Small and Medium-Sized Bridgehead Bicyclic Lactams: A Systematic ab Initio Molecular Orbital Study

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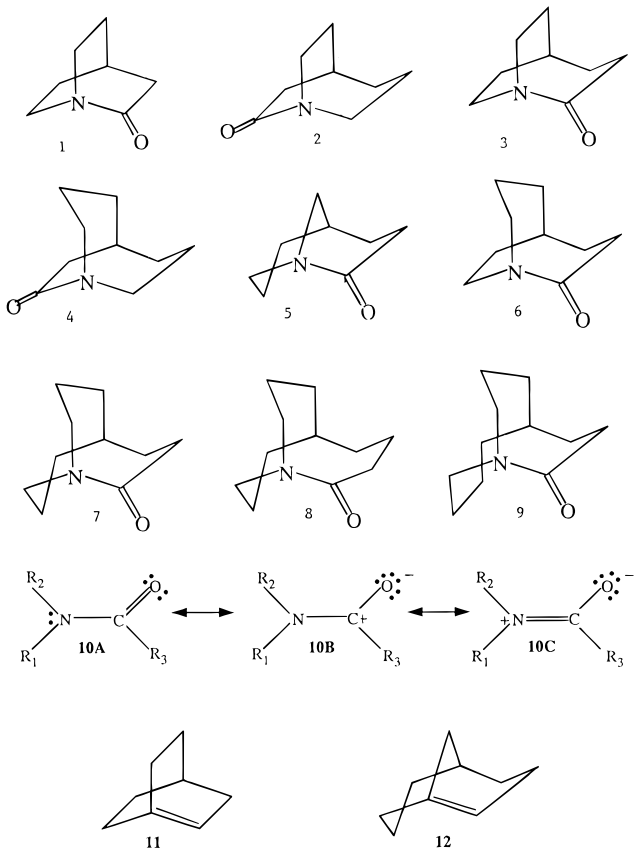
Abstract: Optimized ab initio molecular orbital calculations on nine bridgehead bicyclic lactams ranging from the 2.2.2 to the 4.3.3 series indicate variations in structural properties, resonance energies, proton affinities, and core orbital ionization energies that reflect the *trans*-cycloalkene analogy. The smaller lactams are calculated to be N-protonated, the larger O-protonated, and the "crossover" is predicted to occur around the 3.3.1 system. On the basis of resonance energies, larger bridgehead bicyclic lactams could be considered to be hyperstable as Schleyer and co-workers define the concept for larger bridgehead alkenes. This, hyperstability should be apparent in the kinetics of the nucleophilic substitution reactions of the lactams, such as hydrolysis, but not in the thermochemistry of these reactions.

Introduction

The family of bridgehead bicyclic lactams (e.g. **1**−**9**) offers a systematic series for probing the effects of distortion of the amide linkage upon structure, energy and reactivity.[1−3] The first reported members of this series, derivatives of 1-azabicylo[2.2.2]-octan-2-one (**1**, also called 2-quinuclidone), were reported in the late 1950's[4−6] although the parent remains unknown.[7] The instability of **1** is a verification of the well-known amide−alkene analogy[2] (see resonance contributors **10A**−**C**) since it mimics the anti-Bredt olefin bicyclo[2.2.2]oct-1-ene (**11**)[8] which has not been isolated. In contrast, bicyclo[3.3.1]non-1-ene (**12**)[9] is an isolable bridgehead olefin and its lactam analogue (**5**) is similar in its spectroscopic, structural, and chemical properties to unstrained amides.[10] Of course a critical difference between the two classes is exemplified by the fact that diradical **11** violates the octet rule while "amino ketone" **1** does not. It is thus almost a bit surprising that unsubstituted **1** has not been isolated as yet. Previous structural, spectroscopic, and computational studies have illustrated the variation of properties with distortion.[11−20] The present study extends earlier work on **1** and **5**.[20] For example, the (CO)−N bond length in **1** is calculated to be 1.433 Å−about 0.08 Å longer than in unstrained amides.[20] The corresponding bond length in **5** is 1.386 Å.[20] The resonance energy in **1** was calculated to be about 0.9 kcal/mol, that in **5** at 11.8 kcal/mol, and these values, which were uncorrected for zero-point energy and thermal effects, may be compared with the ca. 20 kcal/mol of resonance energy in unstrained amides.[20] Protonation of **1** is computed to occur at

Chart 1



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N (favored by ca. 24 kcal/mol over O) in contrast to the overwhelmingly favorable O-protonation that is the property of unstrained amides and lactams.[20] Lactam **5** is calculated to favor N-protonation by only 1.9 kcal/mol over O-protonation and, thus, both protonated species may coexist in equilibrium.[20] These predictions are, of course, for the gas phase and one would anticipate significant solvent effects upon the position of equilibrium.

