# Structures and Energetics of Two Bridgehead Lactams and Their N- and O-Protonated Forms: An ab Initio Molecular Orbital Study

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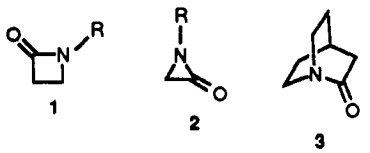
**Abstract:** *Ab initio* molecular orbital calculations optimized with the 6-31G* basis set were employed to investigate the structures, resonance energies, and protonation sites of the two bridgehead bicyclic lactams 1-azabicyclo[2.2.2]-octan-2-one (2-quinuclidone) and 1-azabicyclo[3.3.1]nonan-2-one. The structures and resonance energies reflect the absence of resonance stabilization in the first molecule and somewhat reduced resonance in the second molecule. While planar amides protonate on oxygen, 2-quinuclidone very strongly favors N-protonation while the N- and O-protonated forms in the 3.3.1 system are almost equal in energy. Discussion of structures and energies is given in the context of resonance theory.

## Introduction

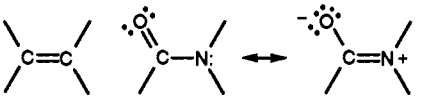
The structure of the amide linkage has been intensively studied for over sixty years.[1] Despite this great wealth of information, relatively little is known about the structures and energies, and their consequences for reactivity and biological activity, of distorted amide linkages.[2-4] That such distortion introduces unusual reactivity has long been recognized, for example, in the enhanced reactivity of β-lactams (2-azetidinones, **1**),[5] including the relationship between strain[6] and biological activity[7] in penicillins, and the extreme difficulty in isolating all but a few α-lactams (aziridinones, **2**).[8] As early as 1938, Lukes[9] recognized the relevance of Bredt's rule and predicted that small bridgehead bicyclic lactams should be very reactive. This is consistent with the subsequent lack of success in isolating 2-quinuclidone (1-azabicyclo[2.2.2]octan-2-one, **3**).[10] The Bredt's rule analogy is



**1** **2** **3**

very robust, originating in structural similarities between the planar olefin linkage and the isoelectronic (ideally) planar amide

**Scheme I**



**A** **B**

linkage (Scheme I).[2-4,11] The high rotational barrier about the C–N bond (ca. 20 kcal/mol)[3] in amides and numerous other chemical and physical properties are generally ascribed to resonance stabilization (see Scheme I).[1,12,13] However, this interpretation has been challenged in recent years by researchers using the atoms-in-molecules approach of Bader.[14-18] The magnitude of the charges on electronegative atoms when this last approach was used has been criticized.[19]

The biological implications of amide distortion include enhanced biological activities of β-lactam antibiotics[7] and applications toward understanding proteolysis.[20-22] A related topic is the recent discovery of peptidyl-prolyl *cis–trans* isomerase ("rotamase"), an enzyme which catalyzes isomerization of certain *cis* and *trans* peptides.[23-25] It plays a crucial role in autoimmunosuppression. Experimental evidence suggests that the transition state has a highly distorted peptide linkage.[23,24]

Severe distortion of an amide linkage produces some profound chemical consequences. First, there may be a dramatic enhancement in hydrolytic reactivity. Hydrolysis of benzo-2-

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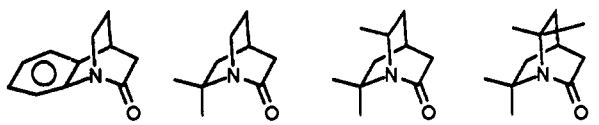
**Table I.** Summary of Selected Bond Lengths and Peptide Distortion Parameters for Lactams (and Amides) Described in the Present Study

| lactam (or amide) | source | N—CO (Å) | C=O (Å) | $X_N$[a] (deg) | $X_C$[b] (deg) | $T$[c] (deg) |
|---|---|---|---|---|---|---|
| planar formamide | calc[14] | 1.349 | 1.193 | 0.0 | 0.0 | 0.0 |
| **15** | X-ray[34,35] | 1.370 | 1.233 | 38.6 | 4.3 | 17.2 |
| | | 1.374 | 1.241 | 38.3 | 3.8 | 18.9 |
| **8** | X-ray[36] | 1.374 | 1.201 | 48.8 | 5.9 | 20.8 |
| **10** | X-ray[4] | 1.374 | 1.217 | 46.5 | 1.1 | 7.5 |
| **11** | X-ray[4] | 1.377 | 1.223 | 38.1 | 0.1 | 0.9 |
| **12** | X-ray[18] | 1.380 | 1.213 | 49.1 | 5.8 | 16.3 |
| **18** | calc[d] | 1.386 | 1.196 | 43.8 | 6.0 | 12.1 |
| **9** | X-ray[4] | 1.399 | 1.215 | 54.9 | 1.6 | 16.7 |
| **13** | X-ray[34,35] | 1.401 | 1.216 | 57.2 | 9.0 | 35.6 |
| **14** | X-ray[34,35] | 1.413 | 1.225 | 52.8 | 11.0 | 37.8 |
| | | 1.419 | 1.233 | 55.1 | 6.7 | 41.2 |
| perpendicular formamide | calc[14] | 1.423 | 1.179 | 63.4 | 0.0 | 90.0 |
| **3** | calc[d] | 1.433 | 1.183 | 55.6 | 0.0 | 90.0 |

