# Gas-Phase Basicities of β-Lactams and Azetidines. Cyclization Effects. An Experimental and Theoretical Study

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**Abstract:** The gas-phase proton affinities of selected β-lactams, amides, cyclic and acyclic ketones, azetidine, and acyclic amines were measured by FTICRMS techniques. SCF and MP2 calculations at different levels of accuracy have been performed for the different neutral and protonated species, as well as a topological analysis of the electronic charge density. Our results, both experimental and theoretical, show that β-lactams are weaker bases, in the gas phase, than acyclic amides. The attenuation of basicity upon cyclization of 2-azetidinone is stronger than that found for cyclic ketones of similar size due to the existence of a negative hyperconjugation effect. Our ab initio calculations indicate that both β-lactams and acyclic amides are oxygen bases, but the gap between the oxygen and nitrogen intrinsic basicities is much smaller in the former due to the aforementioned cyclization effects. This is the result of charge redistributions due to the hybridization changes at the carbonyl carbon, which are very well described by a topological analysis of the corresponding electronic charge densities. On the contrary the cyclization effects on the gas-phase basicities of amines are almost negligible, and azetidine presents a gas-phase basicity practically equal to that of *N*-methylethanamine. Our topological analysis of bond activations of these species upon protonation reveals that for 2-azetidinone these effects are not dramatic when protonation takes place at the oxygen atom, whereas they are quite significant if protonation takes place at the ring nitrogen. Bond activations are also important in protonated azetidine and, in general, are slightly attenuated in the corresponding *N*-methyl derivatives.

## Introduction

Over the past two decades a considerable number of experimental studies have been undertaken with the aim of obtaining quite precise gas-phase protonation energies of organic and inorganic bases. This led to a rapid accumulation of data[1] on the intrinsic basicity of different systems in the absence of any solvent interaction.

In our research on the gas-phase basicity of different organic bases we have focused our attention on the behavior of lactams for several reasons: (a) they are typically bidentate bases with two different active centers, (b) they are basic constituents of antibiotics[2] such as penicillins and cephalosporins, (c) it was assumed that their enhanced reactivity was due to the strain in the four-membered ring,[3] and (d) to our knowledge their gas-phase basicities have not been reported in the literature so far.

Regarding point c, it should be mentioned that there is a continuing interest in the unimolecular decomposition of different molecular ions in the gas phase, in particular of those produced upon protonation of neutral species. A typical example is provided by ethyloxonium ion,[4-7] which is the result of the gas-phase protonation of ethanol. Therefore, it would be quite illustrative to investigate whether lactams may undergo a ring-fragmentation process upon protonation, or whether proton association produces significant activations of the bonds of the four-membered ring even though it does not lead to bond cleavage. The specific study of bond activations in the gas-phase molecular ions is, on the other hand, of great importance in the elucidation of the mechanisms involved in the intramolecular ion-molecule reactions[8-11] and fragmentation pathways of metastable ions related to their mass-analyzed ion kinetic energy (MIKE) spectra,[12-16] as well as in catalysis.[17]

The first problem that will be addressed in this work, both experimentally and theoretically, is whether lactams are oxygen or nitrogen bases in the gas phase. This problem is directly related to the intrinsic basicity of amides, in general. Therefore we shall pay special attention to the comparison of the basicity of lactams with respect to the related aliphatic amides in an effort to understand possible cyclization effects in their intrinsic basicities. As we shall discuss later, a good comprehension of the factors involved in the changes of intrinsic basicity upon cyclization requires a similar analysis for those compounds which present only one type of basic center, i.e., ketones and amines. Accordingly, we shall also present, in this paper, an investigation of the proton

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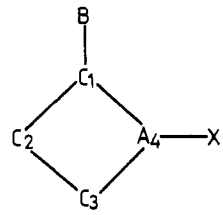
**Chart I**




A= N or C
B= O or H
X= C or H

affinities of azetidine, *N*-methylazetidine, and cyclobutanone with respect to the corresponding aliphatic amines and ketones, respectively. Hence, 10 different neutral species have been considered: cyclobutanone (**1**), 2-butanone (**2**), azetidine (**3**), *N*-methylethanamine (**4**), 2-azetidinone (**5**), *N*-methylacetamide (**6**), *N*-methylazetidine (**7**), *N*,*N*-dimethylethanamine (**8**), *N*-methyl-2-azetidinone (**9**), and *N*,*N*-dimethylacetamide (**10**).

Since, as we have mentioned above, the biochemical activity of some β-lactam derivatives may be directly related to possible C–N or C–C bond cleavage,[3] we have also considered of interest to investigate, from a theoretical point of view, the relative stability of different open isomeric forms of the N-protonated β-lactam.

## Experimental Section

**1. Materials.** Compounds **1**, **3**, and **5** were commercial products of the highest purity available. **1** and **3** were purified by preparative GLC, and **5** was purified by sublimation. Their structures were confirmed by IR, NMR, and MS techniques.

Compound **9** was synthesized[18] as follows: to a solution of ethyl β-(methylamino)propionate, $CH_3NHCH_2CH_2COOC_2H_5$ (1.3 g, 0.01 mol), in 25 mL of dry ether was added a solution of 5 mL (0.01 mol) of 2.0 M ethylmagnesium chloride in ethyl ether as fast as the evolution of gas would permit. The mixture was allowed to stand at room temperature for 1.5 h with stirring. The magnesium compounds were decomposed with an excess of saturated $NH_4Cl$ solution, and the aqueous phase was extracted repeatedly with chloroform. The organic solutions were combined, washed with a 10% HCl solution, and dried over magnesium sulfate. The solution was evaporated under vacuum, and the residue was distilled at 70–75 °C at 20 Torr to yield 1.3 g (15%) of 1-methylazetidine-2-one: IR 1735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) 82.83 (3 H, s), 2.94 (2 H, t, $J$ = 3.9 Hz), 3.23 (2 H, t, $J$ = 3.9 Hz).

**2. Gas-Phase Basicities.** The gas-phase basicities were determined using a modified Brucker CMS-47 FTICR mass spectrometer.[18] Working conditions have already been described.[19] The average cell temperature is ca. 333 K. In every case, the existence of an equilibrium was checked through double-resonance experiments.

## Computational Details

Gradient techniques[20] were used to determine the geometrical structures of the species **1–10** and their corresponding protonated species (see Figure 1). In this respect, it must be taken into account that for those species which present two basic centers, both oxygen-protonated (**5H**$^+$, **6H**$^+$, **9H**$^+$, and **10H**$^+$) and nitrogen-protonated (**5NH**$^+$, **6NH**$^+$, **9NH**$^+$, and **10NH**$^+$) forms have been considered. Figure 1 also includes two isomeric forms (**11** and **12**) of the N-protonated β-lactam (**5NH**$^+$), which were found to be local minima of the corresponding energy surface. These optimizations were carried out at the 3-21G level.[21] Since the inclusion of polarization functions in the basis set may play an important role in descriptions of ion–molecule interactions, the structures of compounds **1–6** and their protonated forms were reoptimized at the 6-31G* level.[22] For the sake of simplicity we have adopted the same numbering scheme for all cyclic compounds including in this study (see Chart I).