The purpose of the present study is to explore selected lactams intermediate in distortion between **1** and **5** as well as to extend the series to larger, more stable species. In particular, we have explored computationally at the 6-31G* level intermediate-sized bridgehead bicyclic lactams in which the framework allows near planarity of the linkage. These lactams may be "hyperstable" in the sense defined by Schleyer and co-workers for "hyperstable" bridgehead olefins.[21,22] We are aware of recent work indicating that *ab initio* studies at higher levels reproduce thermochemical data within the range of experimental noise.[23] However, the systems studied here are too large for these levels of computation and we will show that the 6-31G* does an adequate job in reproducing experimental data and trends.

Methodology

Ab initio molecular orbital calculations were carried out using GAUSSIAN 92 and 94[24] at the 6-31G* level[25] on a Cray YMP-C916 supercomputer using the Unichem interface on a Silicon Graphics Inc. workstation platform. The molecular mechanics (MM2[26a]) program in the SPARTAN 4.0 software[26b] was employed to calculate lowest energy conformations. All conformations within 3 kcal/mol of the energy calculated for the lowest energy conformer were explored using the GAUSSIAN program series. Initial STO-3G and 3-21G optimizations were employed to obtain starting structures for the 6-31G* optimization. The optimized structure was subjected to frequency calculation to include thermal energy at 298 K and 1 atm (uncorrected frequencies) and zero-point vibrational energies. All reported structures were minima (no imaginary frequencies).

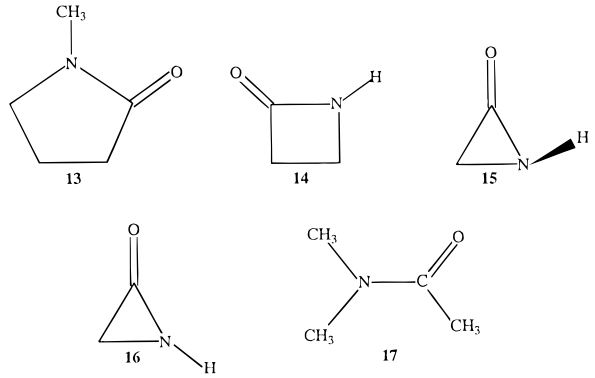
Results and Discussion

Total Energies and Geometries of Lactams. Table 1 lists total energies for bridgehead bicyclic lactams **1**−**9** as well as model lactams and amides **13**−**17** with zero-point energies and thermal corrections as well as selected geometric parameters. The grouping of lactams in Table 1 falls very comfortably into classifications based upon the *trans*-cycloalkene analogy.[27] Thus, 1-azabicyclo[2.2.2]octan-2-one (**1**) is analogous to the most distorted alkene in the series−**11**. The (CO)−N bond length of 1.433 Å is considerably longer than any known in a lactam or amide. The pyramidalization at nitrogen (χ_N)[28] indicates virtual tetrahedral, sp^3-hybridized nitrogen and the twist angle (τ)[28] of 90° indicates no overlap between the nitrogen lone pair and the carbonyl π system. The three *trans*-cycloheptene analogues **2**−**4** have (CO)−N bonds close to 1.400 Å reflecting increased double-bond character. All three compounds maintain highly pyramidal geometries at nitrogen but they have only half the twist (ca. 39−48°) present in **1**.

Table 1. Optimized (6-31G*) E_T (without and with Zero-Point Energy and Thermal Corrections) and Selected Geometric Parameters[28] for Amides and Lactams (the Carbonyl-Containing Bridge Is Specified: e.g. 3.3.2̄ Signifies 1-Azabicyclo[3.3.2]decan-9-one)