[a] $X_N = w_1 - w_3 + \pi$; where $w_1 = w(C_aC'NC_a)$, $w_2 = w(OC'NH)$, $w_3 = w(OC'NC_a)$, $w_4 = w(C_aC'NH)$ ($w$'s are dihedral angles). [b] $X_C = w_2 - w_3 + \pi$. [c] Note: $T = T'/2$ ($T'$ is a spectroscopic parameter).[33] [d] This work.

quinuclidone (**4**) was found to be $10^8$ more rapid than that of model, unstrained amides.[26] In contrast to the exceedingly weak basicities of unstrained amides and lactams, 2-quinuclidones such as **4**–**7**[27-32] are reasonably strong bases, behaving as amino ketones

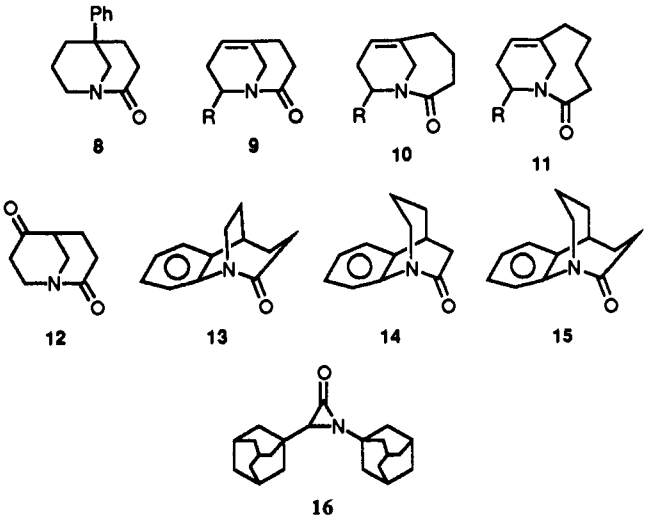


**4** **5** **6** **7**

and, thus, are slightly less basic than simple amides or lactams.[27-29] Consistent with this behavior is the observation that 2-quinuclidones such as **7** are protonated on nitrogen and also alkylate on nitrogen.[30,31] In contrast, unstrained amides and lactams are O-protonated. This raises the following intriguing question: What are the degrees of distortion that mark the boundary between N- and O-protonation of amides (lactams)? This is a fundamental question of bonding and energetics which is likely to have biological implications. There are no published gas-phase proton affinities for distorted amides and lactams (see later discussion). The pH profiles for hydrolysis of 2-quinuclidones have been employed in studies which use these distorted lactams as bioorganic models for proteolysis.[21]

In order to approach amide distortion quantitatively, it must be precisely defined. Dunitz and Winkler[33] identified three independent distortion parameters for the amide linkage: $X_N$, the pyramidalization about nitrogen; $X_C$, the pyramidalization about carbon; and $T$, the torsion about the C–N bond (see Table I). Recognizing that $X_C$ is usually quite small, Dunitz and Winkler suggested that a plot of distortion energy (comprised of classical strain and reduced resonance stabilization) versus $X_N$ and $T$ would be valuable for conformational studies.[33] Brown employed a

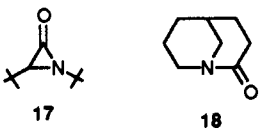
**Chart I**



**8** **9** **10** **11** **12** **13** **14** **15** **16**

simpler two-parameter distortion model ignoring $X_C$.[34,35] X-ray structures for bridgehead lactams are published only for **8**–**15**.[4,36-38] X-ray studies on bridgehead lactams appear to confirm the finding of little change in the C=O bond length as a function of distortion, but the changes,[37] small as they are, follow the trend predicted by resonance theory. Although there is a plethora of published X-ray structures for $\beta$-lactams, the only $\alpha$-lactam for which such data exist is the 1,3-diadamantyl derivative **16**.[39]

With the exception of a singificant body of calculational studies on $\beta$-lactams,[40] almost no calculational work has been done on distorted lactams.[3] Molecular mechanics (MM) studies which treat distorted amides are based upon spectroscopic parameters which are only suitable for small distortions. MM studies of significantly-distorted lactams are, thus, severely restricted due to the small body of structural data referred to earlier and the complete absence of thermochemical data for suitable benchmark compounds. An early MM study, based upon specially-developed parameters for amides and lactams,[11] found a good value for the N–CO twist while overestimating N and CO pyramidalizations for the 1-azabicyclo[3.3.1]nonan-2-one skeleton.[36] A systematic comparison of MM2-calculated structures with X-ray data found pyramidalization at nitrogen to be severely underestimated and the N–CO twist angle much larger than observed.[4] MNDO calculations on 1,3-di-*tert*-butylaziridinone (**17**) and 1-azabicyclo-[3.3.1]nonan-2-one (**18**)[41,42] have been published. They correctly



**17** **18**

predict chair–boat conformation, but the N–CO distances are too long. Thus, in valerolactam, the N–CO distance is calculated with MNDO to be 1.417 Å and the N–CO bond length in

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1-azabicyclo[3.3.1]nonan-2-one is calculated to be 1.449 Å as opposed to *ca.* 1.38 Å as found experimentally. The authors of this study[41] reported an MNDO $\Delta H_f°(g)$ value of –43.5 kcal/mol for the chair–boat conformer. Our unpublished MNDO $\Delta H_f°(g)$ result is –47.8 kcal/mol when we started the calculation using the experimental geometry of 5-phenyl-1-azabicyclo[3.3.1]-nonan-2-one.[36] The $\Delta H_f°(g)$ value obtained with MM2 with the same starting geometry was –56.3 kcal/mol, which corresponds to 12.1 kcal/mol of strain energy. We have previously employed *ab initio* MO calculations to study amides.[43] It is known that small basis sets are not appropriate since they do not properly treat N-inversion barriers.[44] We found that the 6-31G* basis set provides excellent agreement between the calculated (19.9 kcal/mol) and experimental (19.6 kcal/mol) resonance energies of acetamide.[43] The 6-31G* basis set also gives a very good structure for α-lactam (aziridinone) through comparison with the X-ray structure of the diadamantyl derivative.[43] The calculated resonance energy is 12.5 kcal/mol—some 60% that of an unstrained amide.[43] Unfortunately, there are no experimental thermochemical data for comparison.