The harmonic vibrational frequencies were determined by analytical second-derivative techniques and used to characterize stationary points of the potential energy surface and to evaluate zero-point energies, which were scaled by the empirical factor of 0.89.[23]

Protonation energies were obtained as the 6-31G* energy difference between protonated and unprotonated species. For azetidine and *N*-methylethanamine, where cyclization effects on their gas-phase basicities (as we shall show later) are quite small, the protonation energies were recalculated at the 6-31+G(d,p)//6-31+G(d,p) level,[24] since it has been claimed that the inclusion of diffuse p components in the basis set may be important in descriptions of protonation reactions. The protonation energies so obtained are affected by the so-called basis set superposition error (BSSE). This error has been estimated using the counterpoise method of Boys and Bernardi.[25] We cannot assume a priori that correlation effects are negligible when analyzing cyclization effects on the intrinsic basicities of the compounds considered here. Hence for compounds **1–6** correlation contributions to the protonation energies were calculated using the Moller–Plesset perturbation theory at second order (MP2//6-31G*). For azetidine and *N*-methylethanamine these post-Hartree–Fock calculations were also carried out at the 6-31+G(d,p) level. All calculations have been performed using the GAUSSIAN.86 series of programs.[26]

We have shown[27] recently that bond activations in ion–molecule interactions can be described quantitatively by means of a comparative topological analysis of the electronic charge densities of the neutral isolated molecule and that of the molecule within the complex. As it has been shown by Bader,[28-30] the Laplacian of the electronic charge density ($\nabla^2\rho$) identifies regions of space wherein the electronic charge is locally concentrated ($\nabla^2\rho < 0$) or depleted ($\nabla^2\rho > 0$). Therefore, an inspection of the variations of this quantity upon complexation permits one to localize those bonds which have become activated and therefore show a smaller absolute value of $\nabla^2\rho$. This information may be nicely complemented by locating the corresponding bond critical points, i.e., points where the electronic charge density presents one positive curvature ($\lambda_3$) along the bond and two negative ones ($\lambda_1$ and $\lambda_2$) in the other directions. The values of $\rho$ and $\nabla^2\rho$ at these critical points often yield quantitative information on the nature and strength of the linkage.

On the other hand, the nonbonded maxima in the valence-shell charge concentrations of the base may also provide information about its relative base strength.[31] These nonbonded charge concentrations correspond to maxima of $|\nabla^2\rho|$ and are associated with a lone pair of electrons. Therefore, in an effort to rationalize the cyclization effects on the intrisic basicities of the compounds under consideration, we shall also locate the critical points of the Laplacian of the charge density for each neutral base. Then the

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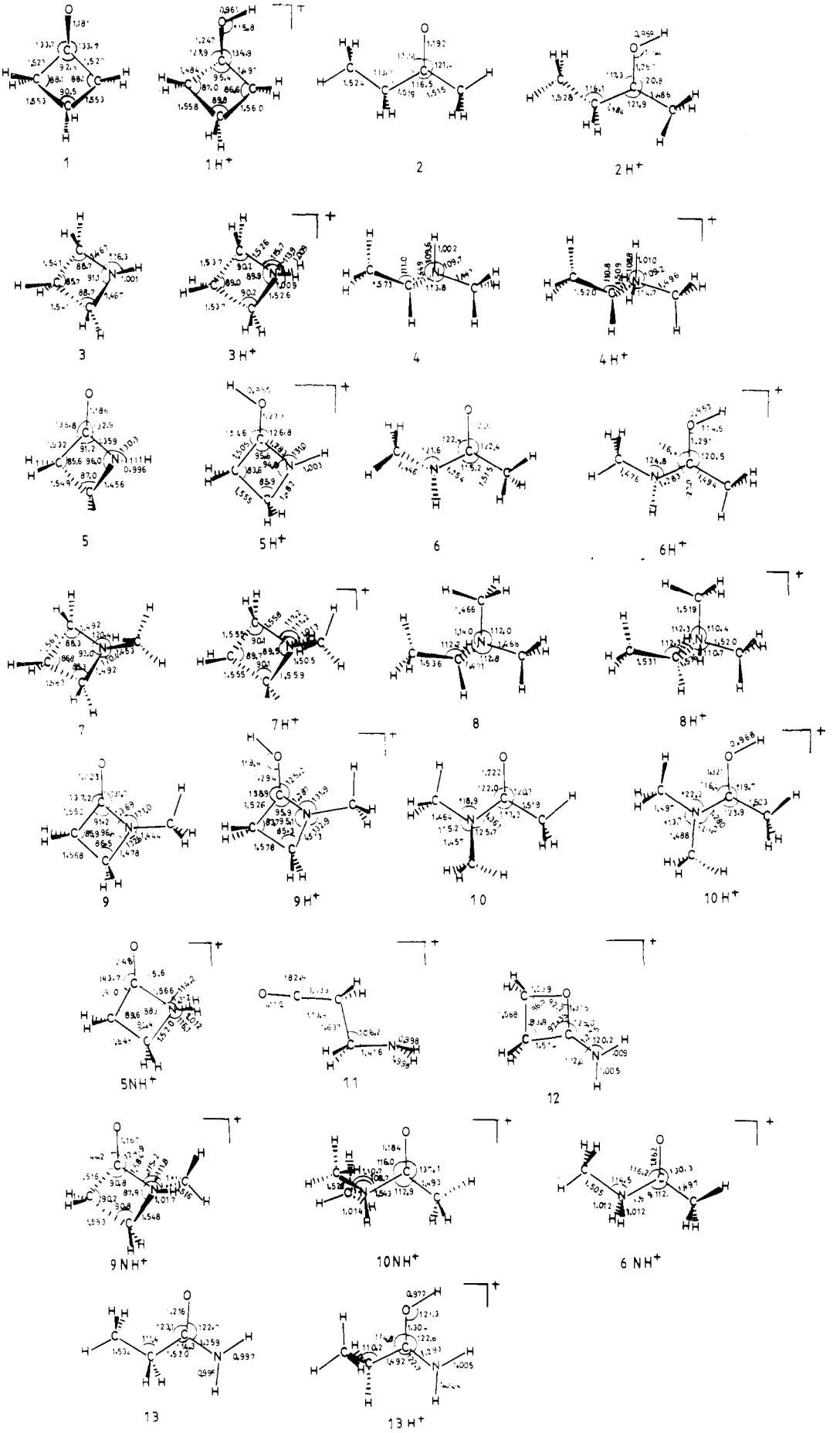


Figure 1. Optimized structures (bond angles in deg, bond lengths in Å). For species **1**, **1H**$^+$, **2**, and **2H**$^+$: 6-31G*. For species **3**, **3H**$^+$, **4**, and **4H**$^+$: 6-31+G(d,p). For the remaining species: 3-21G.

