The First Direct Experimental Determination of Strain in Neutral and Protonated 2-Azetidinone

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Abstract: The standard molar enthalpies of combustion, sublimation, and formation in the crystalline and gaseous state at a temperature of 298.15 K have been experimentally determined for the title compound (**1**) and for *N*-methylacetamide (**2**). These results have been combined with their gas-phase proton affinities to yield the standard enthalpies of formation of the species $\mathbf{1}H^+(g)$ and $\mathbf{2}H^+(g)$. These magnitudes have also been computed at the G2-(MP2) level. The agreement between experimental and theoretical results is very good. This information has been used to determine the strain in the neutral and protonated β-lactam ring in the absence of solvent.

Almost seventy years after the first report on the antibacterial properties of penicillin, β-lactam antibiotics still remain the most widely prescribed compounds for the treatment of infectious diseases.[1]

Most β-lactam antibiotics are bicyclic.[1] Some, including the more recently discovered[2] monobactams, are monocyclic. In all cases, the 2-azetidinone (**1**) ring is present and is currently considered as the minimal structural unit for antibiotic activity for these families of compounds.

A four-membered ring such as that of **1** is strained. The potential influence of this strain in determining the biological activity of these compounds and/or their destruction by bacterial β-lactamases has been the subject of many important studies.[3] As far back as in 1949, Woodward and co-workers reported the first combustion calorimetry studies of penicillins.[4] Thus, it is a remarkable fact that *so far, the quantitative value of the strain in the isolated β-lactam ring has never been experimentally determined*. This situation has prompted us to carry out this determination and to compare the results of this study with theoretically computed values, including our own and those recently obtained by other workers. This information is also combined with gas-phase thermodynamic data for the protonation reaction 1 and similar processes for appropriate reference compounds to determine the intrinsic (i.e., gas phase) strain energy in the protonated form of **1**(g), $\mathbf{1}H^+(g)$. These results, we believe, are also relevant in their own right, inasmuch as **1** features a highly strained amide functionality.

$$\mathbf{1}(g) + H^+(g) \rightarrow \mathbf{1}H^+(g) \qquad (1)$$

The present study involves the following:

(1) The first step is the determination of the standard enthalpies of formation in the gas phase of **1** and *N*-methylacetamide (**2**), an appropriate open-chain reference compound. This was carried out by combustion calorimetry and by the measurement of their vapor pressures over a 18 K temperature interval. The energies of combustion have been determined using a static bomb calorimeter.[5] The vapor pressures of the compounds were measured by means of the Knudsen-effusion technique[6] and the enthalpies of sublimation were deduced from the temperature dependence of the vapor pressures (Clausius−Clapeyron).[6] Heat capacity measurements were carried out by means of Differential Scanning Calorimetry.[6] Full experimental details are given as Supporting Information. From the experimental results, the standard molar enthalpies of combustion, sublimation, and formation in the crystalline and gaseous state at a temperature of 298.15 K have been derived and are reported in Table 1.

Consider reaction 2, the hydrogenation of **1** to yield **2**:

$$\mathbf{1}(g) + H_2(g) \rightarrow \mathbf{2}(g) \qquad \Delta H^\circ_{(2)} \qquad (2)$$

Using the data given in Table 1, we get $\Delta H^\circ_{(2)} = -(152.0 \pm 5.6)$ kJ/mol.

The values of the standard enthalpies of formation in the gas phase of cyclobutane (**3**) and butane (**4**) are respectively equal to 28.5 ± 0.8 and $-(126.4 \pm 0.4)$ kJ/mol.[7] Thus, we get a value of $-(154.9 \pm 0.9)$ kJ/mol for $\Delta H^\circ_{(3)}$, the standard enthalpy

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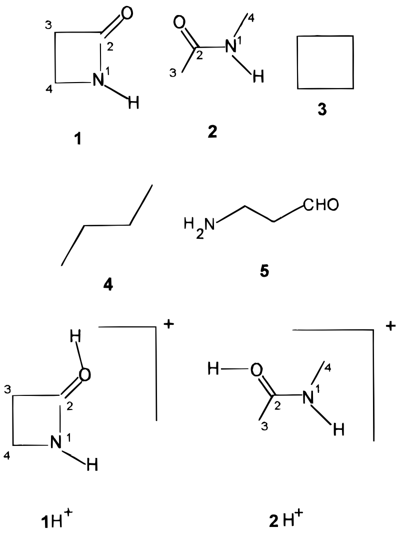
Table 1. Experimentally Determined Standard Molar Energies of Combustion and Standard Molar Enthalpies of Combustion, Sublimation, and Formation in the Crystalline and Gaseous State at Temperature $T = 298.15$ K