In the present study, we employ *ab initio* molecular orbital calculations using the 6-31G* basis set to calculate the structures of the two bridgehead lactams 1-azabicyclo[2.2.2]octan-2-one (**3**) and 1-azabicyclo[3.3.1]nonan-2-one (**18**). The latter structure is distorted but should retain significant resonance while the former should lack resonance. Model amines, ketones, and alkanes are also calculated in order to derive resonance energies from isodesmic equations. In addition, N- and O-protonated structures are calculated for these two lactams in order to understand the factors which favor one site of protonation over the other.

The fairly rigid constraints of the bridgehead bicyclic lactams severely limit the degrees of conformational freedom in these molecules. This greatly reduces the computer time required to fully optimize them since the constraints produce very steep energy/parameter curves. This means that a good initial guess, e.g. using an X-ray crystallographic structure, is virtually certain to lead to the energy minimum.

## Computational Methodology

The computational methodology employed in this continuing study is *ab initio* molecular orbital theory[45] using the GAUSSIAN 90 Program Series.[46] Calculations were performed on the Cray YMP-44 at the Pittsburgh Supercomputing Center. The level of theory which we find is acceptable employs the 6-31G* basis set, since as noted above, it reproduces the structures and resonance energies of amides and is practical from the point of view of computational time. Another important point in this connection is the necessity to use such an extended basis set to properly mimic the nitrogen inversion barriers in amides (or lactams) and amines.[44] Full optimization of 1-azabicyclo[3.3.1]nonan-2-one (**18**), which has 10 C, N, O atoms, starting with the experimental structure of the 5-phenyl derivative,[36] takes under 15 cycles to optimize fully at the 6-31G* level. This is due to the geometric constraints of the bicyclic system and the relative rigidity of the amide linkage. For isodesmic comparisons in the "3.3.1" system, we employed the published chair–chair structure of bicyclo[3.3.1]nonane[47] as the starting geometry and performed full optimization. SImilarly, the chair–chair conformations were used as starting geometries for the 1-aza and 2-keto derivatives.

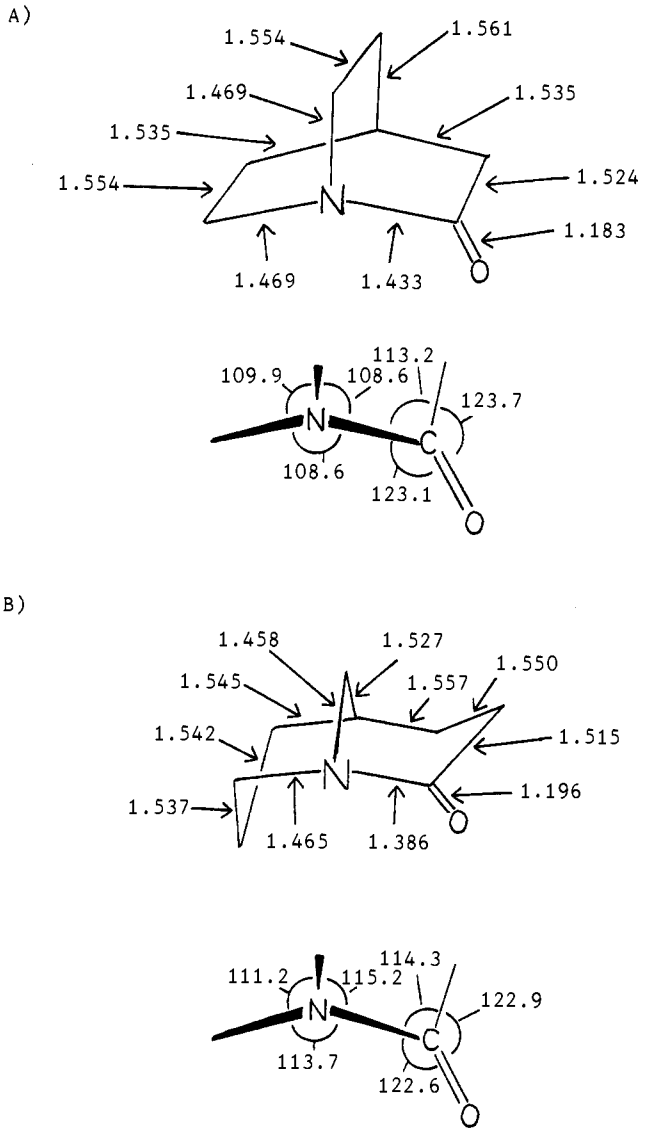


**Figure 1.** Structures and selected bond parameters for (A) the 6-31G* structure of 1-azabicyclo[2.2.2]octan-2-one (2-quinuclidone) (**3**) and (B) the 6-31G* structure of 1-azabicyclo[3.3.1]nonan-2-one (**18**).

