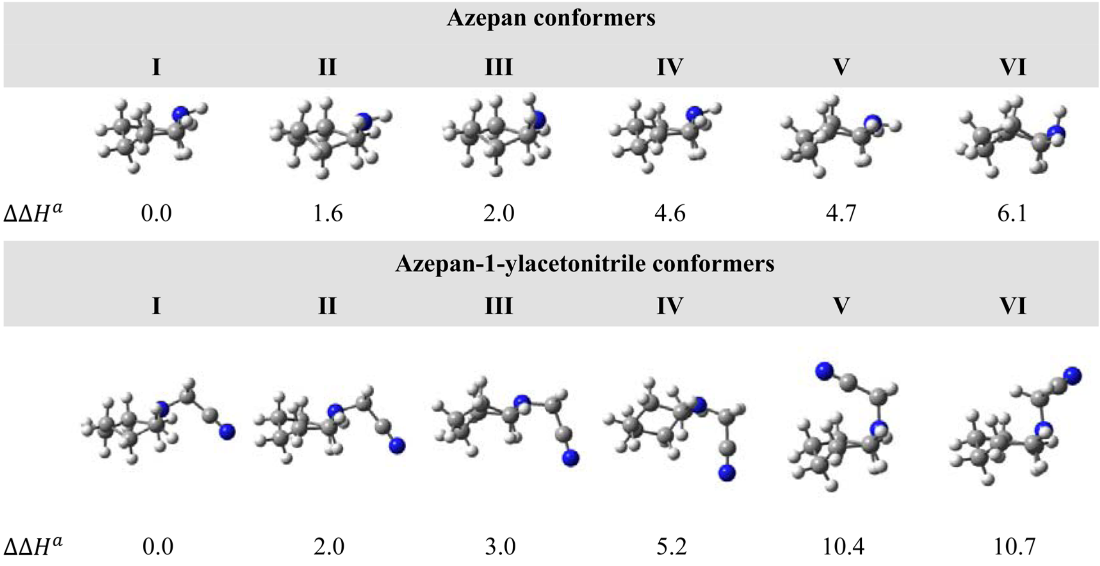


Figure 2. Molecular structures of the six most stable conformers for azepan and azepan-1-ylacetonitrile. Atom color code: gray, C; blue, N; white, H. [a]Enthalpy difference relative to the global minimum conformer.

some amine derivatives. These data are compared and discussed with our experimental one.

The conformational analysis of azepan and azepan-1-ylacetonitrile has been performed using theoretical calculations to identify the stationary points on the potential energy surfaces. The equilibrium geometries and the thermodynamic properties of six minimum energy conformers were used to determine the conformational composition of the compounds studied, by means of Boltzmann's distribution. The computed gas-phase standard molar enthalpies of formation of azepan and azepan-1-ylacetonitrile have been determined taking into account the conformational compositions of each one of the species. This parameter together with the corresponding experimental one are compared and discussed in terms of enthalpic effects.

The computational study was also extended to compute gas-phase molar heat capacities at different temperatures, dipole moments, electrostatic potential energy maps mapped onto an electron density isosurface, and frontier orbitals.

2. RESULTS AND DISCUSSION

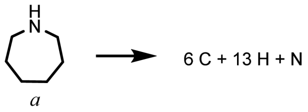
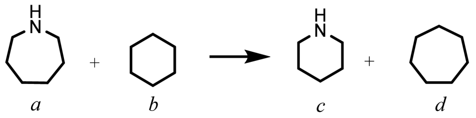
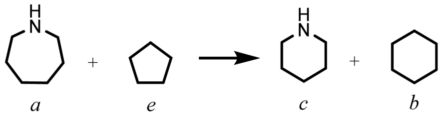
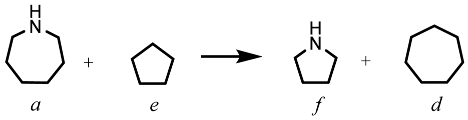
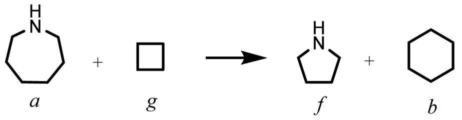
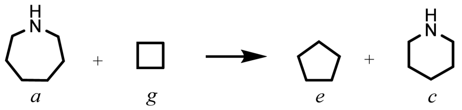
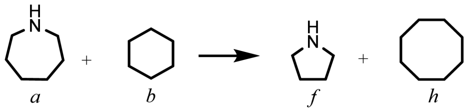
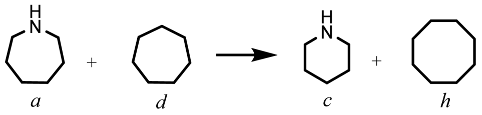
2.1. Experimental Enthalpies of Vaporization. Results of vaporization experiments of azepan and azepan-1-ylacetonitrile performed using the vacuum drop microcalorimetric technique are reported in Table 1 (the values correspond to the mean of six experiments) which includes the enthalpies of vaporization at the experimental (T) and reference temperatures (298.15 K), $\Delta_{\mathrm{l},298.15\mathrm{K}}^{\mathrm{g},T}H_{\mathrm{m}}^{\circ}$ and $\Delta_{\mathrm{l}}^{\mathrm{g}}H_{\mathrm{m}}^{\circ}$, respectively, and the molar enthalpic correction for the gaseous phase, $\Delta_{298.15\mathrm{K}}^{T}H_{\mathrm{m}}^{\circ}(\mathrm{g})$, used to adjust the enthalpy of vaporization from the experimental to the reference temperature. This last parameter is calculated via eq 1, using the gas-phase molar heat capacities derived from statistical thermodynamics by means of the vibrational frequencies arising from the Hartree−Fock calculations with the 6-31G(d) basis set.[12] The individual values of the molar heat capacities in the gaseous phase for each temperature, in the range 100 to 600 K, are given as Supporting Information (Table S1).