**Table I.** Total Energies[a] and Scaled Zero Point Energies[b] for the Systems Included in This Study

| | 3-21G//3-21G | | 6-31G*//3-21G | 6-31G*//6-31G* | | | 6-31+G(d,p)//6-31+G(d,p) | | |
|---|---|---|---|---|---|---|---|---|---|
| compd | SCF | ZPE | SCF | SCF | ZPE | MP2 | SCF | ZPE | MP2 |
| **1** | −228.511 58 | 61.3 | −229.796 95 | −229.798 19 | 61.6 | −230.481 09 | | | |
| **1H$^+$** | −228.832 81 | 69.1 | −230.117 60 | −230.120 00 | 69.9 | −230.789 56 | | | |
| **2** | −229.709 34 | 75.9 | −230.997 08 | −230.998 04 | 75.8 | −231.688 35 | | | |
| **2H$^+$** | −230.039 60 | 83.7 | −231.324 16 | −231.326 11 | 84.2 | −232.004 72 | | | |
| **3** | −171.117 35 | 66.8 | −172.075 89 | −172.078 77 | 67.5 | −172.628 03 | −172.095 60 | 67.0 | −172.696 34 |
| **3H$^+$** | −171.513 69 | 76.6 | −172.457 58 | −172.459 78 | 77.3 | −173.001 74 | −172.477 03 | 77.0 | −173.069 37 |
| **4** | −172.316 58 | 81.2 | −173.275 14 | −173.276 49 | 81.5 | −173.833 01 | −173.296 27 | 80.8 | −173.918 12 |
| **4H$^+$** | −172.709 05 | 91.4 | −173.654 42 | −173.655 64 | 91.8 | −174.208 47 | −173.675 66 | 91.1 | −174.291 99 |
| **5** | −244.432 94 | 54.5 | −245.808 77 | −245.810 39 | 54.7 | −246.525 07 | | | |
| **5H$^+$** | −244.779 23 | 62.9 | −246.152 12 | −246.155 05 | 63.8 | −246.854 58 | | | |
| **5NH$^+$** | −244.775 81 | 62.9 | −246.138 94 | −246.141 46 | 63.6 | −246.859 44 | | | |
| **6** | −245.629 67 | 68.7 | −247.005 14 | −247.006 10 | 68.7 | −247.726 79 | | | |
| **6H$^+$** | −245.993 91 | 77.5 | −247.360 77 | −247.362 68 | 78.0 | −248.075 12 | | | |
| **6NH$^+$** | −245.967 79 | 77.6 | −247.333 83 | −247.335 71 | 78.0 | −248.056 54 | | | |
| **7** | −209.934 65 | 85.5 | −211.109 50 | | | | | | |
| **7H$^+$** | −210.336 16 | 95.6 | −211.496 46 | | | | | | |
| **8** | −211.129 55 | 100.2 | −212.302 73 | | | | | | |
| **8H$^+$** | −211.528 98 | 110.4 | −212.688 67 | | | | | | |
| **9** | −283.250 56 | 73.2 | −284.843 85 | | | | | | |
| **9H$^+$** | −283.605 89 | 81.6 | −285.195 30 | | | | | | |
| **9NH$^+$** | −283.600 85 | 82.0 | −285.180 33 | | | | | | |
| **10** | −284.439 34 | 87.9 | −286.029 11 | | | | | | |
| **10H$^+$** | −284.810 35 | 96.3 | −286.390 43 | | | | | | |
| **10NH$^+$** | −284.791 40 | 96.8 | −286.371 58 | | | | | | |
| **11** | −244.749 81 | 60.9 | −246.121 54 | | | | | | |
| **12** | −244.782 61 | 63.3 | −246.155 68 | | | | | | |
| **13** | −245.637 90 | 69.3 | −247.010 85 | | | | | | |
| **13H$^+$** | −245.990 68 | 78.0 | −247.356 64 | | | | | | |

[a] In atomic units. [b] In kilocalories/mole.

value of the electronic density at these critical points, which will be a measure of the electronic density associated with the corresponding lone pair, will be evaluated.

## Results and Discussion

**1. Structures.** The optimized structures of the species under investigation have been schematized in Figure 1. All of them correspond to minima (they have no imaginary harmonic frequencies) of the potential surface. The corresponding total energies as well as the scale ZPE corrections are given in Table I. Although some of these structures, as that of azetidine[32] ($C_s$), cyclobutanone[33] ($C_s$), *N*-methylacetamide,[34] and 2-azetidinone,[35] already have been reported in the literature at the same or similar levels of calculation, we have included them in Figure 1 for the sake of a better comparison with the structures of the corresponding protonated species. Although a detailed discussion of the geometrical characteristics of the species under investigation is not the aim of this paper, several features deserve some comment: (a) The 6-31+G(d,p) optimized structure of azetidine is very similar to the 6-31G* structure,[32] and more importantly, the degree of puckering (25.3°) does not change appreciably when diffuse components are included in the basis set and is not significantly different from recent microwave and electron diffraction estimates (29° ± 1.4°).[36] (b) Our 3-21G and 6-31G* results predict a puckering angle for cyclobutanone of 9.8° and 9.9°, respectively, in contrast with previous ab initio calculations[33] but in fairly good agreement with the most recent experimental estimates.[37] Also the vibrational frequency (45 cm$^{-1}$) calculated for the puckering vibration is in reasonable agreement with the experimental assignment.[38] The remaining structural parameters are also in accord with microwave values.[37-39] (c) Our results for 2-azetidinone are in good agreement with microwave and electron diffraction data,[35] but in contrast with the ab initio calculations reported in ref 35, our 6-31G* calculations predict a non-negligible degree of pyramidalization of the N–H group, with the hydrogen atom 10.0° out of the molecular plane. This discrepancy has its origin in the fact that, in ref 34, the dihedral angles involving the two hydrogens of the methylene groups were kept indentical, hence the rocking movement of these two groups was not allowed, and accordingly the NH group was found to lie in the plane of the molecule. A comparison of our results with those of Sedano et al.[40] also shows that an appropriate description of the pyramidalization at the nitrogen in these kinds of systems requires the inclusion of polarization functions in the basis set.[41] (d) The structure found for the cycle of 2-azetidinone is not very different from the structures experimentally found for some β-lactam antibiotics.[42] (e) Our optimized structure for *N*-methylacetamide is in fairly good agreement with the electron diffraction structure of Kitano et al.[43]

**2. Protonation Energies.** FTICRMS[1a,b,g] measurements provide the standard free-energy change, $\delta\Delta G_{H^+}$ (g), for proton-transfer reaction 1 in the gas phase between a given base B and a reference compound $B_{ref}$:

$$BH^+(g) + B_{ref}(g) \rightarrow B(g) + B_{ref}H^+(g) \qquad \delta\Delta G_{H^+}(g) \quad (1)$$