These assumptions are reasonable in light of published studies.[48] Even if the ketone were to have a more stable chair structure, the energy difference would be very small[48] and would hardly affect the resonance energy computation. The optimized structures realized for these three model compounds have the chair–chair conformation. Starting geometries in the "2.2.2" series employed idealized bond lengths and angles and a symmetric starting structure. Protonated structures started with the optimized geometries of the lactams.

## Results and Discussion

**Structures and Resonance Energies.** Figure 1 depicts the calculated structures of two bridgehead lactams: 1-azabicyclo-[3.3.1]nonan-2-one (**18**), which is moderately strained, and 1-azabicyclo[2.2.2]octan-2-one (**3**), which is very highly strained due to the orthogonality within the lactam linkage. The structure of the larger lactam is in excellent agreement with experiment.[36] The N–CO bond length of 1.386 Å is that of a somewhat distorted lactam since it is 0.03–0.04 Å longer than that in unstrained lactams. The calculated C=O bond length (1.196 Å) is essentially a normal amidic bond length. The overall structure is the chair–boat structure depicted, which places the *trans* amide linkage in

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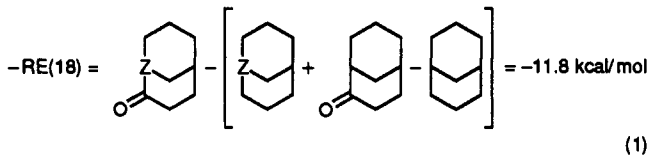
the eight-membered ring. The N-pyramidalization ($X_N = 43.8°$) is a bit smaller than that in **8** (48.8°). There is clearly considerable N-pyramidalization in the 3.3.1 system (60° corresponds to tetrahedral geometry). The $X_C$ value is the same as in **8** while the twist angle (12.1°) is smaller than that in **8** (20.8°). In Table I we list N—CO and C=O bond lengths as well as $X_N$, $X_C$, and $T$ for bicyclic bridgehead lactams for which there are X-ray or high level *ab initio* calculational data.

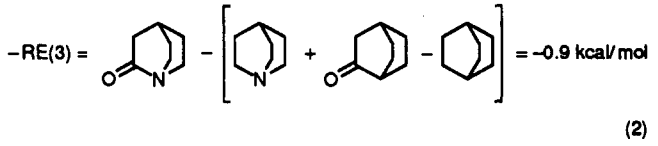
Brown and co-workers were not successful in obtaining crystals for any member of the 1-azabicyclo[2.2.2]octane series.[34,35] This is unfortunate since this is the most distorted member of the series. The calculated structure of this molecule is consistent with the absence of resonance. Its $C_s$ symmetry precludes amide resonance since the nitrogen lone pair and the $\pi$ orbitals of the carbonyl group are orthogonal. The N–CO bond (1.433 Å; see Table I) is longer than any published amide bond and appears to be limiting in the series. It is interesting that the calculated N–CO bond length in the 2.2.2 system is even longer than that calculated for twisted formamide (Table I). Although the C=O bond lengths vary little, in accordance with theoretical prediction[14] and experiment,[34,35] the C=O bond length in **3** is calculated to be 0.009 Å shorter, and the C=O bond length in **18** is calculated to be 0.002 Å longer, than in the corresponding ketones. The effects, albeit small, are in the direction predicted by resonance theory. The sum of the three bond angles around N in the 2.2.2 lactam is 327.1° (*less* planar than in the amine; $X_N$ = 55.6°), while the sum in the 3.3.1 lactam is 340.2° (more planar than in the amine), which is consistent with enhanced resonance. An interesting structural feature is that the angle C3–C2–O (123.7°) is larger than the angle N1–C2–O (123.1°). This effect is reminiscent of the early stage in N–CO cleavage of forming a $-C^+=O$ fragment, concomitant with an elongated N–CO bond, in line with published observations.[49] In **18** C3–C2–O (122.9°) is still slightly larger than N1–C2–O (122.6°), concomitant with less distortion and a shorter, yet still elongated N–CO bond. Similar effects were noted in $\alpha$- and $\beta$-lactams while the larger rings had N1–C2–O slightly larger than C3–C2–O.[49] These effects are strongly exaggerated in the N-protonated lactams (see below).

Another interesting point relates to the $C_s$ symmetry calculated for 1-azabicyclo[2.2.2]octan-2-one. As such, the geometry about the carbonyl linkage is prefectly planar. Since this is the most reactive of the bridgehead lactams,[27-32] our finding contradicts the view that the key determinant of reactivity in this series is deviation of the carbonyl group from planarity.[18]

Table II lists optimized 6-31G* total energies for all species calculated in the present study. Isodesmic eqs 1 and 2 are used




(1)




(2)

to calculate resonance energies in the 3.3.1 and 2.2.2 lactams **18** and **3**. We have previously demonstrated[43] that the 6-31G* basis set reproduces the resonance energies of acyclic amides (*ca.* 20 kcal/mol) excellently. The resonance energy of 1-azabicyclo-[3.3.1]nonan-2-one is calculated to be 11.8 kcal/mol—a very reasonable value for a mildly distorted lactam. For 1-azabicyclo-[2.2.2]octan-2-one, the resonance energy (0.9 kcal/mol) virtually disappears and any apparent residue is within the "noise" of the assumptions in these techniques or may disappear with corrections for zero-point energies and thermal energies in the isodesmic equations.