$$\Delta_{298.15\mathrm{K}}^{T}H_{\mathrm{m}}^{\circ}(\mathrm{g}) = \int_{298.15K}^{T} C_{p,\mathrm{m}}^{\circ}(g)\,\mathrm{d}T \qquad (1)$$

An et al.[11] reported the standard molar enthalpy of vaporization for azepan of $\Delta_{\mathrm{l}}^{\mathrm{g}}H_{\mathrm{m}}^{\circ} = 44.3$ kJ·mol^{-1}, which differs by 2.4 kJ·mol^{-1} from our experimental value.

2.2. Experimental Enthalpies of Formation in the Liquid and Gas Phases. The mean values of the standard ($p°$ = 0.1 MPa) massic energy of combustion, $\Delta_{\mathrm{c}}u°(l)$, obtained for azepan and azepan-1-ylacetonitrile were (−41 524.3 ± 8.7) J·

Table 3. Calculated Values for the Gas-Phase Standard Molar Enthalpies of Formation, $\Delta_f H_m^o(g)$, at T = 298.15 K for Azepan Conformers Derived From Working Reactions[a]

Working reactions	Eq.	$\Delta_f H_m^o(g)$ / kJ·mol^{-1}					
		I	II	III	IV	V	VI
	(4)	-45.40	−43.80	−43.40	−40.76	−40.69	−39.33
	(5)	-45.41	−43.81	−43.41	−40.77	−40.70	−39.34
	(6)	−46.06	−44.46	−44.06	−41.43	−41.35	−40.00
	(7)	−47.36	−45.76	−45.36	−42.72	−42.65	−41.29
	(8)	−49.54	−47.95	−47.54	−44.91	−44.83	−43.48
	(9)	−47.59	−46.00	−45.59	−42.96	−42.88	−41.53
	(10)	−47.62	−46.02	−45.62	−42.99	−42.91	−41.56
	(11)	−46.32	−44.73	−44.32	−41.69	−41.61	−40.26
Mean values / kJ·mol^{-1}		−46.9	−45.3	−44.9	−42.3	−42.2	−40.8
$\Delta\Delta_f H_m^o$/ kJ·mol^{-1}		0	1.6	2.0	4.6	4.7	6.1
Conformer composition (χ_i)		0.404	0.205	0.189	0.075	0.082	0.045
Considering the conformer composition / kJ·mol^{-1}		−45.2 ± 3.7[b]					

[a] (a) Azepan; (b) cyclohexane; (c) piperidine; (d) cycloheptane; (e) cyclopentane; (f) pyrrolidine; (g) cyclobutane; (h) cyclooctane. [b] Standard deviation of the mean for eight working reactions.

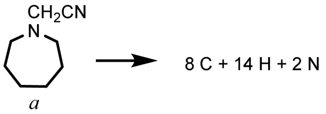
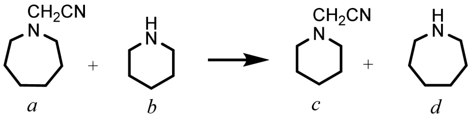
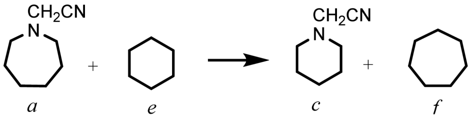
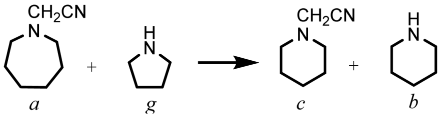
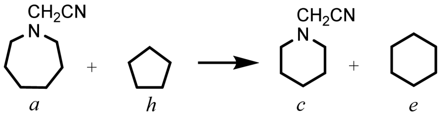
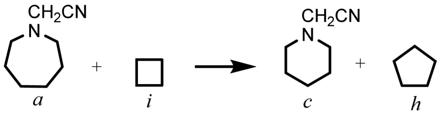
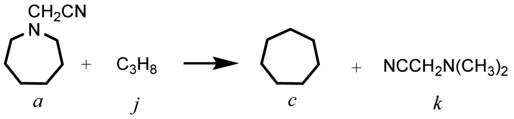
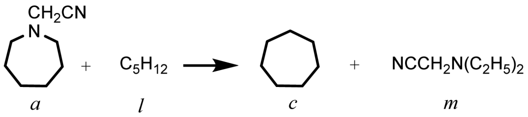
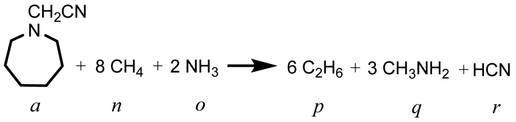
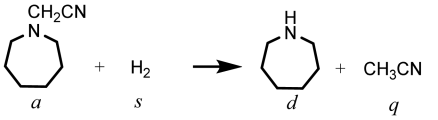
g^{-1} and (−37 335.8 ± 1.2) J·g^{-1}, respectively; the quoted uncertainties correspond to the standard deviation of the mean. The results for typical combustion experiments for each compound are given as Supporting Information (Tables S2 and S3).