The gas-phase proton basicity GB of B is the negative of $\Delta G_{H^+}(g)$, the standard free-energy change for reaction 2:

$$B(g) + H^+(g) \rightarrow BH^+(g) \qquad \Delta G_{H^+}(g) \quad (2)$$

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Table II. Experimental Determination of the Gas-Phase Basicities of Selected Ketones, Imines, and Lactams[a]

| compd[b] | std | $\Delta\Delta G_{H^+}$ (std)[c] | $\delta\Delta G_{H^+}$(g) | $\Delta\Delta G_{H^+}$(g) | $\Delta\Delta G_{H^+}$(g) (av) | $\Delta PA$[d] |
|---|---|---|---|---|---|---|
| 1 | $HCO_2$-$n$-$C_3H_7$ | $11.0_3$ | $-0.0_6$ | $10.9_7$ | | |
| | $n$-$C_3H_7CN$ | $12.1_5$ | $-1.1_8$ | $10.9_7$ | 10.9 ± 0.1[e] | −12.4 |
| | $C_6H_5CN$ | $9.0_0$ | $+1.8_1$ | $10.8_1$ | | |
| 3 | 3-$CH_3C_5H_4N$ | $-22.8_4$ | $+0.3_5$ | $-22.4_9$ | | |
| | $t$-$C_5H_{11}NH_2$ | $-21.6_0$ | $-0.8_2$ | $-22.4_2$ | −22.4 ± 0.2[f] | +20.3 |
| | 4-$CH_3C_5H_4N$ | $-23.7_4$ | $+1.4_8$ | $-22.2_6$ | | |
| 5 | camphor | $-2.1_4$ | $-1.2_0$ | $-0.9_4$ | | |
| | $(i$-$C_3H_7)_2CO$ | $-0.4_5$ | $-0.2_2$ | $-0.6_7$ | −0.8 ± 0.2 | +0.6 |
| | $(C_2H_5)_2S$ | $-1.8_0$ | $+0.8_8$ | $-0.9_2$ | | |
| 6 | 2-$FC_5H_4N$ | $-8.3_3$ | $-0.5_4$ | $-8.8_7$ | −8.8 ± 0.1 | +9.1 |
| | $HC{\equiv}CCH_2NH_2$[g] | $-8.7_8$ | $-0.0_5$ | $-8.8_3$ | | |
| 9 | 2-$FC_5H_4N$ | $-8.3_3$ | $+0.4_8$ | $-7.8_5$ | −7.7 ± 0.2 | +6.3 |
| | 1,4-diazine | $-6.4_1$ | $-1.1_6$ | $-7.5_7$ | | |

[a] All values in kilocalories/mole. [b] Numbered as in text. [c] Taken from refs 1d,f. [d] Calculated as indicated in the text. [e] Agrees within 0.5 kcal/mol with the value given in ref 1f. [f] Agrees within 0.2 kcal/mol with the value in ref 1f. [g] From ref 18c.

Table III. Experimental and 6-31G* Calculated Proton Affinities (PA) of the Compounds Included in This Study[a]

| | PA | | | | $(\Delta PA)_{cyc}$ | | |
|---|---|---|---|---|---|---|---|
| | | calcd | | | | calcd | |
| compd | exptl[b] | SCF[c] | MP2[d] | $\Delta PA$[b] | exptl | SCF[c] | MP2[d] |
| 1 | 195.9 | 194.0 | 186.2 | −12.4 | +5.3 | +3.8 | +4.9 |
| 2 | 201.2 | 197.8 | 191.1 | −7.1 | | | |
| 3 | 228.6 | 229.8 | 225.8 | +20.3 | | | |
| | | 229.7[f] | 225.2[f] | | | −1.7 | +0.7 |
| | | | | | +0.5 | −1.4[f] | +0.2[f] |
| 4 | 229.1 | 228.1 | 226.5 | +20.8 | | | |
| | | 228.3 | 225.4[f] | | | | |
| 5 | 208.9 | 199.4 (N) | 198.8 (N) | +0.6 | | | |
| | | 207.7 (O) | 201.7 (O) | | | −1.5 (N) | −0.2 (N) |
| | | | | | +8.5 | +7.3 (O) | +8.6 (O) |
| 6 | 217.4 | 197.9 (N) | 198.6 (N) | +9.1 | | | |
| | | 215.0 (O) | 210.3 (O) | | | | |
| 7 | – | 242.8[e] | – | – | | | |
| 8 | 234.2 | 242.2[e] | – | −25.9 | – | −0.6[e] | – |
| 9 | 214.6 | 211.1 (N)[e] | – | +6.3 | | | |
| | | 220.5 (O)[e] | | | | +3.8 (N)[e] | |
| | | | | | +6.3 | +6.2 (O)[e] | – |
| 10 | 220.9 | 214.9 (N)[e] | – | +12.6 | | | |
| | | 226.7 (O)[e] | | | | | |

[a] $\Delta PA$ are the proton affinities relative to ammonia. $(\Delta PA)_{cyc}$ represents the cyclization effect on gas-phase proton affinities (see text for definition). All values in kilocalories/mole. [b] $PA(NH_3)$ = 208.3 kcal/mol. [c] SCF values include BSSE and ZPE corrections. [d] MP2 values include ZPE corrections scaled by the empirical factor 0.89. [e] Values obtained at the 6-31G//3-21G level. [f] Values obtained at the 6-31+G(d,p)//6-31+G(d,p) level.

GB values can be obtained by combining $\delta\Delta G_{H^+}$(g) data with the GB of the reference bases.

It is important to emphasize that a "ladder" of relative GB values is obtained from a ladder of equilibrium constants, $K_p$, determined at a given temperature $T$ by means of eq 3:

$$\delta\Delta G_{H^+}(g) = -RT \ln K_p \quad (3)$$

One of the largest sets of GB values (relative to ammonia) obtained under the same experimental conditions has been provided by Taft and Anvia's (T-A) ICR studies. Whenever possible, these results, which are well disseminated,[1f] have been used to obtain the values of $\Delta\Delta G_{H^+}$(g) for the various reference bases used in this work [$\Delta G_{H^+}(B) - \Delta G_{H^+}(NH_3)$]. It was generally accepted (private communication from Prof. R. W. Taft) that the T-A data set was obtained at ca. 320 K. Now, Meot-Ner (Mautner) and Sieck[44] have just reported the results of variable-temperature pulsed-high-pressure mass spectrometric studies carried out under conditions of very precise temperature monitoring. These studies strongly suggest that the actual temperature in T-A's ICR experiments is close to 360 K.[44] The T-A $\Delta\Delta G_{H^+}$(g) values have hence been corrected by a factor of (360/320) = 1.125 (see eq 3). The experimental results thus obtained are presented in Table II.