lactam	$-E_T$ (au)	corr $-E_T$ (au)	$r_{C=O}$ (Å)	r_{CO-N} (Å)	χ_N (deg)	χ_{CO} (deg)	τ (deg)
trans-Cyclohexene Analogue							
2̄.2.2 (**1**)	400.78202	400.58594	1.183	1.433	55.6	0.0	90.0
trans-Cycloheptene Analogues							
3.2̄.2 (**2**)	439.82191	439.59319	1.193[a]	1.400[a]	46.7	8.9	44.0
3̄.2.2 (**3**)	439.82106	439.59199	1.193[b]	1.402[b]	51.2	9.7	39.2
3.3.2̄ (**4**)	478.84770	478.58666	1.193	1.397	36.7	10.4	47.8
trans-Cyclooctene Analogues							
3̄.3.1 (**5**)[c]	439.83632	439.60731	1.196[d]	1.386[d]	49.9	6.0	21.9
3̄.3.2 (**6**)	478.86017	478.59850	1.200[e]	1.374[e]	32.6	7.1	20.0
3̄.3.3 (**7**)	517.88266	517.58912	1.200	1.372	18.9	12.0	35.6
trans-Cyclononene Analogues							
4̄.3.3 (**8**)	556.91145	556.58542	1.205	1.359	0.3	7.5	19.6
4.3̄.3 (**9**)	556.91758	556.59167	1.205	1.362	5.0	8.1	20.5
Model Compounds							
1-MePyr (**13**)	323.91275	323.75649	1.198	1.356	12.8	1.0	1.4
Azet (**14**)[f]	245.81043	245.71880	1.186	1.357	*g*	*g*	*g*
pyr Azir (**15**)[f]	206.72612	206.66778	1.178	1.348	*g*	*g*	*g*
Pl Azir (**16**)[f]	206.71929	206.66212	1.183	1.302			
N,N-DMA (**17**)	286.03017	285.88252	1.202	1.363	16.9	1.2	3.1

[a] X-ray data for the 8,9-benzo derivative of **2** (two polymorphs): r_{CO} = 1.225, 1.233 Å; r_{CO-N} = 1.413, 1.419 Å (see refs 14, 15, and 29). [b] X-ray data for the 6,7-benzo derivative of **3**: r_{CO} = 1.216 Å; r_{CO-N} = 1.401 Å (see refs 14, 15, and 29). [c] See ref 20. [d] X-ray data for the 5-phenyl derivative of **5**: r_{CO} = 1.201 Å; r_{CO-N} = 1.374 Å (see: Buchanan, G. L.; Kitson, D. H.; Mallinson, P. R.; Sim, G. A.; White, D. N. J.; Cox, P. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1709). [e] X-ray data for the 9,10-benzo derivative of **6** (two polymorphs): r_{CO} = 1.233, 1.241 Å; r_{CO-N} = 1.370, 1.374 Å (see refs 14, 15, and 29). [f] See ref 58. [g] Azetidinone is planar and the parameters in aziridinone are not quite the same as those defined by Winkler and Dunitz.[28]



It is interesting that **2**−**4** have a calculated $r_{C=O}$ of 1.193 Å, only 0.010 Å longer than in **1**. The conventional resonance view of amides, which usually focuses on canonical structures **10A** and **10C**, implies that shortening of the (CO)−N bond should be accompanied by (presumably comparable) lengthening of the CO bond. Laidig and Wiberg[11] first noted, in their calculational study, the very small changes in the carbonyl bond length as a function of distortion and this was later verified experimentally by Brown and co-workers.[14,15,29] The study described here verifies the small changes in carbonyl bond length as a function of distortion. Small as these changes are they are in the direction predicted by classical resonance theory. Table 1 also notes the calculated and experimental (CO)−N and CO bond lengths for the four bridgehead bicyclic lactam families

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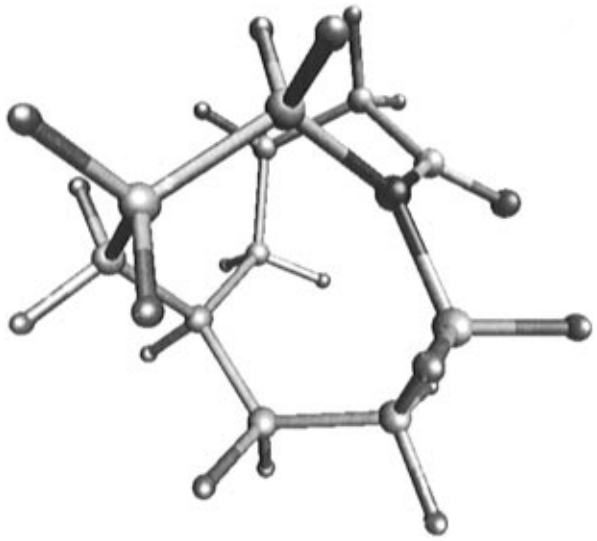
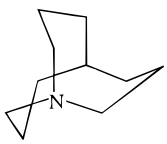


Figure 1. Ball-and-stick structure of 1-azabicyclo[4.3.3]dodecan-2-one (**8**) depicting near coplanarity of the lactam linkage.

for which experimental data exist. Since the X-ray data are obtained at ambient temperatures with population of thermal vibrational modes, the experimental bond lengths all exceed the calculated values. The general trends appear to be reproduced although both sets of bond length values in the two polymorphs of the 3.2.2 benzo derivative appear to be anomalously high.