The derived standard molar energies, $\Delta_c U_m^o(l)$, and enthalpies, $\Delta_c H_m^o(l)$, from the combustion reactions of azepan ($C_6H_{13}N$) and azepan-1-ylacetonitrile ($C_8H_{14}N_2$), described by eqs 2 and 3, respectively, as well as the standard molar enthalpies of formation, $\Delta_f H_m^o(l)$, in the liquid phase are reported in Table 2. The uncertainties assigned to the standard molar enthalpies of combustion and of formation are twice the overall standard deviation of the mean and include the uncertainties in calibration and in the auxiliary quantities used, in accordance with thermochemical practice.[13] To derive $\Delta_f H_m^o(l)$ from $\Delta_c H_m^o(l)$, the standard molar enthalpies of formation of $H_2O(l)$, $CO_2(g)$, at T = 298.15 K, respectively, (−285.830 ± 0.042) kJ·mol^{-1}[14] and (−393.51 ± 0.13) kJ·mol^{-1},[14] were used.

$$C_6H_{13}N(l) + 9.25O_2(g) \rightarrow 6CO_2(g) + 6.5H_2O(l) + 0.5N_2(g) \quad (2)$$

$$C_8H_{14}N_2(l) + 11.5O_2(g) \rightarrow 8CO_2(g) + 7H_2O(l) + N_2(g) \quad (3)$$

Table 4. Calculated Values for the Gas-Phase Standard Molar Enthalpies of Formation, $\Delta_f H_m^o(g)$, at T = 298.15 K for Azepan-1-ylacetonitrile Conformers Derived From Working Reactions[a]

Working reactions	Eq.	$\Delta_f H_m^o(g)$ / kJ·mol^{-1} I	II	III	IV	V	VI
	(12)	85.62	87.64	88.59	90.86	96.05	96.28
	(13)	87.28	89.31	90.25	92.52	97.71	97.94
	(14)	89.38	91.40	92.34	94.62	99.81	100.04
	(15)	90.67	92.70	93.64	95.61	101.10	101.33
	(16)	88.72	90.75	91.69	93.96	99.15	99.38
	(17)	87.19	89.22	90.16	92.43	97.62	97.85
	(18)	82.34	84.36	85.31	87.58	92.77	93.00
	(19)	86.55	88.57	89.51	91.79	96.98	97.21
	(20)	79.60	81.62	82.56	84.84	90.03	90.26
	(21)	81.13	83.16	84.10	86.37	91.56	91.79
Mean values / kJ·mol^{-1}		85.8	87.9	88.8	91.1	96.3	96.5
$\Delta\Delta_f H_m^o$/ kJ·mol^{-1}		0	2.1	3.0	5.3	10.5	10.7
Conformer composition (χ_i)		0.500	0.249	0.177	0.062	0.006	0.007
Considering the conformer composition / kJ·mol^{-1}		87 ± 11[b]					

[a] (a) Azepan-1-ylacetonitrile; (b) piperidine; (c) ; 1-piperidineacetonitrile; (d) azepan; (e) cyclohexane; (f) cycloheptane; (g) pyrrolidine; (h) cyclopentane; (i) cyclobutane; (j) propane; (k) (dimethylamino)acetonitrile; (l) pentane; (m) (diethylamino)acetonitrile; (n) methane; (o) ammonia; (p) ethane; (q) methylamine; (r) hydrogen cyanide; (s) hydrogen. [b] Standard deviation of the mean for ten working reactions.

The combination of the $\Delta_f H_m^o(l)$ and $\Delta_l^g H_m^o$ yield the following gas-phase standard molar enthalpies of formation at 298.15 K (Table 2): $\Delta_f H_m^o$(g, azepan) = (−47.4 ± 2.4) kJ·mol^{-1} and $\Delta_f H_m^o$(g, azepan-1-ylacetonitrile) = (79.7 ± 2.3) kJ·mol^{-1}.

The study of An et al.[11] also reported the standard molar enthalpy of formation in the liquid and gas phases of azepan with values of $\Delta_f H_m^o(l)$ = −89.3 ± −1.6 kJ·mol^{-1} and $\Delta_f H_m^o(g)$ = −45.0 ± −2.0 kJ·mol^{-1}, respectively, The enthalpy formation value for the condensed phase is 4.8 higher than our experimental value, slightly out of our range of uncertainty; however, the gas-phase enthalpy of formation is in good agreement with our experimental value.