**Table II.** Total Energies (au) Calculated for Optimized Structures Using the 6-31G* Basis Set

| compound | -total energy |
|---|---|
| 1-azabicyclo[2.2.2]octan-2-one (**3**) | 400.782023 |
| N-protonated | 401.162612 |
| O-protonated | 401.124250[a] |
| 1-azabicyclo[2.2.2]octane | 327.078799 |
| bicyclo[2.2.2]octan-2-one | 384.805384 |
| bicyclo[2.2.2]octane | 311.103598[b] |
| 1-azabicyclo[3.3.1]nonan-2-one (**18**) | 439.836323 |
| N-protonated | 440.200274 |
| O-protonated | 440.197294 |
| 1-azabicyclo[3.3.1]nonane | 366.117251 |
| bicyclo[3.3.1]nonan-2-one | 423.841924 |
| bicyclo[3.3.1]nonane | 350.141642 |

[a] True minimum structure (checked using frequency calculation) obtained only after parameters corresponding to high internal coordinate forces were minimized in each subsequent run. [b] Energy corresponds to one imaginary frequency. Attempts to further optimize through stepwise minimization of parameters corresponding to high internal coordinate forces[a] were not successful. However, bicyclo[2.2.2]octane is known to be very slightly more stable in the $D_3$ conformation, calculated here, than in the $D_{3h}$ conformation (Greenberg, A.; Liebman, J. F., *Strained Organic Molecules*; Academic Press: New York, 1978; p 23). The very shallow minimum is the source of the problem and has negligible consequences for our conclusions.

There is an alternative to using isodesmic equations such as 1 and 2, which require computation of three model compounds for each lactam. This is the use of atomic increments[50,51] analogous to the Benson-type group increments[52] used in calculating $\Delta H_f°(g)$. The summation of *ab initio* atomic increments modified by experimental[53] or estimated[52,54,55] $\Delta H_f°(g)$ data allows evaluation of stabilization or destabilization with isodesmic equations such as 1 and 2 without employing the actual 6-31G* optimizations of model compounds. The published approach does not explicitly consider zero-point energy or thermal corrections, but these largely cancel in isodesmic applications.[50,51] Thus, Ibrahim and Schleyer[51] published 6-31G* increments for H–(C), C–(H)$_2$(C)$_2$, C–(H)(C)$_3$, and O$_d$0(C). The sum of group increments for bicyclo[2.2.2]octane may be added to the experimental $\Delta H_f°(g)$ [-23.7 kcal/mol[53] (-0.03777 au)] to yield an energy of -311.10557 au. Comparison with the 6-31G*/6-31G* value (Table II) indicates a discrepancy of about 1.2 kcal/mol. Similarly, addition of the $\Delta H_f°(g)$ of bicyclo[3.3.1]nonane [-30.5 kcal/mol[53] (-0.04856 au)] to the sum of group increments yields -350.14320 au, a value that differs from the optimized value (Table II) by 1.0 kcal/mol.

There are no values[50,51] listed specifically for N–(C)$_3$ and C$_d$–(O$_d$), but these may be estimated. If one employs the summation of atomic increments [excluding N–(C)$_3$] for 1-azabicyclo[2.2.2]-octane (quinuclidine), adds $\Delta H_f°(g)$,[53] and compares this sum with the total energy (Table III), then the N–(C)$_3$ increment is -54.46597 au. Use of this increment to calculate 1-azabicyclo-[3.3.1]nonane ($\Delta H_f°(g)$ estimated by comparing $\Delta H_f°(g)$[53] values of bicyclo[2.2.2]octane, quinuclidine, and bicyclo[3.3.1]nonane) yields a value differing by 0.5 kcal/mol from the value in Table

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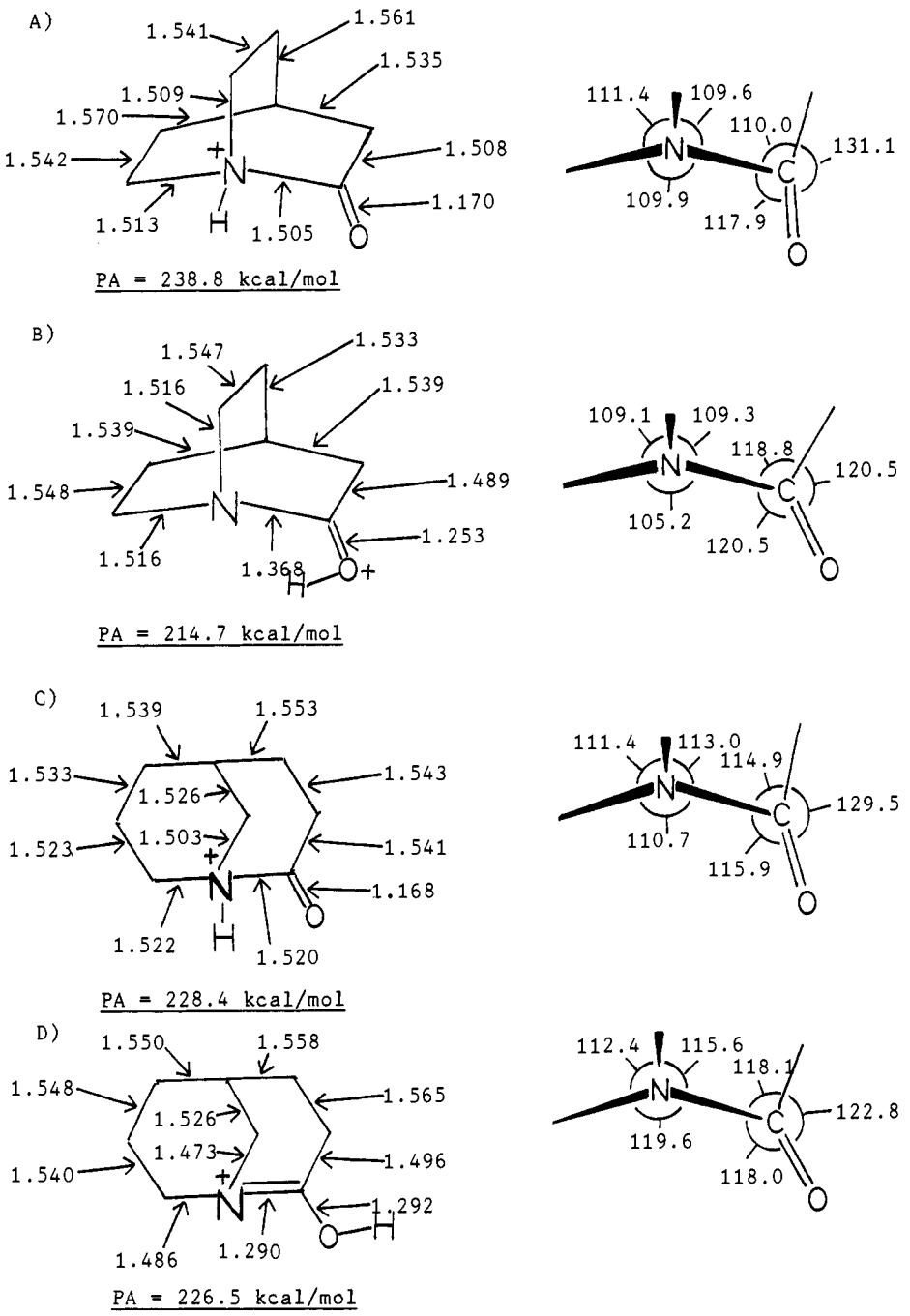