Proton affinities, PA (defined as $PA = -\Delta H°_{H^+}$(g) for reaction 2) are not determined directly from ICR spectrometry, but entropy terms were evaluated in our SCF ab initio calculations.[45] These

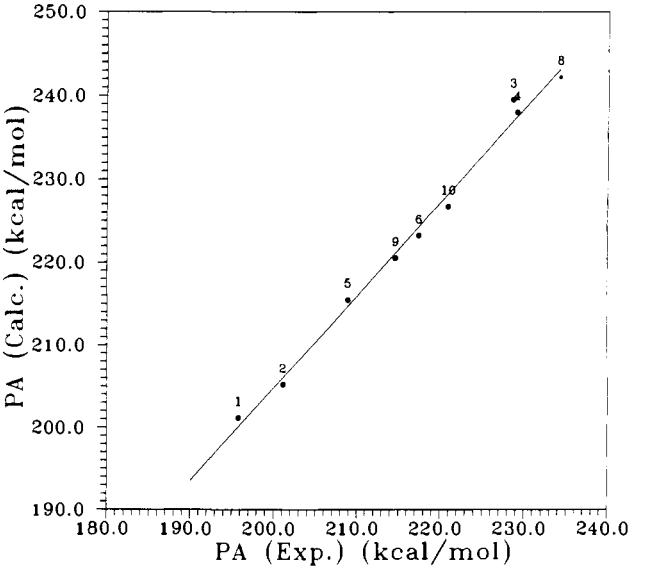


Figure 2. Linear correlation between experimental and calculated proton affinities. For the sake of consistency, the latter were obtained at the 6-31G*//3-21G level.

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**Table IV.** 6-31G* Values of $\rho^a$ and $\nabla^2\rho^b$ for the Nonbonded Charge Concentrations (Points Where $|\nabla^2\rho|$ Is Maximum) of The Compounds Included in This Study

| | oxygen lone pairs | | nitrogen lone pairs | |
|---|---|---|---|---|
| compd | $\rho$ | $\nabla^2\rho$ | $\rho$ | $\nabla^2\rho$ |
| **1** | 0.984 | −6.584 | – | – |
| **2** | 0.998 | −6.847 | – | – |
| **3** | – | – | −0.597 | −3.354 |
| **4** | – | – | 0.601 | −3.397 |
| **5** | 0.954 | −6.029 | 0.523 | −2.350 |
| **6** | 0.970 | −6.298 | 0.527 | −2.399 |
| **7** | – | – | 0.607[c] | −3.492[c] |
| **8** | – | – | 0.609[c] | −3.523[c] |
| **9** | 0.951[c] | −6.000[c] | 0.519[c] | −2.290[c] |
| **10** | 0.969[c] | −6.311[c] | 0.522[c] | −2.380[c] |

[a] In e/(au)$^3$. [b] In e/(au)$^5$. [c] Values obtained at the 6-31G* level using 3-21G optimized structures.

absolute PA values and those relative to ammonia, ΔPA, are collected in Table III.

Table III also presents the theoretical proton affinities obtained at different levels of accuracy, as well as the cyclization effect on the intrinsic basicities of the compounds considered, $(\Delta PA)_{cyc}$ defined in each case as the PA of the aliphatic form minus the PA of the corresponding cyclic species. It may be observed that there is a good linear correlation ($r^2$ = 0.996 for MP2 results) between experimental and theoretical PA values (see Figure 2) and between experimental and theoretical predictions regarding the cyclization effects on the intrinsic basicities of ketones, amides, and amines. Both sets of values indicate that the aliphatic ketones and aliphatic amides are considerably more basic than cyclic ketones and β-lactams, respectively. It should also be emphasized that similar behavior has been observed in solution. Cyclobutanone (**1**) has been found[46] to be some 4.5 kcal/mol less basic than methyl ethyl ketone, when protonated in $FSO_3H$. Similarly, McClelland and Reynolds[47] have found that **1** presents in solution a $pK_a$ value much lower (>2.3 $pK_a$ units) than that of 2-butanone. Analogously, azetidin-2-one is a weaker base[48] than lactams having larger cycles and open-chain amides of comparable size.

Our theoretical results also show that both amides and β-lactams are oxygen bases, but the gap between oxygen and nitrogen intrinsic basicities is noticeably smaller for the latter. This is a consequence of the fact that while cyclization of the molecule induces a significant decrease (≈8 kcal/mol) of its oxygen basicity, it causes an almost negligible change in its nitrogen intrinsic basicity. Both experimental and theoretical results also indicate that the oxygen basicity attenuation upon cyclization is quantitatively smaller for ketones than for β-lactams. We shall come later to this problem.

The good agreement between experimental outcomes and theoretical predictions permits us to conclude that the species formed in the gas phase upon protonation of amides and lactams are always the oxygen-protonated species, and in view of the previous discussion, this is also very likely the situation in solution.

The question which needs to be addressed now is why cyclization produces a noticeable decrease in the basicities of ketones and amides, while it produces almost negligible effects on the gas-phase basicity of amines. Following the arguments outlined above, the behavior of ketones and amides points to the appearance of electronic changes upon cyclization which affect specifically the carbonyl group and which result in a poorer capacity of the molecule to transfer electronic charge to the bare proton. Actually, upon protonation, there is a substantial charge transfer from the base to the proton, and the amount of charge transferred is usually a good measure of the intrinsic basicity of the base.[49] Our

**Table V.** 6-31G* Values of $\rho^a$ and $\nabla^2\rho^b$ for the Bond Critical Points of the C=O and N—X Bonds of the Compounds Included in This Study and Their Protonated Forms

| | C=O bond | | N—X[c] bond | |
|---|---|---|---|---|
| compd | $\rho$ | $\nabla^2\rho$ | $\rho$ | $\nabla^2\rho$ |
| **1** | 0.435 | 0.761 | – | – |
| **1H$^+$** | 0.367 | 0.426 | – | – |
| **2** | 0.426 | 0.693 | – | – |
| **2H$^+$** | 0.360 | 0.395 | – | – |
| **3** | – | – | 0.346 | −1.750 |
| **3H$^+$** | – | – | 0.339 | −1.789 |
| **4** | – | – | 0.347 | −1.752 |
| **4H$^+$** | – | – | 0.342 | −1.811 |
| **5** | 0.438 | 0.438 | 0.340 | −1.756 |
| **5H$^+$** | 0.355 | 0.020 | 0.333 | −1.763 |
| **5NH$^+$** | 0.472 | 1.026 | 0.331 | −1.737 |
| **6** | 0.428 | 0.337 | 0.348 | −1.791 |
| **6H$^+$** | 0.343 | −0.017 | 0.344 | −1.818 |
| **6NH$^+$** | 0.460 | 0.872 | 0.334 | −1.754 |
| **7** | – | – | 0.278[d] | −0.946[d] |
| **7H$^+$** | – | – | 0.233[d] | −0.447[d] |
| **8** | – | – | 0.273[d] | −0.908[d] |
| **8H$^+$** | – | – | 0.228[d] | −0.477[d] |
| **9** | 0.424[d] | 0.262[d] | 0.266[d] | −0.650[d] |
| **9H$^+$** | 0.337[d] | −0.064[d] | 0.238[d] | −0.247[d] |
| **9NH$^+$** | 0.454[d] | 0.790[d] | 0.222[d] | −0.355[d] |
| **10** | 0.412[d] | 0.089[d] | 0.265[d] | −0.752[d] |
| **10H$^+$** | 0.321[d] | −0.183[d] | 0.236[d] | −0.362[d] |
| **10NH$^+$** | 0.440[d] | 0.614[d] | 0.216[d] | −0.404[d] |