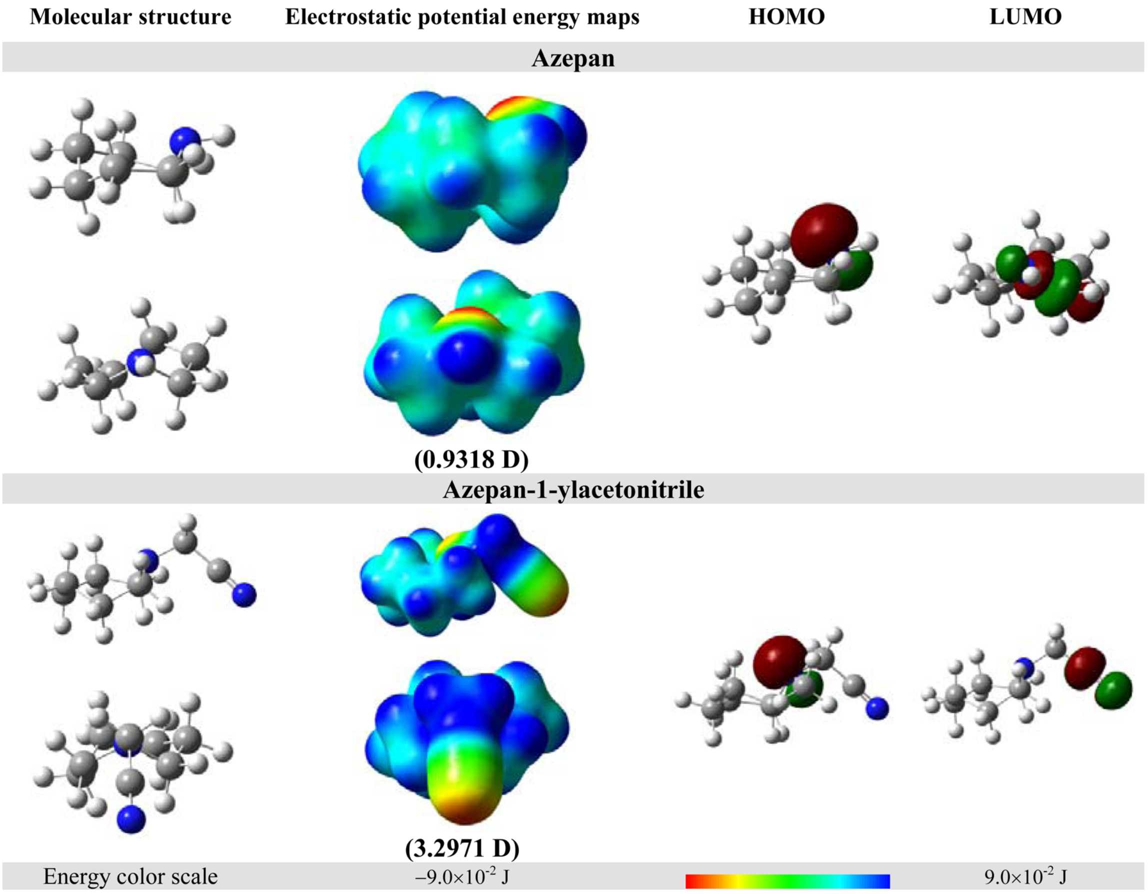


Figure 3. Molecular structures, electrostatic potential energy maps mapped onto an electron density isosurface (isodensity value of 0.015 e·a_0^{-3}, where a_0 is the Bohr radius), and HOMO and LUMO (isodensity value of 0.06 e·a_0^{-3}) calculated for azepan and azepan-1-ylacetonitrile.

2.3. Computed Gas-Phase Enthalpies of Formation and Conformational Equilibrium Analysis.

The flexible heptagonal ring of azepan and azepan-1-ylacetonitrile enables several possible conformers, so a conformational analysis of the two compounds optimizing the molecular structures of the lowest-energy conformers using the G3 method[15] was undertaken. From the conformational analysis performed several possible twist-chair, boat, and twist-boat conformations with the N−R bond (R = H, CH_2CN) with axial or equatorial arrangements were obtained. The molecular structures of the six most stable conformers, within 6.1 and 10.7 kJ·mol^{-1} for azepan and azepan-1-ylacetonitrile, respectively, are presented in Figure 2. Atom coordinates obtained for azepan and azepan-1-ylacetonitrile optimized structures are reported, respectively, in Tables S4 and S5 of Supporting Information. Conformer I corresponds to the global minimum, and the others correspond to the local minima on the potential energy surfaces.

The gas-phase standard molar enthalpies of formation at T = 298.15 K, $\Delta_f H_m^o(g)$, for each one of the six conformers of the two compounds studied were obtained from different working reactions presented in Tables 3 (eqs 4 to 11) and 4 (eqs 12 to 21) for azepan and azepan-1-ylacetonitrile, respectively; the enthalpy of each reaction was calculated using the absolute enthalpies for each species derived from the G3 approach[15] and the experimental values of the gas-phase enthalpies of formation of the remaining species in the reaction. These values are given as Supporting Information in Table S6. The results for azepan and azepan-1-ylacetonitrile are reported in Tables 3 and 4, respectively.