The 3.3.3 system is a particularly interesting case. The corresponding amine, 1-azabicyclo[3.3.3]undecane (**18**), has been known for about 25 years.[30] It has a near coplanar geometry for the nitrogen and three attached carbons as does its N-protonated salt (**19**).[31] Although the IP of the amine is low due to the high p-character of its lone pair, its proton affinity is also low due to the strain in the four-coordinate species and the poor overlap of the high p-character orbital with the hydrogen 1s orbital.[32] The approach toward planarity at N makes the related and presently unknown lactam 1-azabicyclo-[3.3.3] undecan-2-one (**7**) a potential candidate for a hyperstable lactam.



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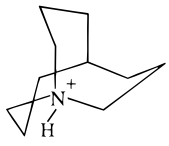

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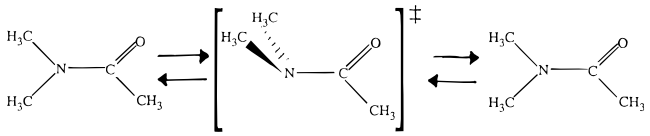
Although the 3.3.3 system approaches the geometric requirements for an unstrained amide linkage, the 4.3.3 system is much closer to this goal. This is very apparent from the computed data in Table 1 as well as Figure 1 which indicate virtual planarity at nitrogen and negligible twisting about the (CO)−N bond. We will describe other features of the 4.3.3 and 4.3.3 lactams below but for now note that they appear to be viable candidates for "hyperstable" bridgehead lactams (see title of Table 1 for a description of shorthand bridgehead lactam nomenclature).

Resonance Energies. Resonance energies and strain energies are secondary properties whose definition depends on the primary properties referenced. For the amides there are actually two practical and quite independent overall schemes which must give rise to slightly different resonance energies. First, amides

Scheme 1



are capable of undergoing C−N rotation in which the transition state appears to have pyramidal geometry at nitrogen.[33] The experimental enthalpy of activation for C−N rotation in *N*,*N*-dimethylacetamide in the gas phase is 15.8 ± 1.1 kcal/mol.[33] However, the transition state differs from the planar amide in having various changes in bond length, including a significantly longer (CO)−N bond,[11,12] but most notably in the pyramidalization at N (see Scheme 1).[11,12,33] If one were to "planarize" the nitrogen of the transition state structure, then the additional ca. 6 kcal/mol required (typical N inversion barrier[34]) would correspond to a rotational barrier of ca. 21−23 kcal/mol which might be taken to be the amide resonance energy although the changes in CO−N bond length complicate this interpretation.[45]

Alternatively, one might compare the amide with its model amine and ketone components in isodesmic processes to obtain resonance energy (RE). We depict three such approaches here. The first can be termed "Methyl Capping based on Experimental data" (MCE).[35] It is exemplified by the approach in eqs 1−3.

$$\mathrm{RE}(\mathbf{17})_{\mathrm{MCE}} = \Delta H_f^\circ\,[(CH_3)_3N] + \Delta H_f^\circ\,[(CH_3)_2CO] - \Delta H_f^\circ\,[CH_3CON(CH_3)_2] - \Delta H_f^\circ\,[CH_3CH_3] \quad (1)$$

$$\mathrm{RE}(\mathbf{13})_{\mathrm{MCE}} = \Delta H_f^\circ[CH_3CO(CH_2)_3N(CH_3)_2] + \mathrm{strain}(\mathbf{13}) - \Delta H_f^\circ(\mathbf{13}) - \Delta H_f^\circ\,[CH_3CH_3] \quad (2)$$

$$\mathrm{RE}(\mathbf{1})_{\mathrm{MCE}} = \Delta H_f^\circ[CH_3{-}\overline{NCH_2CH_2C(CH_2COCH_3)CH_2CH_2}] + \Delta\mathrm{strain}[\mathbf{1} - \mathrm{piperidine}] - \Delta H_f^\circ(\mathbf{1}) - \Delta H_f^\circ[CH_3CH_3] \quad (3)$$