[a] In e/(au)$^3$. [b] In e/(au)$^5$. [c] X = H or C (in the methyl derivatives). [d] Values obtained at the 6-31G* level using the 3-21G optimized structures.

theoretical results confirm that lactams and cyclic ketones transfer less electronic charge to the incoming proton than the aliphatic counterparts. The question is whether their effect can be considered a specific characteristic of the carbonyl oxygen. To answer this question we have evaluated the electronic charge density associated with the nonbonded charge concentrations near the carbonyl oxygen. As indicated in the previous section, this implies a need to evaluate $\rho$ for those points where $|\nabla^2\rho|$ is maximum. The values obtained (see Table IV), which are a quantitative measure of the electronic density at the oxygen lone pairs, clearly show that this density is smaller (as well as the corresponding absolute value of the Laplacian) for lactams and cyclic ketones than for aliphatic amides or ketones, respectively. More importantly, from the values of Tables III and IV, it is easy to realize that there is a direct relationship between the relative basicity loss upon cyclization and the relative decrease in the charge density at the oxygen lone pairs. However, another question is still open: why is there a significant decrease of the electronic charge density at the oxygen lone pairs upon cyclization? To answer this question we must take into account that the C–C–C (or C–C–N) angle centered at the carbonyl carbon atom closes from about 116° to about 90° on going from the aliphatic ketone (or amide) to the cyclic counterpart. This dramatic structural change requires a drastic alteration of the hybridization pattern at the carbonyl carbon atom. In the cyclic structure the two hybrids which participate in the C–C (or C–N) bonds must increase their "p" character considerably. As a consequence, the hybrid which participates in the C–O bond must increase its "s" character by orthogonality to the other two. The result of these hybridization changes is that in cyclic ketones and β-lactams the carbonyl carbon atom behaves with respect to the oxygen atom as a carbon with enhanced electronegativity (greater "s" character). Accordingly there is a sizable polarization of the C=O bonding charge toward the carbon atom and a decrease of the charge density at the oxygen lone pairs. This change in the hybridization of the carbonyl carbon atom seems to be reflected in the abnormal behavior of the chemical shifts of atoms α to carbonyl groups with respect to the

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parent hydrocarbon in four-membered-ring ketones, lactams, and lactones.[50] This is also in harmony with the fact that the charge density at the C–O bond critical point is greater for β-lactams and cyclic ketones than for the aliphatic amides or ketones, respectively (see Table V). This, in turn, is in agreement with the well-known increase in the C=O stretching frequency observed upon cyclization[51] with the shortening of the C=O bond in cyclobutanone with respect to aliphatic ketones[52] and with the quite different values of the $^1J_{CC}$ coupling constant to the carbonyl carbon in cyclobutanone with respect to similar aliphatic ketones.[53] Furthermore, there is an additional negative hyperconjugative interaction, which explains why the cyclization effect on intrinsic basicities is larger for β-lactams than for ketones. This negative hyperconjugative effect has been postulated by Norskov-Lauritsen et al.[54] and Sudhakar et al.[55] to explain the fact that systematically in lactones and lactams the C—C=O angle is larger than the O—C=O or N—C=O, respectively. As explained in refs 53 and 54, this effect is lactams may be considered as the result of the stabilizing two-electron interaction between the lone pair of the carbonyl O atom and the empty antibonding σ*(C–N), while in cyclobutanone this competes with a destabilizing four-electron repulsion.

Similar arguments are valid for the case of azetidine (**3**) with respect to *N*-methylethanamine (**4**). The hybrids which participate in the N–C bonds increase their p character on going from **4** to **3**, whereas the hybrid involved in the N–H bond increases its s character.[56] As a consequence the degree of pyramidalization in azetidine increases, and the amino proton becomes more acidic. This electron-withdrawing effect is reflected by our topological analysis, which shows that the charge density at the nitrogen lone pair is smaller for azetidine than for *N*-methylethanamine (see Table IV) and should be accompanied by a decrease of its intrinsic basicity which is not predicted by the SCF ab initio calculations. However, it should be mentioned that, in agreement with these arguments, the vertical ionization potential of azetidine is higher than that of *N*-methylethanamine.[57] This seems to indicate that the model of the isolated molecule is not appropriate to describe the gas-phase basicity of azetidine. In other words, according to the intrinsic characteristics of neutral azetidine and *N*-methylethanamine, the former should be slightly less basic than the latter, unless some other effects, such as structural changes, appear upon protonation. Our guess is that protonation partially alleviates the ring strain in azetidine, and accordingly the stability of the protonated species becomes enhanced. Actually the four bond lengths and the four angles of the ring become practically equal in the protonated form (see Figure 1), and on the other hand, our topological analysis shows that in protonated azetidine the C–N bonds are less bent than in neutral azetidine. It must also be noticed that, in general, (a) correlation contributions to the description of cyclization effects although small are not negligible and (b) MP2 values are within 1 kcal/mol of the experimental values. For the particular case of azetidine, at both levels of accuracy considered, 6-31G* and 6-31+G(d,p), the MP2 results predict it to be slightly less basic than *N*-methylethanamine, in very good agreement with our experimental findings. Therefore in this particular case we should conclude that the gas-phase basicity of these species are about equal.

Table III also shows that N-methylation produces a 5.7 kcal/mol increase of the β-lactam basicity, which is slightly underestimated at the theoretical level. Quite interestingly, Table IV shows that *N*-methyl substitution does not affect in any significant way the charge density at the oxygen lone pairs (forms **5** and **9**). Therefore we may conclude that the greater basicity of *N*-methyl β-lactam is basically due to its greater polarizability, rather than to specific changes in the active oxygen atom. A similar finding was reported recently[58] for a homologous series of aliphatic alcohols and fluoroalkanes.

**Table VI.** 6-31G* Values of $\rho^a$ and $\nabla^2\rho^b$ for the Bond Critical Points of the Relevant Ring Bonds of Cyclic Compounds and Their Cyclic Protonated Forms[c]

| | $C_1$–$C_2$ bond | | $C_1$–$A_4$ bond | | $C_3$–$A_4$ bond | |
|---|---|---|---|---|---|---|
| compd | $\rho$ | $\nabla^2\rho$ | $\rho$ | $\nabla^2\rho$ | $\rho$ | $\nabla^2\rho$ |
| **1** | 0.266 | 0.733 | 0.266 | −0.733 | 0.245 | −0.616 |
| **1H$^+$** | 0.279 | −0.865 | 0.274 | −0.821 | 0.241 | −0.607 |
| **3** | 0.252 | −0.659 | 0.275 | −0.922 | 0.275 | −0.922 |
| **3H$^+$** | 0.256 | −0.688 | 0.220 | −0.388 | 0.220 | −0.388 |
| **5** | 0.264 | −0.727 | 0.329 | −0.821 | 0.266 | −0.747 |
| **5H$^+$** | 0.267 | −0.771 | 0.388 | −0.738 | 0.241 | −0.439 |
| **5NH$^+$** | 0.269 | −0.780 | 0.215 | −0.525 | 0.224 | −0.433 |
| **7** | 0.242[d] | −0.608[d] | 0.263[d] | −0.812[d] | 0.263[d] | −0.812[d] |
| **7H$^+$** | 0.247[d] | −0.643[d] | 0.212[d] | −0.485[d] | 0.212[d] | −0.485[d] |
| **9** | 0.255[d] | −0.679[d] | 0.325[d] | −0.862[d] | 0.259[d] | −0.783[d] |
| **9H$^+$** | 0.256[d] | −0.705[d] | 0.386[d] | −0.728[d] | 0.232[d] | −0.553[d] |
| **9NH$^+$** | 0.264[d] | −0.751[d] | 0.213[d] | −0.506[d] | 0.218[d] | −0.524[d] |