In the penultimate rows of the Tables 3 and 4 are reported the conformational composition, χ_i, of each isomer calculated assuming a Boltzmann distribution of the n possible conformers. Details of the conformational analysis performed are given in the Supporting Information in Tables S7 and S8. The final estimated values of $\Delta_f H_m^o$ (g) for azepan and azepan-1-ylacetonitrile were adjusted for the contributions of each conformation with values of (−45.2 ± 3.7) kJ·mol^{-1} and (87 ± 11) kJ·mol^{-1}, respectively. These values are in good agreement with the experimental ones reported in Table 2, considering the uncertainties given.

2.4. Molecular Structures, Electrostatic Potential Energy Maps, and Frontier Orbitals of the Global Minimum Conformers.

Views of the molecular structures optimized at the MP2(FU)/6-31G(d) level of theory of azepan and azepan-1-ylacetonitrile conformers corresponding to the global minimum on the potential energy surface are presented in Figure 3. In the same figure the graphical representations of the electrostatic potential energy mapped onto an electron density isosurface and the highest-occupied molecular orbital (HOMO) and the lowest-unoccupied molecular orbital (LUMO) obtained from the Natural Atomic Orbital and Natural Bond Orbital analyses performed with Gaussian NBO Version 3.1[16] are also presented. The global minimum energy structures for both compounds adopt twist-chair conformations with an equatorial N−R bond and have a C_1 point group. The molecular structure of the other five stable conformers, i.e., local minima on the potential energy surface, found for azepan and azepan-1-ylacetonitrile are presented in Figure 2.

Scheme 1. Gas-Phase Enthalpies of Reaction Derived from Computational Studies[a]

Hydrocarbons

$$\begin{tikzcd}
\text{acyclic} & C_3H_8 \arrow[r, "H_2+C", "735.58"'] & C_4H_{10} \arrow[r, "H_2+C", "735.63"'] & C_5H_{12} \arrow[r, "H_2+C", "735.56"'] & C_6H_{14} \arrow[r, "H_2+C", "735.83"'] & C_7H_{16} \\
\text{cyclic} & C_3H_6 \arrow[u, "H_2", "-160.14"'] \arrow[r, "H_2+C", "742.07"'] & C_4H_8 \arrow[u, "H_2", "-153.65"'] \arrow[r, "H_2+C", "817.32"'] & C_5H_{10} \arrow[u, "H_2", "-71.96"'] \arrow[r, "H_2+C", "761.65"'] & C_6H_{12} \arrow[u, "H_2", "-45.87"'] \arrow[r, "H_2+C", "710.20"'] & C_7H_{14} \arrow[u, "H_2", "-71.49"']
\end{tikzcd}$$

Amine derivatives

$$\begin{tikzcd}
\text{acyclic} & C_2H_6NH \arrow[r, "H_2+C", "735.31"'] & C_3H_8NH \arrow[r, "H_2+C", "735.27"'] & C_4H_{10}NH \arrow[r, "H_2+C", "735.81"'] & C_5H_{12}NH \arrow[r, "H_2+C", "735.75"'] & C_6H_{14}NH \\
\text{cyclic} & C_2H_4NH \arrow[u, "H_2", "-176.97"'] \arrow[r, "H_2+C", "743.04"'] & C_3H_6NH \arrow[u, "H_2", "-169.24"'] \arrow[r, "H_2+C", "817.56"'] & C_4H_8NH \arrow[u, "H_2", "-86.94"'] \arrow[r, "H_2+C", "760.50"'] & C_5H_{10}NH \arrow[u, "H_2", "-62.26"'] \arrow[r, "H_2+C", "713.61"'] & C_6H_{12}NH \arrow[u, "H_2", "-84.40"']
\end{tikzcd}$$

[a] All values are in kJ·mol^{-1}.

The electrostatic potential energy maps for azepan and azepan-1-ylacetonitrile (Figure 3) show the presence of large "neutral" regions (marked in green) for the carbon atoms and a concentration of negative charge (marked in red) in the region surrounding the lone pair of the nitrogen atoms. The dipole moment values obtained were 0.9318 D for azepan and 3.2971 D for azepan-1-ylacetonitrile.

The HOMOs of azepan and azepan-1-ylacetonitrile are of the type $n_{(N)}$, and the LUMOs are, respectively, $\sigma^*_{(C-N)}$ and $\pi^*_{(C-N)}$. The electronic energy transitions from the HOMO to LUMO, E_{GAP}, obtained are $E_{GAP}(n_{(N)} \rightarrow \sigma^*_{(C-N)}) = 17.83$ eV for azepan and $E_{GAP}(n_{(N)} \rightarrow \pi^*_{(C-N)}) = 10.10$ eV for azepan-1-ylacetonitrile. These frontier orbitals determine the way a molecule interacts with other species and helps to characterize its chemical reactivity and kinetic stability. Molecules with low frontier orbital gaps are more polarizable and are generally associated with a high chemical reactivity and low kinetic stability.[17] The comparison of HOMO−LUMO gap energies between the two compounds shows that the azepan-1-ylacetonitrule has a lower energy gap than azepan, suggesting greater chemical reactivity.