**Figure 2.** Structures, selected bond parameters, and corresponding proton affinities (kcal/mol) of the corresponding lactam for (A) N-protonated **3**, (B) O-protonated **3**, (C) N-protonated **18**, and (D) O-protonated **18**.

**Table III.** Eigenvalues (au; 1 au = 627.5 kcal/mol; 1 eV = 23.06 kcal) of the O1s, N1s, and Carbonyl C1s Orbitals of Bridgehead Lactams **3** and **18** and Their Model Amines and Ketones

| compound | O1s | N1s | C1s |
|---|---|---|---|
| 1-azabicyclo[2.2.2]octan-2-one (**3**) | −20.5519 | −15.5577 | −11.3449 |
| 1-azabicyclo[2.2.2]octane | | −15.5361 | |
| bicyclo[2.2.2]octan-2-one | −20.5439 | | −11.3167 |
| 1-azabicyclo[3.3.1]nonan-2-one (**18**) | −20.5248 | −15.5695 | −11.3372 |
| 1-azabicyclo[3.3.1]nonane | | −15.5338 | |
| bicyclo[3.3.1]nonan-2-one | −20.5432 | | −11.3173 |

II. A value of −37.89244 au was similarly derived for $C_d$–($O_d$) and the result gave equally strong agreement with the values in Table II.

This approach may be employed to calculate the total energy of a lactam with use of the above group increments. Comparison with the optimized total energy will provide a net stabilization (total resonance stabilization). Alternatively, one can estimate a value for the $N(CO)(C)_2$ group increment of +4.6 kcal/mol through comparison of the group increments[52] N(C)(C)(H), $N(C)_2(H)$, and $N(C)_3$. Thus, if one employs this "full-resonance" increment for a twisted lactam such as **18**, the net destabilization of the optimized value corresponds to resonance energy lost. Both approaches are conceptually useful.

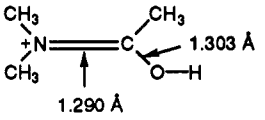
**Protonation Sites and Proton Affinities.** Normal acyclic amides and undistorted lactams are much weaker bases than amines and, indeed, protonate on oxygen. This is usually explained by invoking resonance stabilization and the formal negative charge on oxygen in the zwitterionic resonance contributor. The removal of resonance in the 2.2.2 system changes the site of protonation (and methylation) to nitrogen[27-31] by negating this effect.

The issue of N- versus O-protonation in distorted amide linkages may be an important one in proteolysis. It is conventional to assume that acid-catalyzed cleavage involves protonation or Lewis

acid complexation of the carbonyl oxygen. However, if binding of a peptide substrate distorts the peptide linkage, it is possible that nitrogen may be the basic site. This would have important consequences for enzyme mechanisms.

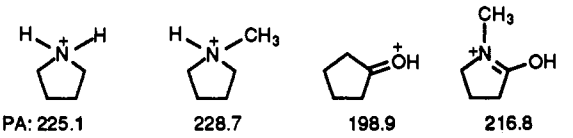
The calculated proton affinities (PA) for N- and O-protonation and the corresponding structures of the conjugate acids are depicted in Figure 2. These optimized structures started from the placement of the proton on N or O of the neutral lactam. For O-protonated **18**, the proton was attached *trans* to N so as to mimic the known structure of a simple O-protonated amide (*vide infra*). For O-protonated **3**, the proton was placed *cis* to the N in order to test the possibility of stabilizing chelation. The differences in energy between *cis* and *trans* O-protonated lactams is likely to be quite small and assuredly much smaller than the intrinsic N- vs O-protonation difference in unstrained amides. Some important insights are obtained through examination of these structures. First, the highest PA is for N-protonation of the 2.2.2 system. This is because the nitrogen is truly basic since the compound is effectively a keto amine. Although the N–CO bond length increases by 0.07 Å, this is due to an increase in the covalent radius of $N^+$ rather than to lost resonance (see the other N–C bond lengths in this structure). The C3–C2–O angle (131.2°) has opened enormously while the N1–C2–O3 angle (118.0°) has closed, hinting at the early stages of N–CO cleavage.[49] In the O-protonated 2.2.2 structure, shortening of N–CO and lengthening of C=O reflect carbonium ion structure. The PA for O-protonation of the 2.2.2 system is the lowest of the four shown.