[a] In e/(au)$^3$. [b] In e/(au)$^5$. [c] See Chart I for numbering. [d] Values obtained at the 6-31G* level using 3-21G optimized structures.

**3. Bond Activations.** As mentioned previously, the charge transfer from the base to the attaching proton leads, in many cases, to a selective depopulation of some of the bonds of the base[58-61] which become activated and in some extreme cases may break apart.[58] Although our theoretical optimized structures do not show evidence of any bond cleavage, there are, however, quite important bond activations in these systems.

For obvious reasons let us concentrate our attention specifically on the cyclic structures β-lactam, cyclobutanone, and azetidine. In Figure 3 we present a three-dimensional plot, as well as the corresponding topological projection, of the Laplacian of the charge density of neutral β-lactam and its oxygen-protonated form. This figure clearly illustrates that upon protonation a new covalent O–H bond is formed, because a substantial amount of charge density, which in the neutral molecule was around the oxygen atom, has moved into the O–H bonding region. However, this charge redistribution has affected, quite importantly, the C–O bond, which becomes partially depopulated (see Table V). The effects of protonation are much smaller, although not negligible, in the bonds of the four-membered cycle. As indicated before, the oxygen of the carbonyl group recovers part of the electronic charge by depopulating the C–O bond. As a consequence there is a charge withdrawal which polarizes the C1–C2 and C1–N4 bonds of the ring toward the carbonyl carbon atom (C1). Then their bond critical points move away from C1, part of the valence charge density around C2 and N4 moves into the corresponding bonding regions (see Table V), and as a consequence, these bonds become slightly reinforced.

The C–O bond activation is also made evident by a shifting of about 150–250 cm$^{-1}$ of the corresponding harmonic stretching frequencies toward lower frequency values. A similar bond activation process is observed in cyclic ketones and aliphatic amides and ketones.

Figure 4 represents the Laplacian of the charge density of the N-protonated β-lactam. It is clear from this figure that N-protonation implies a remarkable activation of the C1–N4 and C3–N4 bonds, although this effect is quantitatively more important for the former (see also Table VI). This would imply that C1–N4

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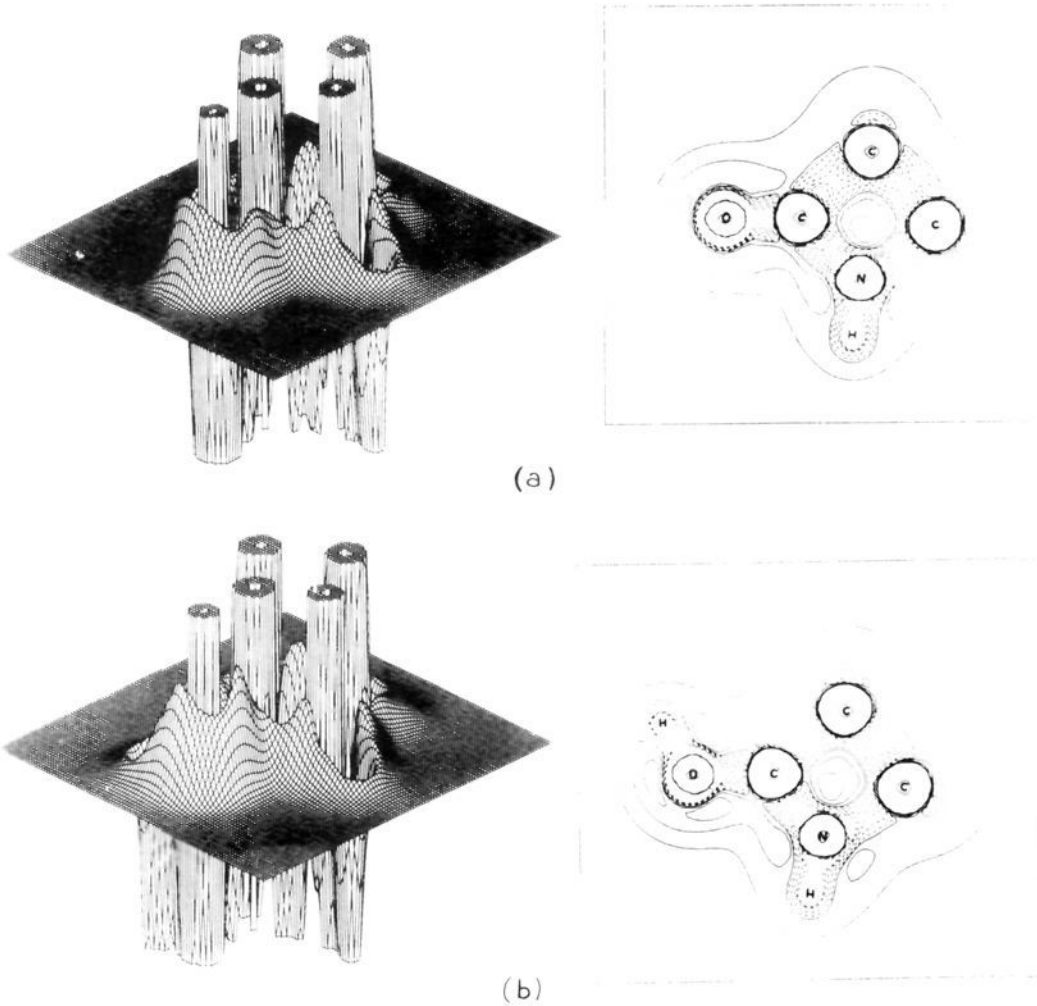


**Figure 3.** Three-dimensional plot and contour map of the Laplacian of the charge density of (a) β-lactam and (b) O-protonated β-lactam. Positive values of $\nabla^2\rho$ are denoted by solid lines and negative values by dashed lines. Contour values in au are ±0.05, ±0.25, ±0.50, ±0.75, and ±0.95.