2.5. Play of Increments. The absolute enthalpies of some acyclic ($C_nH_{(2n+2)}$) and cyclic (C_nH_{2n}) hydrocarbons, together with primary acyclic amines ($C_nH_{(2n+2)}NH$) and secondary cyclic amines ($C_nH_{2n}NH$), with n between 2 and 7, were calculated by the G3 method[15] (the values are reported in Supporting Information, Table S6). From these absolute enthalpies the enthalpies of reaction reported in Scheme 1 are related to the increase of one CH_2 fragment in the chain (represented by horizontal arrows) and to the opening of the cyclic chain (represented by vertical arrows). The enthalpy of reaction for the insertion of one CH_2 fragment in acyclic compounds has a value of ~735 kJ·mol^{-1} in both hydrocarbons and amines derivatives. The same insertion in cyclic compounds has enthalpies of reaction in the range of 710 to 818 kJ·mol^{-1}. The agreement between cyclic hydrocarbons and cyclic amines with the same number of atoms in the ring is good. The enthalpies of reaction between a cycloalkane and an acyclic primary amine to form an acyclic alkane and a cyclic secondary amine, with the same n value, have differences of (15.3 ± 3.1) kJ·mol^{-1} calculated by eq 22 (with n between 2 and 7).

$$C_nH_{[(2n)+2]}NH + C_{(n+1)}H_{[(n+1)\times 2]} \xrightarrow{15.3\pm3.1\ \text{kJ·mol}^{-1}} C_nH_{(2n)}NH + C_{(n+1)}H_{[(n+1)\times 2+2]} \quad (22)$$

Scheme 2 was constructed similarly to Scheme 1, but using the experimental gas-phase standard molar enthalpies of formation available in the literature instead of computational enthalpies. The increment for enthalpy of formation for the insertion of one CH_2 fragment in acyclic compounds has a

Scheme 2. Gas-Phase Enthalpic Increments for Cyclic and Acyclic Hydrocarbons and Amines[a]

Hydrocarbons

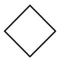
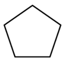
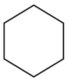
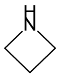
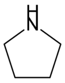
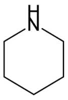
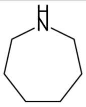
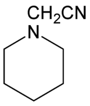
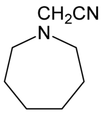
$$\begin{tikzcd}
\begin{array}{c}C_3H_8\\(-104.7\pm0.5)^a\end{array} \arrow[r, "(\mathbf{-21.0\pm0.8})"] & \begin{array}{c}C_4H_{10}\\(-125.7\pm0.6)^a\end{array} \arrow[r, "(\mathbf{-21.2\pm1.0})"] & \begin{array}{c}C_5H_{12}\\(-146.9\pm0.8)^a\end{array} \arrow[r, "(\mathbf{-20.0\pm1.1})"] & \begin{array}{c}C_6H_{14}\\(-166.9\pm0.8)^a\end{array} \arrow[r, "(\mathbf{-20.7\pm1.5})"] & \begin{array}{c}C_7H_{16}\\(-187.6\pm1.3)^a\end{array} \\
\begin{array}{c}C_3H_6\\(53.3\pm0.5)^a\end{array} \arrow[u, "(\mathbf{-158.0\pm0.7})"] \arrow[r, "(\mathbf{-25.6\pm1.2})"] & \begin{array}{c}C_4H_8\\(27.7\pm1.1)^a\end{array} \arrow[u, "(\mathbf{-153.4\pm1.3})"] \arrow[r, "(\mathbf{-104.1\pm1.3})"] & \begin{array}{c}C_5H_{10}\\(-76.4\pm0.7)^a\end{array} \arrow[u, "(\mathbf{-70.5\pm1.1})"] \arrow[r, "(\mathbf{-46.9\pm1.1})"] & \begin{array}{c}C_6H_{12}\\(-123.3\pm0.8)^a\end{array} \arrow[u, "(\mathbf{-43.6\pm1.1})"] \arrow[r, "(\mathbf{5.2\pm1.2})"] & \begin{array}{c}C_7H_{14}\\(-118.1\pm0.9)^a\end{array} \arrow[u, "(\mathbf{-69.5\pm1.6})"]
\end{tikzcd}$$

Amine derivatives

$$\begin{tikzcd}
\begin{array}{c}C_2H_6NH\\(-47.5\pm0.6)^a\end{array} \arrow[r, "(\mathbf{-22.6\pm0.7})"] & \begin{array}{c}C_3H_8NH\\(-70.1\pm0.4)^a\end{array} \arrow[r, "(\mathbf{-21.7\pm1.2})"] & \begin{array}{c}C_4H_{10}NH\\(-91.8\pm1.1)^a\end{array} \arrow[r, "(\mathbf{-20.0\pm1.1})"] & \begin{array}{c}C_5H_{12}NH\\(-111.8\pm1.6)^b\end{array} \arrow[r, "(\mathbf{-20.7\pm1.5})"] & \begin{array}{c}C_6H_{14}NH\\(-132.5\pm2.2)^b\end{array} \\
\begin{array}{c}C_2H_4NH\\(126.5\pm0.8)^a\end{array} \arrow[u, "(\mathbf{-174.0\pm1.0})"] \arrow[r, "(\mathbf{-25.6\pm1.2})"] & \begin{array}{c}C_3H_6NH\\(100.9\pm1.4)^b\end{array} \arrow[u, "(\mathbf{-171.0\pm1.5})"] \arrow[r, "(\mathbf{-104.3\pm1.6})"] & \begin{array}{c}C_4H_8NH\\(-3.4\pm0.8)^a\end{array} \arrow[u, "(\mathbf{-88.4\pm1.4})"] \arrow[r, "(\mathbf{-43.8\pm1.0})"] & \begin{array}{c}C_5H_{10}NH\\(-47.2\pm0.6)^a\end{array} \arrow[u, "(\mathbf{-64.6\pm1.7})"] \arrow[r, "(\mathbf{-0.2\pm2.5})"] & \begin{array}{c}C_6H_{12}NH\\(-47.4\pm2.4)^c\end{array} \arrow[u, "(\mathbf{-85.1\pm3.3})"]
\end{tikzcd}$$