A second approach, which is virtually equivalent although the data set do not identically match MCE, is one using Benson[36] (or similar) group increments (GI), which is very similar to another methyl-capping approach. This approach, termed "Methyl Capping Group Increment" (MCGI), is depicted in eq 4 (the Benson convention[36] for representing group increments is employed). The strain energies in eqs 1−4 would have to be estimated perhaps using the alkane, amine, ketone or a combination of (amine + ketone − alkane).

$$\mathrm{RE}(\mathbf{1})_{\mathrm{MCGI}} = \mathrm{GI}\,[N(C)_3] + \mathrm{GI}[CO(C)_2] + \mathrm{GI}[C(H)(C)_3] + 3 \times \mathrm{GI}\,[C(H)_2(C)_2] + 2 \times \mathrm{GI}\,[C(H)_2(N)(C)] + \mathrm{strain}(\mathbf{1}) - \Delta H_f^\circ(\mathbf{1}) \quad (4)$$

The third approach is one we dub "CarbOnyl Substitution Nitrogen Atom Replacement" (COSNAR). It is exemplified by eqs 5−7. The strain energy is explicitly in the model

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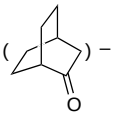
Table 2. Gas-Phase Enthalpies of Formation (kcal/mol) for Amides and Lactams and the Corresponding Resonance Energies (RE, kcal/mol) According to the Methyl Capping Experimental (MCE) Approach (Eqs 1−3) and the Carbonyl Substitution Nitrogen Atom Replacement (COSNAR) Approach (Eqs 5−7)[h]

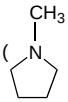
	$\Delta H_f°$(g) (kcal/mol)				RE (kcal/mol)	
compd	Pedley[a]	Lias[b]	Abboud[c]	**selected**	MCE	COSNAR
$HCONH_2$	−46.3	−44		−46.3	21.0	21.0
$HCON(CH_3)_2$	−46.0	−45.8		−46.0	20.7	20.7
CH_3CONH_2	−57.0	−57.0		−57.0	19.5	18.8
$C_2H_5CONH_2$	−61.9			−61.9	19.3	18.2
n-$C_3H_7CONH_2$	−67.4			−67.4	19.9	18.7
i-$C_3H_7CONH_2$			−67.5	−67.5	19.1	17.9
n-$C_4H_9CONH_2$	−69.4*			−69.4*	17.1*	(15.8)*
t-$C_4H_9CONH_2$			−74.8	−74.8	19.7	17.8
n-$C_5H_{11}CONH_2$	−77.5			−77.5	(20.2)	(19.0)
n-$C_7H_{15}CONH_2$	−86.7			−86.7	19.7	(18.2)
1-adamantyl-$CONH_2$			−76.2	−76.2	19.3	(18.2)
CH_3CONH-*n*-C_4H_9	−73.1			−73.1	(19.9)	(18.2)
1-MePyr (**13**)	(−50.2/−49.6)[d]	−50.4		−50.1[e]	(22.4)	(20.5)
$CH_3CON(CH_3)_2$ (**17**)	−54.5	−56		−54.5	18.0[f]	(16.9)[f]
$C_2H_5CON(CH_3)_2$			−59.8	−59.8	18.2[f]	(16.7)[f]
n-$C_3H_7CON(CH_3)_2$			−64.7	−64.7	18.2[f]	(15.9)[f]
t-$C_4H_7CON(CH_3)_2$			−68.4	−68.4	[13.3]	[(6.8)]
1-adamantyl-$CON(CH_3)_2$			−68.4	−68.4	[11.5]	[(10.9)]
$C_6H_5CONH_2$	−24.1	−24		−24.1	17.8*	*g*
$C_6H_5CON(CH_3)_2$		−23	−20.6	−20.6	15.3[f]	*g*
$CH_3CONHC_6H_5$	−30.8	−31		−30.8	(19.7)	18.3

[a] See ref 38. [b] See ref 39. [c] See refs 40 and 41. [d] The Pedley (ref 38) value for $\Delta H_f°$(1) (1-methylpyrrolidinone, **13**) is −262.2 ± 0.5 kJ/mol (−62.7 ± kcal/mol). Employing the experimental values for ΔH_v and T_b yielded $\Delta H_v/T_b$ for *N*,*N*-dimethylformamide (110.1 J/K•mol) and *N*,*N*-dimethylacetamide (114.8 J/K•mol). Use of these values with the experimental T_b of 1-methylpyrrolidinone (475 K) generated ΔH_v = 52.3−54.5 kJ/mol (12.5−13.0 kcal/mol) and these data yield the $\Delta H_f°$(g) range shown for 1-methylpyrrolidinone. [e] The average of −50.2, −49.6, and −50.4 kcal/mol. [f] 1.0 kcal/mol Benson *cis*-olefin correction added. [g] Benson group increment data lacking for a model compound. [h] RE values in parentheses denote cases in which one or more of the model compounds have been estimated using group increments. RE values in square brackets denote cases in which there are *cis*-olefin-like repulsions considerably larger than 1.0 kcal/mol[36] and the value listed is uncorrected for steric repulsions. An asterisk denotes that $\Delta H_f°$(g) judged by Pedley (ref 38) to have relatively high experimental uncertainty.