	2-azetidinone[a,b]	*N*-methylacetamide[a,b]
$\Delta_c U°_m$[c]	-1721.1 ± 0.8	-1860.2 ± 5.1
$\Delta_c H°_m$[d]	-1721.7 ± 0.8	-1862.1 ± 5.1
$\Delta_s H°_m$[e]	77.4 ± 0.3	70.8 ± 2.0
$\Delta_f H°_m(\text{cr})$[f]	-173.4 ± 0.9	-318.8 ± 5.1
$\Delta_f H°_m(\text{g})$[g]	-96.0 ± 0.9	-248.0 ± 5.5

[a] All values in kJ/mol. [b] This work. [c] Standard molar energy of combustion. [d] Standard molar enthalpy of combustion. [e] Standard molar enthalpy of sublimation. [f] Standard molar enthalpy of formation in the crystalline state. [g] Standard molar enthalpy of formation in the gaseous state.

Chart 1



change for the model hydrogenation reaction 3:

$$\mathbf{3}(g) + H_2(g) \rightarrow \mathbf{4}(g) \qquad \Delta H°_{(3)} \qquad (3)$$

$\Delta H°_{(2)}$ and $\Delta H°_{(3)}$ are essentially equal within the combined limits of error and this strongly suggests that the differential strain effects in the couples **1**/**2** and **3**/**4** are practically the same. Indeed, eqs 2 and 3 can be combined to give eq 4. Its standard enthalpy change, $\Delta H°_{(4)}$, equals 2.9 ± 5.7 kJ/mol and is practically nil on account of the size of the experimental error.

$$\mathbf{1}(g) + \mathbf{4}(g) \rightarrow \mathbf{2}(g) + \mathbf{3}(g) \qquad \Delta H°_{(4)} \qquad (4)$$

We notice that reactions 2 and 3 involve the breaking of one C−C bond and the formation of two C−H bonds. In the case of **1**, however, one might also consider the breaking of the C−N bond in the lactam (amide) moiety. One model reaction for this process would be the hydrogenation of **1**(g) to yield gaseous 3-aminopropanal (**5**). It is unfortunate, however, that the experimental standard enthalpy of formation of this compound is not available. An alternative approach is the comparison of the standard enthalpies for the hydrolysis reactions (in the gas phase) of **1** and **2**, reactions 5 and 6:

$$\mathbf{1}(g) + H_2O(g) \rightarrow H_2N(CH_2)_2COOH(g) \qquad \Delta H°_{(5)} \qquad (5)$$

$$\mathbf{2}(g) + H_2O(g) \rightarrow H_2NCH_3(g) + CH_3COOH(g) \qquad \Delta H°_{(6)} \qquad (6)$$

Using the experimental standard enthalpies of formation in the gas phase for the various species,[7] we get $\Delta H°_{(5)} = -(84.8 \pm 2.3)$ kJ/mol and $\Delta H°_{(6)} = 34.6 \pm 5.2$ kJ/mol. The difference between these magnitudes, $\Delta H°_{(6)} - \Delta H°_{(5)} = 119.4 \pm 5.7$ kJ/mol, can be taken as a phenomenological measure of the relief of strain attending the opening of the β-lactam ring. The possibility exists for $H_2N(CH_2)_2COOH(g)$ to have a chelated structure.[8] Thus, the value of 119.4 kJ/mol is perhaps better considered as an upper limit for the value of this strain. These results can be compared to Domalski's[9] tabulated ring strain for **3**(g), 110.9 kJ/mol. Important information on the β-lactamase-catalyzed hydrolysis of aqueous penicillin G has become available through work by Kishore, Tewari, Yap, and Goldberg.[10] These authors were able to determine the difference between the standard enthalpies of hydrolysis of penicillin G(aq) and *N*,*N*-dimethylacetamide(aq), getting a value of 116 kJ/mol. In the hydrolysis of penicillin G(aq), the β-lactam ring opens up, in a reaction akin to reaction 5, and it seems fair to compare this value with $\Delta H°_{(6)} - \Delta H°_{(5)} = 119.4 \pm 5.7$ kJ/mol. Clearly, the agreement is excellent. This strongly suggests that the difference between the enthalpies of hydrolysis of penicillin G and *N*,*N*-dimethylacetamide reflects indeed the release of the internal strain of the β-lactam ring and also that differential medium effects between both processes are very small.