[a]Taken from ref 18. [b] Calculated according to the increment scheme. [c] This work.

Scheme 3. Enthalpic Increments for the Replacement of a CH_2 by a NH Fragment in Cyclic Compounds

	 cyclopropane (53.3 ± 0.5)[a]	 cyclobutane (27.7 ± 1.1)[a]	 cyclopentane (−76.4 ± 0.7)[a]	 cyclohexane (−123.3 ± 0.8)[a]	 cycloheptane (−118.1 ± 0.9)[a]
↑ $\Delta\Delta_f H^o_m$(NH)	(73.2 ± 0.9)	(73.2 ± 1.8)	(73.0 ± 1.1)	(76.1 ± 1.0)	(70.7 ± 2.6)
	 aziridine (126.5 ± 0.8)[a]	 azetidine (100.9 ± 1.4)[b]	 pyrrolidine (−3.4 ± 0.8)[a]	 piperidine (−47.2 ± 0.6)[a]	 azepan (−47.4 ± 2.4)[c]
↑ $\Delta\Delta_f H^o_m$(NCH_2CN)				(130.2 ± 1.3)	(127.1 ± 3.3)
				 1-piperidine acetonitrile (83.0 ± 1.2)[d]	 azepan-1-ylacetonitrile (79.7 ± 2.3)[c]

[a]Taken from ref 18. [b] Estimated according to Scheme 2. [c] This work. [d] Taken from ref 19.

value of (21.0 ± 0.9) kJ·mol^{-1} in both hydrocarbons and amines, confirming the constancy observed in Scheme 1. For compounds such as azetidine (C_3H_6NH), 1-pentanamine ($C_5H_{12}NH$), and 1-hexanamine ($C_6H_{14}NH$), there are no experimental data in the literature. To determine their enthalpy values from the hydrocarbons, the increments for insertion of one CH_2 fragment have been used, due to good agreement shown in Scheme 1.

2.6. Increments for Amine and Acetonitrile Functional Groups. The enthalpic increments for the replacement of a CH_2 by a NH fragment, $\Delta\Delta_f H_m^o(NH)$, in cyclic compounds in three to seven membered rings were calculated with values reported in Scheme 3. These incremental values are in excellent agreement, with a mean value of (73.2 ± 4.3) $kJ\cdot mol^{-1}$. In the same scheme are reported the enthalpic differences for the replacement of NH by the NCH_2CN fragment, $\Delta\Delta_f H_m^o(NCH_2CH)$, in cyclic compounds with six and seven membered rings, exhibiting a good consistency in the results.

3. CONCLUSIONS

This study presents an important contribution for understanding the strong link that exists between the effects of the conformational structure and energy.

The experimental data obtained for azepan and azepan-1-ylacetonitrile by calorimetric techniques enabled the calculation of the gas-phase enthalpy of formation of both compounds in fairly good agreement with the values obtained by theory. This good agreement suggests that the computational approach is appropriate for providing reliable estimates of enthalpies of formation in the gas phase for this class of compounds if accurate data exist for the other chemical species included in the working reactions. This is an important improvement on the evaluation of the energetic properties of this class of compounds and will have an inherent effect on their reactivity.

4. EXPERIMENTAL AND THEORETICAL METHODS

4.1. Materials, Purification Process, and Purity Control. The commercial samples of azepan (CAS Registry No. 111-49-9) supplied from Sigma-Aldrich and azepan-1-ylacetonitrile (CAS Registry No. 54714-50-0) from Alfa Aeser had mole fractions of 0.997 and 0.983, respectively. These samples were submitted to purification processes before the calorimetric studies, which consisted of distillation under reduced pressure until a degree of purity higher than 0.999 required for these studies was reached. The purity of the samples were assessed by gas−liquid chromatography, using a nonpolar capillary column with a bonded and cross-linked stationary phase composed by (5%-phenyl)-methylpolysiloxane (15 m of length × 0.530 mm i.d. × 1.5 μm film thickness). The average ratio of the mass of carbon dioxide recovered in the combustion experiments to those calculated from the mass of sample used in each experiment was also used to confirm the composition.

The compounds used in the calibration of the calorimetric systems were benzoic acid (CAS Registry No. 65-85-0) supplied by National Institute of Standard & Technology (NIST), Standard Reference Material (SRM) 39j,[20] and undecane (CAS Registry No. 1120-21-4) with a mole fraction purity higher than 0.99, obtained commercially from Sigma-Aldrich.