molecules and need not be added for isodesmic processes of this type. It is a form of "macroincrementation".[37]

RE(**1**)COSNAR = $\Delta H_f°$[] +

$\Delta H_f°$() − $\Delta H_f°$(**1**) − $\Delta H_f°$() (5)

RE(**13**)COSNAR = $\Delta H_f°$() +

$\Delta H_f°$() − $\Delta H_f°$(**13**) − $\Delta H_f°$() (6)

RE(**17**)COSNAR = $\Delta H_f°[C_2H_5N(CH_3)_2]$ +

$\Delta H_f°[CH_3COCH(CH_3)_2] - \Delta H_f°$(**17**) − $\Delta H_f°[C_2H_5CH(CH_3)_2]$ (7)

Table 2 lists $\Delta H_f°$(g) data[38−41] for amides and lactams that we are aware of as well as resonance energies based upon the MCE and COSNAR approaches since the MCE and MCGI data are extremely similar. It is clear that these approaches generally provide quite comparable data.

Table 3. Computation of Benson Group Increment for N(CO) $(C)_2$[c]

compd	$\Delta H_f°$(g)[a] (kcal)	GI_{Benson} (kcal)	with cis correction	calcd N(CO)$(C)_2$
$HCON(CH_3)_2$	−46.0	−49.8		+3.8
$CH_3CON(CH_3)_2$	−54.5	−63.0	−62.0	+7.5
1-MePyr (**13**)	−50.1	−53.3[b]		+3.2
$C_2H_5CON(CH_3)_2$	−59.8	−68.4	−67.4	+7.6
n-$C_3H_7CON(CH_3)_2$	−64.7	−73.3	−72.3	+7.6

[a] See **selected** value in Table 2. [b] We employ Benson's ring correction[36] for cyclopentane (6.3 kcal/mol), not that for cyclopentanone or the sum and difference of pyrrolidine, cyclopentanone, and cyclopentane in order to be consistent with later work. The three values are in any case quite similar. [c] The $\Delta H_f°$(g) are the **selected** values in Table 2. The sum of group increments is obtained from Benson's text.[36] The value **chosen** for N(CO)$(C)_2$ is +7.6 kcal/mol as further explained in the text.

When the Benson book[36] was published, no group increment value was listed for N(CO)$(C)_2$ due to the paucity of data available. We have listed in Table 3 five molecules it might appear, *a priori*, are useful for estimating the value of this parameter. We did not employ the pivaloyl (*tert*-butylcarbonyl), adamantylcarbonyl, and benzoyl species from Table 2 since these included unspecified steric and/or resonance effects which would confound our estimates. This is obvious from the low resonance energy values in Table 2 for these three compounds. Three of the five compounds in Table 3 gave close values averaging +7.6 kcal/mol. The low value for *N*,*N*-dimethylformamide (+3.8 kcal/mol) was judged to reflect the unusual nature of the HCO increment in part reflecting enhanced resonance (see Table 2) and this was not employed further.

The low calculated value for the group increment N(CO)-$(C)_2$ derived from 1-methylpyrrolidinone (+3.2 kcal/mol) listed in Table 3 is a bit more difficult to explain. This discrepancy is due, we feel, to a ca. 4 kcal/mol stabilization (arising from reduced steric repulsion) in 1-methylpyrrolidinone that has to our knowledge hitherto escaped comment. It appears from the

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(41) Abboud, J. L. M.; Jiménez, P.; Roux, M. V.; Turrión, L. M. *J. Chem. Thermodynam.* **1989**, *21*, 859.

data in Table 2 that the apparent resonance energy of 1-methylpyrrolidinone is 3.6−4.4 kcal/mol greater than that of *N*,*N*-dimethylacetamide for example. We note further that the MM2 program version in SPARTAN 4.0 obtains an anomalously low strain energy (1.13 kcal/mol) for 1-methylpyrrolidinone. Thus, we employ the value +7.6 kcal/mol for the $GI_{Benson}[N(CO)(C)_2]$.