The 3.3.1 system nicely demonstrates that not much distortion is needed to change the site of protonation. Although the *ca.* 1.9 kcal/mol difference favoring N-protonation needs to be verified at higher calculational levels, the above point is clear and awaits experimental verification. The N-protonated species has increased its N–CO length compared to the lactam by 0.135 Å—a clear indication of loss of resonance. The C=O bond length is shortened by 0.03 Å which is consistent with resonance arguments, but it is not a large effect as previously noted. In the O-protonated structure the predicted shortening of the N–CO bond length to a value shorter than the C–O bond length is a striking validation of the resonance concept. Furthermore, there is experimental verification in the published X-ray structure of dimethylacetamide hydrochloride which is depicted below.[56]

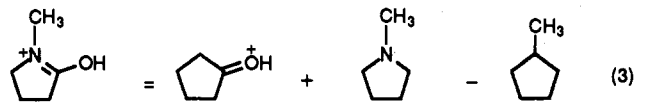



It is worth noting that in the N-protonated 3.3.1 species C3–C2–O (129.5°) is also much larger than N1–C2–O (115.9°), concomitant with N–CO bond lengthening, indicating a tendency toward cleavage as in the 2.2.2 system.[49]

These findings contribute a great deal of insight into the O- versus N-protonation question. We can provide insight as follows. A recent MP2/6-31G*//4-31G study provided PA values of 203.7 kcal/mol for O-protonation and 192.1 kcal/mol for N-protonation of formamide.[57] The experimental value is 198.4 kcal/mol,[58] in fairly good agreement with the calculated O-protonated value. Larger amides and lactams have higher PA values (*e.g.* 216.8 kcal/mol for butyrolactam[58]). We will use the calculated 11.5 kcal/mol as the difference favoring O-protonation in unstrained amides. What is the origin of this difference? Conceptually, we can examine the question in three stages by using the energetics of neutral and protonated species.[58] First, if we compare proton affinities (kcal/mol) of the four species below:




we seen that protonation of an amine is intrinsically 26–30 kcal/mol more favorable than protonation of a ketone. However, the resonance energy of an O-protonated amide of lactam is about 35–45 kcal/mol as opposed to only 20 kcal/mol in the neutral lactam and 0 kcal/mol in the N-protonated lactam. This is demonstrated in isodesmic eq 3. The net result is that O-protonation is favored by 8–18 kcal/mol. In the 2.2.2 system there is no resonance lost in N-protonation nor gained in O-protonation and the former is calculated to be favored by 24 kcal/mol, a value which approaches the intrinsic amine versus ketone difference. For the 3.3.1 case the loss of resonance energy upon N-protonation is only 12 kcal/mol while the gain in resonance energy upon O-protonation is comparable—both as the result of mild distortion. The result is the precarious balance shown for 3.3.1 system.




(3)

RE = 120.9 + (−2.0) − (−25.4) − 98.5 = 45.8 kcal/mol

It is also worth briefly comparing the resonance energies of an O-protonated amide and the corresponding amino carbocation. These are compared in isodesmic eqs 4 and 5 with data obtained from ref 58. The results indicate that the added RE due to N–$C^+$ resonance for the aminocarbocation is about 15 kcal/mol greater than that in the O-protonated amide.

$$\underset{(94\ \text{kcal/mol})}{CH_3(COH^+)N(CH_3)_2} = \underset{(117\ \text{kcal})}{CH_3(COH^+)CH_3} + \underset{(-5.7\ \text{kcal})}{(CH_3)_3N} - \underset{(-20.1\ \text{kcal})}{C_2H_6}$$

$$RE = 117 + (-5.7) - (-20.1) - 94 = 37\ \text{kcal/mol} \quad (4)$$

$$\underset{(153\ \text{kcal/mol})}{CH_3(CH^+)N(CH_3)_2} = \underset{(190.9\ \text{kcal/mol})}{CH_3(CH^+)CH_3} + \underset{(-5.7\ \text{kcal})}{(CH_3)_3N} - \underset{(-20.1\ \text{kcal})}{C_2H_6}$$

$$RE = 190.9 + (-5.7) - (-20.1) - 153 = 52\ \text{kcal/mol} \quad (5)$$

The conclusion from this section is that relatively mild distortion of the amide linkage appears to be sufficient to change the site of protonation. Del Bene has demonstrated that much more extended basis sets than 6-31G* are required for truly accurate calculations of proton affinities.[59] Nonetheless, the 6-31G* basis set provides values close to experiment, as demonstrated above. The conclusions concerning protonation site will hold for higher calculational levels except where the differences are small (perhaps < 5 kcal/mol). Thus, 1-azabicyclo[3.3.1]nonan-2-one (**18**) has a relatively large pyramidalization at nitrogen and a fairly small twist of the N–CO bond and these distortions may be sufficient to produce N-protonation. This prediction must be checked with condensed-phase and gas-phase experiments.