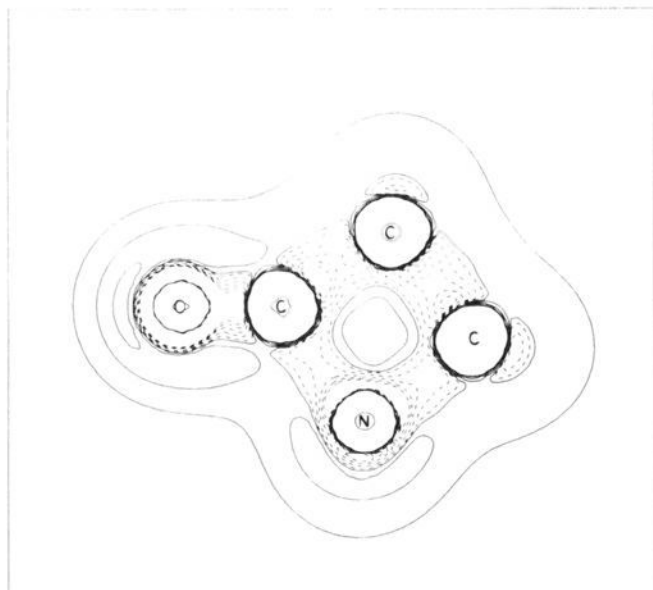


**Figure 4.** Laplacian of the charge density of N-protonated β-lactam. Same conventions as in Figure 3.

bond cleavage should be much more favorable than C3–N4 bond cleavage. This is in fairly good agreement with the fact that the former process leads to an open stable cation (**11**). However, when one tries to optimize the open cationic form corresponding to a C3–N4 bond breaking process, one recovers the cyclic N-protonated form (**5NH$^+$**). It must be noted, however, that if the C3–N4 bond is broken and the terminal $CH_2$ group is allowed to rotate around the C1–C2 bond, one arrives at an alternative

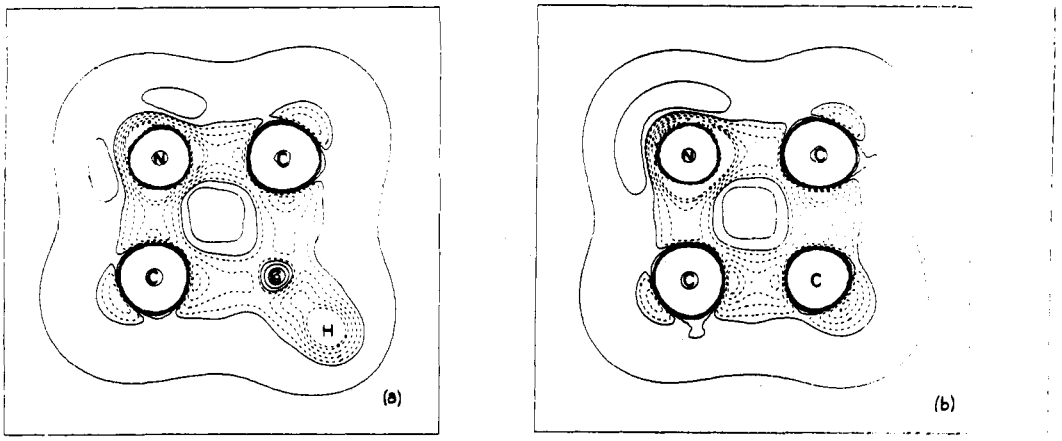


**Figure 5.** Laplacian of the charge density of (a) azetidine (**3**) and (b) protonated azetidine (**3H**$^+$). Same conventions as in Figure 3.

cyclic cation (**12**), which is 6 kcal/mol more stable than the N-protonated $\beta$-lactam. We consider this result quite interesting taking into account that although our results indicate that $\beta$-lactam is an oxygen base in the gas phase, the gap between oxygen and nitrogen basicity is predicted to be much smaller than in aliphatic amides, and on the other hand specific solvation interactions might change this basicity ordering. Actually, we have shown[61] recently that although the nitrogen intrinsic basicity of hydroxylamine is about 18 kcal/mol higher than its oxygen basicity, this gap becomes drastically reduced by specific solvation by one molecule of water or ammonia.

Bond activations upon protonation are also dramatic in azetidine (see Figure 5 and Table V). The charge transfer from the nitrogen atom to the bare proton now depopulates both C–N bonds for symmetry reasons. The effect is transmitted to the other bonds of the ring which become polarized and reinforced in a way similar to that described above for the lactams.

Quite interestingly, our results show that these bond activation processes are attenuated upon *N*-methyl substitution, in both $\beta$-lactam and azetidine. This occurs because in the N-methylated systems the nitrogen atom recovers part of the charge transferred to the incoming proton by depopulating not only the C1–N4 and C3–N4 bonds but also the *N*–methyl bond, this being due to the greater ability of the methyl group to accommodate a positive charge with respect to the proton. This activation of the *N*–methyl bonds in N-protonated *N*-methylazetidine (**7H**$^+$) and N-protonated *N*-methyl $\beta$-lactam (**9NH**$^+$) is evident by the characteristics exhibited by the corresponding bond critical points with respect to those of the neutral forms (see Table V).

## Conclusions

Our results, both experimental and theoretical, show that $\beta$-lactams are weaker bases, in the gas phase, than acyclic amides. The attenuation of basicity upon cyclization is stronger than that found for cyclic ketones of similar size due to the existence of a negative hyperconjugation effect which is present in $\beta$-lactams but not in cyclic ketones. Our ab initio calculations indicate that both $\beta$-lactams and acyclic amides are oxygen bases, but the gap between the oxygen and nitrogen intrinsic basicities is much smaller in the former due to the aforementioned cyclization effects. This decrease of the oxygen intrinsic basicity of $\beta$-lactams with respect to the aliphatic amides of the same size is a direct consequence of the hybridization changes undergone by the carbonyl carbon and is very well described by a topological analysis of the corresponding electronic charge densities. Hence we may conclude that $\beta$-lactams are intrinsically less basic than amides. Quite on the contrary, the cyclization effects on the gas-phase basicities of amines are almost negligible, and azetidine exhibits a gas-phase basicity practically equal to that of *N*-methylethanamine. Furthermore, a theoretical analysis of both the hybridization changes upon cyclization and the topological characteristics of their charge densities indicates that azetidine should be slightly less basic than *N*-methylethanamine. This is in agreement with the fact that the vertical ionization potential of the former is higher than that of the latter but in contrast with our estimations of their gas-phase basicities. Hence we must conclude that, although azetidine should be intrinsically a weaker base than *N*-methylethanamine, the slight decrease of the ring strain of the former when protonated results in an enhanced stability of the system.

Our topological analysis of bond activations of these species upon protonation reveals that for 2-azetidinone these effects are not dramatic when protonation takes place at the oxygen atom and only the C=O bond becomes appreciably activated, whereas these effects are quite significant if protonation takes place at the ring nitrogen. The most favorable C–N bond cleavage would yield a stable acyclic cation (**11**). The breaking of the other C–N bond leads, after rearrangement, to a very stable cyclic structure (**12**). Bond activations are also important in protonated azetidine and, in general, are a little attenuated in the corresponding *N*-methyl derivatives.

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