4.2. High Temperature Calvet Microcalorimetry. The standard (p° = 0.1 MPa) molar enthalpies of vaporization, $\Delta_l^g H_m^o$, of azepan and azepan-1-ylacetonitrile were determined using a Calvet high-temperature microcalorimeter. The technique used was adapted[21] from the drop-microcalorimetric technique for vacuum sublimation described by Skinner et al.[22] The details of the apparatus and experimental procedure are available in the literature.[23]

The temperature, T, of the hot reaction vessel of the calorimeter was predefined for the vaporization study of each compound: 334.6 K for azepan and 334.4 K for azepan-1-ylacetonitrile. The amounts of the samples ranged from 4 to 5 mg in the case of azepan and from 5 to7 mg in the case of azepan-1-ylacetonitrile. Thermal corrections for the glass capillary tubes were determined by performing individual blank correction experiments. This was done by dropping empty tubes of nearly equal mass, to within $\pm(1 \times 10^{-4})$ g, into each of the twin calorimetric cells.[23]

The microcalorimeter was calibrated in situ for the two working temperatures by performing vaporization experiments with undecane as a reference material, using its standard (p° = 0.1 MPa) molar enthalpy of vaporization at T = 298.15 K, $\Delta_l^g H_m^o$ = (56.58 ± 0.57) $kJ\cdot mol^{-1}$.[24] The calibration constants obtained from the average of six independent calibration experiments were k_{cal} = (1.0298 ± 0.0016) at T = 334.6 K and k_{cal} = (1.0202 ± 0.0035) at T = 334.4 K for azepan and azepan-1-ylacetonitrile vaporization experiments, respectively; the quoted uncertainty refers to the standard deviation of the mean for a level of confidence of 95%.

4.3. Combustion Calorimetry. The energies of combustion were determined by combustion calorimetry using an isoperibol calorimeter equipped with a static bomb (a twin valve bomb with an internal volume of 0.290 dm^3). Details of the apparatus and experimental procedure have been described previously.[25−27]

The energy equivalent of the calorimeter, ε(calor), was determined from the combustion of benzoic acid (NIST benzoic acid SRM 39j) having a certified massic energy of combustion of (−26434 ± 3) $J\cdot g^{-1}$,[20] when burnt under standard bomb conditions. The calibration procedure followed was the one suggested by Coops et al.[28] From six calibration experiments, ε (calor) was found to be (15551.2 ± 1.6) $J\cdot K^{-1}$, for an average mass of water added to the calorimeter of 2900.0 g; the quoted uncertainty refers to the standard deviation of the mean for a level of confidence of 95%.

For the combustion experiments, the liquid samples were sealed in Melinex bags (0.025 mm thickness). The samples were ignited in oxygen at T = (298.150 ± 0.001) K under a pressure of 3.04 MPa (the bomb was previously flushed to remove air) and with 1.00 cm^3 of deionized water inside the bomb. The combustion products were analyzed as follows: the carbon dioxide formed was collected in absorption tubes,[29] and the nitric acid produced was quantified by acid−base volumetry. The amount of compound burnt in each experiment was determined from the total mass of carbon dioxide produced, taking into account that formed from the combustion of the cotton thread fuse and of the Melinex. An estimated pressure coefficient of specific energy, $(\partial u/\partial p)_T$, at T = 298.15 K, was assumed to be −0.2 $J\cdot g^{-1}\cdot MPa^{-1}$, a typical value for organic compounds.[30] Corrections to the standard state, ΔU_Σ, and the calculation of the standard (p° = 0.1 MPa) massic energies of combustion of both compounds, $\Delta_c u^\circ$, were made following the procedure given by Hubbard et al.[31]

The relative atomic masses used throughout this paper were those recommended by the IUPAC Commission in 2011.[32]

4.4. Computational Methods. Standard ab initio molecular orbital calculations concerned were performed with the Gaussian03 series of programs.[33] Energies were obtained using the Gaussian03 theory, at the G3 level.

The natural bonding orbitals (NBO) analysis[16] were performed using the NBO 3.1 program as implemented in the Gaussian03 package software[33] at the B3LYP/6-31G(*d*,*p*) level.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Table S1 with the standard molar heat capacities in the gaseous phase for azepan and azepan-1-ylacetonitrile, derived from statistical thermodynamics using the vibrational frequencies calculated at the HF/6-31G(*d*) level of theory; Tables S2 and S3 with the typical combustion results and standard massic energy of combustion, at T = 298.15 K, for azepan and azepan-1-ylacetonitrile, respectively; Tables S4 and S5 with MP2-(Full)/6-31G(*d*) optimized atom coordinates for azepan and azepan-1-ylacetonitrile, respectively; Table S6 with the G3 enthalpies, and experimental gas-phase standard molar enthalpies of formation, at T = 298.15 K, for azepan, azepan-1-ylacetonitrile, and the auxiliary species used; Tables S7 and S8 with the absolute standard enthalpies and entropies obtained by the G3 method for the azepan and azepan-1-ylacetonitrile conformers, respectively, and the corresponding derived gas-phase standard molar enthalpies, entropies, and Gibbs energies of formation, at T = 298.15 K, and the conformational composition. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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