(2) The next step is the determination, using entirely experimental data, of the standard enthalpy changes for reaction 7, namely $\Delta H°_{(7)}$:

$$\mathbf{1}H^+(g) + H_2(g) \rightarrow \mathbf{2}H^+(g) \qquad \Delta H°_{(7)} \qquad (7)$$

The $\Delta_f H°_m(g)$ values for $\mathbf{1}H^+(g)$ and $\mathbf{2}H^+(g)$ can be determined by combining the $\Delta_f H°_m(g)$ values for **1**(g) and **2**(g) given in Table 1 with the proton affinities of these compounds[11,12] available from a previous study.[13−15] These values are the following: $\Delta_f H°_m(\mathbf{1}H^+,g) = 586.4 \pm 2.3$ and $\Delta_f H°_m(\mathbf{2}H^+,g) = 398.8 \pm 5.9$ kJ/mol. From these results we get $\Delta H°_{(7)} = -(187.6 \pm 6.4)$ kJ/mol. By analogy with reaction 4, reaction 8 can be constructed. A value of $-(32.7 \pm 6.4)$ kJ/mol obtains for $\Delta H°_{(8)}$:

$$\mathbf{1}H^+(g) + \mathbf{4}(g) \rightarrow \mathbf{2}H^+(g) + \mathbf{3}(g) \qquad \Delta H°_{(8)} \qquad (8)$$

The difference between $\Delta H°_{(8)}$ and $\Delta H°_{(4)}$ equals 35.6 kJ/mol. This indicates that, with respect to the neutral couple **3**/**4**, *the strain in the couple* ***1/2*** *increases by this amount upon protonation*. We emphasize that this measure of "strain" is purely phenomenological. The electronic origin of the structural

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(7) Values taken from: Lias, S. G.; Liebman, J. F.; Levin, R. D.; Kafafi, S. A. *NIST Standard Reference Database 25. Structures and Properties, Version 2.02*; National Institute of Standards and Technology: Gaithersburg, MD 20899, 1994.

(8) This structure would be that of a six-membered ring.

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(11) The proton affinity of a base B in the gas phase is the negative of the standard enthalpy change for the reaction $B(g) + H^+(g) \rightarrow BH^+(g)$.

(12) The proton affinities of **1** and **2** relative to ammonia amount to 2.5 and 38.1 kJ/mol respectively.[13] These values were combined with that of the proton affinity of ammonia, 851.4 kJ/mol,[14] and the standard enthalpy of formation of $H^+(g)$, 1530 kJ/mol.[15]

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Table 2. Computed (MP2=FULL/6-31G(d))[a] and Experimental Values for Selected Structural Parameters for **1**(g), **1H**$^{+}$(g), **2**(g), and **2H**$^{+}$(g)

structural parameters	**1**(g) exptl[c]	**1**(g) computed	**1H**$^{+}$(g)[b] computed	**2**(g) exptl[d]	**2**(g) computed	**2H**$^{+}$(g)[b] computed
bond distances[e,f]						
N−C2	1.380(2)	1.375	1.305	1.386(2)	1.366	1.300
N−C4	1.479(3)	1.463	1.488	1.469(6)	1.449	1.474
C2−C3	1.537(3)	1.541	1.502	1.520(5)	1.513	1.486
C3−C4	1.553(5)	1.547	1.556			
C2=O	1.201(1)	1.215	1.296	1.225(3)	1.231	1.315
N−H	0.990(3)	1.014	1.022		1.010	1.017
O−H			0.981			0.980
bond angles[f,g]						
NC2C3	91.1(2)	90.8	95.7	114.1(15)	115.0	123.4
NC4C3	87.6(1)	87.3	86.5			
C2NC4	95.3(2)	95.8	93.9	119.7(8)	122.1	123.8
C2C3C4	86.0(2)	86.1	83.9			
NC2O	132.3(5)	133.1	126.1	121.8(4)	123.0	115.1
OC2C3	136.6(3)	136.2	138.2	118.5(12)	122.0	121.5
C2OH			112.4			112.1
C4NC2C3[h]	0.0	0.0	0.0	0.0	2.9	0.0

[a] This work. [b] Only the computed values are available. [c] From ref 18. [d] From ref 19. [e] All values in Å. [f] Experimental uncertainties given in parentheses. [g] All values in degrees. [h] Dihedral angle.

effects on the difference in basicity of **1**(g) and **2**(g) has been discussed in ref 13 and in an important theoretical study by Greenberg, Liebman, and Hsing.[16] It is interesting that, in a different study, Greenberg[17] was able to estimate the ring strain in **1** at 127 kJ/mol, a value in fair agreement with our present findings.