The Methyl Capping and COSNAR approaches outlined above can also be employed using computed enthalpies of formation or total energies. The latter are best modified using zero-point energies and thermal corrections. However, since both approaches are isodesmic[42] in nature, the corrections largely cancel. Our previous 6-31G* *ab initio* study[20] used the COSNAR approach to obtain resonance energies for the $\bar{2}$.2.2 system (**1**) and the $\bar{3}$.3.1 system (**5**) of 0.9 kcal/mol and 11.8 kcal/mol employing total energies of the lactam and all three model molecules in each case.

Wiberg[43] developed an atom increment estimation approach for 6-31G* calculations later extended by Ibrahim and Schleyer[44] (both are not modified by ZPE and thermal corrections) similar in concept and nomenclature to the Benson approach. We have employed the data and approach of Ibrahim and Schleyer.[44] In principle, one may obtain an excellent total energy (E_T) for a given compound by summing the "Schleyer" increments with the experimental $\Delta H_f°(g)$— the latter may be experimental or appropriately estimated using Benson increments according to eq 8. The "Schleyer" increments were shown to be remarkably insensitive to environment while the subtleties of molecular environment are reflected in $\Delta H_f°(g)$.

$$\text{estimated } E_T^{6-31G^*} = \sum \text{"Schleyer" increments (6-31G*)} + \Delta H_f°(g) \quad (8)$$

The advantage of this approach is quite clear. Rather than calculating the lactam and its three model molecules to obtain a value for $\Delta H_f°(g)$, strain, resonance, etc., an optimized value can be compared with the sum of increments to obtain $\Delta H_f°(g)$ and related parameters. We have added two slight variations to this approach. The first variation is to calculate a hypothetical $\Delta H_f°(g)$ for a *fully* resonance stabilized bridgehead lactam which can then be modified by the strain energy of the bicyclic framework. One simply uses the Benson amide group increments for CO(N)(C) and $N(CO)(C)_2$—the latter derived above—plus the other group increments and adds the experimental strain of the bicyclic system. The second variation is to compute a $\Delta H_f°(g)$ for a hypothetical *zero*-resonance bridgehead lactam using the Benson $N(C)_3$ and $CO(C)_2$ group increments, again adding the experimental strain of the appropriate framework. This is termed the Amide Zero Resonance Model. These two variations employing Benson group increments are depicted in Scheme 2. Indeed, merely subtracting one set of group increments from the other, as in eq 9, yields an idealized resonance energy for normal (i.e. unstrained) tertiary amides or lactams of 18.2 kcal/mol. This value is comparable to those in Table 2 since all of these approaches compare planar amides to separated ketones and pyramidal amines or their equivalents. This number should not be directly compared with the amide rotational barrier as a measure for resonance since, in the latter, the same groups of atoms remain attached throughout.

$$\text{tertiary amide RE} = [N(C)_3 + CO(C)_2 - N(CO)(C)_2 - CO(N)(C)] = 18.2 \text{ kcal/mol} \quad (9)$$

Scheme 2

amide zero resonance model (strainless) Benson group increments	amide full resonance model (strainless) Benson group increments
assume: $N(C)_3 \equiv N(CO)(C)_2 = +24.4$kcal/mol	$N(CO)(C)_2 =$ +7.6 kcal/mol (see text)
assume: $CO(C)_2 \equiv CO(N)(C) =$ −31.4 kcal/mol	$CO(N)(C) = -32.8$ kcal/mol

It is worth noting here that the isodesmic techniques employed here (MCE, MCGI, COSNAR) and the amide rotational barrier explicity compare a planar N with a pyramidal one. In the isodesmic comparison the pyramidal N is in the amine model, whereas in the rotational barrier, the pyramidal N is in the transition state. Explicit consideration of the ca. 6 kcal/mol inversion barrier of amines[34] could arguably raise the amide resonance by 6 kcal/mol.[45,46] In order to obtain the $\Delta H_f°(g)$ (fully resonance stabilized or zero-resonance energy), the appropriate strain energy must be added.

Although Ibrahim and Schleyer[44] suggest relatively nonspecific atomic increments for the computation of 6-31G* total energies, these work reasonably well for amides. Thus, the estimated $E_T^{6-31G^*}$ (eq 8) is only 0.0023 au (1.5 kcal/mol) lower (more negative) than the optimized value for *N*,*N*-dimethylacetamide and 0.0044 au (2.8 kcal/mol) lower than that for *N*-methylpyrrolidinone. Thus, although it might be tempting to generate a set of amide atomic parameters, we will employ the Ibrahim/Schleyer set. The sum of the atomic increments as well as the $\Delta H_f°(g)$ (full resonance or zero resonance models including the ring strain of the bicyclic framework) will then be added to yield an estimated E_T which may then be compared with the optimized E_T in order to compute net destabilization or stabilization, respectively.