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**Core Orbital Energies.** If conventional amide resonance contributors are interpreted literally, then a planar amide should have a more positive nitrogen, more negative oxygen, and less positive carbon than the corresponding distorted amide. Electron spectroscopy for chemical analysis (ESCA) has been used to test this idea.[13] The N1s, O1s, and carbonyl C1s core energies for 1-azabicyclo[3.3.1]nonan-2-one (**18**) are consistent with these predictions.[13] Unfortunately, no data could be obtained for 5,6-benzo-1-azabicyclo[2.2.2]octan-2-one (**4**) and 6,6,7,7-tetramethyl-1-azabicyclo[2.2.2]octan-2-one (**7**). Thus, the calculation of the 2.2.2 and its comparison with the 3.3.1 system was desirable. The energies of the O1s, N1s, and carbonyl C1s orbitals calculated for the two bridgehead lactams and their model amines and ketones are listed in Table III. In the simplest approximation, one can apply Koopmans' theorem and assume that relaxation effects are constant when comparing very similar molecules. Although Koopmans' theory is oversimplistic, it is worth noting that the calculated C1s orbital energies for a variety of substituted compounds gave an excellent correlation with experimental core ionization energies, exhibiting a slope of unity,[60] and the approach is considered to be useful.[61] In the present study, variables are reduced by considering the same type of lactam linkage in different distortions. The N1s ionization energy is 0.0216 au (0.59 eV) higher in 2-quinuclidone than in the model amine while the value in 1-azabicyclo[3.3.1]nonan-2-one is 0.0357 au (0.97 eV) higher. This is consistent with enhanced resonance in the latter. In the 2.2.2 system the O1s ionization energy is 0.0080 au (0.22 eV) higher than the ketone while it is 0.0184 au (0.50 eV) lower in the 3.3.1 system. Similarly, the carbonyl C1s ionization energy is 0.0282 au (0.77 eV) higher in 1-azabicyclo[2.2.2]octan-2-one than in the ketone while the 3.3.1 value is 0.0199 au (0.54 eV) higher than in the corresponding ketone. This too is consistent with simple arguments grounded in resonance theory.[13] A succinct comparison is furnished by the (O1s – N1s) difference in **18** (134.8 eV) compared to that in **3** (135.9 eV), which is consistent with resonance-based arguments.

## Conclusions

The structure of 1-azabicyclo[2.2.2]octan-2-one (2-quinuclidone) is consistent with the absence of amide resonance. Its $C_s$ symmetry requires orthogonality between the nitrogen lone pair and the $\pi$ orbitals of the carbonyl group. The N–CO bond length is 1.433 Å and may represent the limit for amide linkages. Although the C=O bond length is barely shorter (0.009 Å) than that of the corresponding ketone, the effect is in the direction predicted by resonance theory. In contrast, the C=O bond length is calculated to be 0.002 Å longer in the less strained 1-azabicyclo[3.3.1]nonan-2-one than in the corresponding ketone. The N–CO bond length (1.386 Å) is longer than in planar amides (*ca* 1.34 Å) but much shorter than in 2-quinuclidone. The carbonyl group in 2-quinuclidone is calculated to be perfectly planar. The fact that this is the most reactive of the bridgehead lactams is contrary to a published view that reactivity correlates with pyramidalization at the carbonyl carbon.

The resonance energy of the 3.3.1 system is calculated to be 11.8 kcal/mol, about 60% of that in a planar amide or lactam. In contrast, the resonance energy in 2-quinuclidone is calculated to be 0.9 kcal/mol, indicating its disappearance within the limits of the errors in the technique and our approximations.

The O-protonation normally observed in planar amides and lactams is a balance governed by the intrinsically greater basicity of amino nitrogen relative to carbonyl oxygen, the loss of *ca.* 20 kcal/mol of resonance energy accompanying protonation of N, and the *gain* of an additional *ca.* 20 kcal/mol upon O-protonation. In 2-quinuclidone, no resonance is lost upon N-protonation nor gained upon O-protonation. The PA values reflect the intrincic basicities of amines and ketones. Thus, 2-quinuclidone is N-protonated and behaves as a keto amine. 1-Azabicyclo-[3.3.1]nonan-2-one loses only about 12 kcal/mol on N-protonation and gains only a comparable amount upon O-protonation since resonance is reduced relative to planar amides. In effect, O-protonation suffers a "double handicap" relative to N-protonation in distorted amides. The result is that the N-protonated and O-protonated structures of **18** are very similar in energy. Although much more extended basis sets with diffuse functions are required for accurate predictions of proton affinities, the conclusion that relatively mild distortion of the amide linkage will cause a change of protonation site should stand. The geometries of the N-protonated species show the signs of incipient N–CO cleavage. The structure of N-protonated 1-azabicyclo-[3.3.1]nonan-2-one has the C=N bond shorter than the C—O bond, in striking agreement with a published X-ray determination of dimethylacetamide hydrochloride.

The calculated O1s, N1s, and carbonyl C1s orbital energies are consistent with reduced positive charge at N, increased positive charge at C, and reduced negative charge at O in 2-quinuclidone relative to 1-azabicyclo[3.3.1]nonan-2-one. These arguments are also consistent with classical resonance theory.

**Acknowledgment.** We gratefully acknowledge informative discussions with Professor Joel F. Liebman and receipt of a generous grant of service units at the Pittsburgh Supercomputing Center.

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