(3) In the latter work, it was shown that, as regards several thermodynamic magnitudes of **1**(g) and **1**H^{+}(g), HF/6-31G(d)//6-31G(d) data outperformed in some cases the results obtained at the MP2/6-31G(d)//6-31G(d) level. We thus felt it necessary to carry out a study at the G2(MP2) level. Smith and Radom have shown that G2 theory predicts energetic properties of neutral molecules and positive ions to within the so-called "chemical accuracy" (roughly 2 kcal mol^{-1}). The G2 level of theory corresponds effectively to QCISD(T)/6-311+G(3df,2p)//MP2=FU/6-31G(d) calculations with HF/6-31G(d) scaled zero-point vibrational and isogyric corrections. G2(MP2) is a variation of G2 theory providing substantial savings in computational time and disk storage. In this method, the basis-set-extension corrections are obtained at the MP2 level.

Selected structural parameters for **1**, **2**, **1**H^{+}, and **2**H^{+} as determined in this study at the MP2=FU/6-31G(d) level are presented in Table 2 together with the experimental data obtained by electron diffraction alone (**2**(g)) or by the combination of electron diffraction and microwave spectrometry (**1**(g)).

From these data it can be seen that the agreement between the experimental and calculated values (whenever available) is quite satisfactory. Thus, the average unsigned differences in heavy-atom distances and bond angles are 0.009 and 0.013 Å and 0.4° and 2° respectively for **1** and **2**.

The energetics for the relevant species involved in this study are presented in Table 3.

From these data, the following conclusions are drawn:

Table 3. Results of the G2(MP2) ab Initio Calculations on the Neutral and Protonated Forms of **1** and **2** (All values in hartrees)

compd	*E* (0 K)[a]	ZPE[b]	TCE[c]	*H* (298 K)[d]
2-azetidinone, **1**	−246.87622	0.08705	0.09258	−246.87039
1H^{+} (at N)	−247.19068	0.10141	0.10697	−247.18478
1H^{+} (at O, syn to N)	−247.19843	0.10151	0.10682	−247.19275
1H^{+} (at O, anti to N)	−247.20113	0.10164	0.10697	−247.19544
N-methylacetamide, **2**	−248.09195	0.10956	0.11702	−248.08413
2H^{+} (at O, syn to N)	−248.42585	0.12422	0.13131	−248.41833
2H^{+} (at O, anti to N)	−248.43009	0.12425	0.13144	−248.42248

[a] Energy values at 0 K, at the G2(MP2) level. [b] Zero-point vibrational energies, at the HF/6-31G(d) level. [c] Thermal correction to enthalpies, at the HF/6-31G(d) level. [d] Enthalpy values at 298 K, at the G2(MP2) level.

(a) Combining the G2(MP2) enthalpies of **1**(g) and **2**(g) with the appropriate experimental and G2(MP2) enthalpies for the isolated atoms, we obtain the computed G2(MP2) values for the standard enthalpies of formation of **1**(g) and **2**(g), namely −(100.0) and −(237.7) kJ/mol. These results agree quite satisfactorily with the experimental values.

(b) At this level, oxygen-protonation of **1**(g) is seen to be favored over nitrogen-protonation. We also confirm that in the most stable tautomer of **1**H^{+}(g), the OH group is in an *anti* position with respect to the NH group and that an analogous situation prevails in the case of **2**H^{+}(g).

(c) The proton affinities of **1**(g) and **2**(g) computed at the G2(MP2) level are 859.6 and 894.5 kJ/mol, in excellent agreement with the experimental values,[13] respectively equal to 854.0 ± 3.1 and 889.5 ± 5.9 kJ/mol.

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Supporting Information Available: Experimental details and results and tables of physical properties, results of combustion experiments, vapor pressures, and standard molar energies and enthalpies of combustion and ethalpies of formation (12 pages). See any current masthead page for ordering and Internet access instructions.

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