The strain energies of the bicyclic alkanes corresponding to the lactams studied are listed in Table 4. We employ the experimental numbers but it is clear that the 6-31G* numbers are quite similar. Arguably, the best approach might be to add the strain energies (experimental or molecular mechanics) of the ketone and amine and subtract that of the alkane. There will be more discussion of this point in the conclusions.

Table 4 lists data relevant to the comparison of the lactam (or amide) with the Amide Full Resonance model. The 1-azabicyclo[2.2.2]octan-2-one (**1**) system suffers a loss of 23.0 kcal/mol of resonance energy. In constrast, the three *trans*-cycloheptene analogues **2**−**4** lose 16.4−17.1 kcal/mol of resonance stabilization and the three *trans*-cyclooctene analogues lose between 7.8 and 12.5 kcal/mol of resonance stabilization. The negative resonance loss value listed in Table 4 for the 4.$\bar{3}$.3 lactam (**9**) implies "hyperstability".

The seemingly straightforward 18.2-kcal/mol difference between the Amide Full-Resonance and Zero-Resonance Models (Scheme 2) depicted in eq 9 needs to be explained a bit further. The application of these Benson group increments involves comparison of a full amide linkage (planar N) with separated ketone and amine (pyramidal N) and is virtually comparable to the MCE, MCGI, and COSNAR approaches depicted in eqs 1−7 and Table 2. As noted previously, if one wishes to correct this value to make a comparison with the free planar amine

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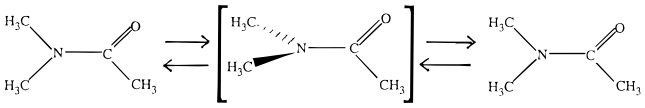
Table 4. Calculation of the **Loss** in Resonance Energy (RE **Loss**, kcal/mol) for Bridgehead Lactams Using the Full Resonance Benson Group Increments for Amides (including, +7.6 kcal/mol for N(CO)$(C_2)_2$, see Scheme 2), Adding the Experimental Strain Energies (Strain) of the Bicyclic Frameworks (Taken Here as the Bicycloalkanes) to the Sum of the "Schleyer" Atom Increments[41] (all in au) and Comparing the Resulting E_T(est) with the Actual E_T(o pt)[g]

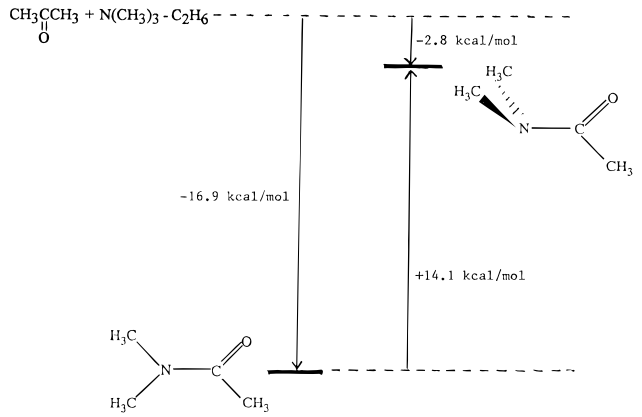
lactam	−Scheleyer (au)	GI_{Benson}[a] (kcal/mol)	strain (kcal/mol)	$-E_T$(est) (au)	$-E_T$(opt) (au)	RE **Loss** (kcal/mol)
			trans-Cyclohexene Analogue			
$\bar{2}$.2.2 (**1**)	400.7458	−55.36	9.7[b]	400.8186	400.78202	23.0
			trans-Cycloheptene Analogues			
3.$\bar{2}$.2 (**2**)	439.7726	−60.29	13[c]	439.8480	439.82191	16.4
$\bar{3}$.2.$\underline{2}$ (**3**)	439.7726	−60.29	13[c]	439.8480	439.82106	16.9
3.3.$\bar{2}$ (**4**)	478.7994	−65.22	17.8[b]	478.8750	478.84770	17.1
			trans-Cyclooctene Analogues			
$\bar{3}$.3.1 (**5**)	439.7726	−60.29	7.8[b]	439.8562	439.83632	12.5
$\bar{3}$.3.2 (**6**)	478.7994	−65.22	17.8[b]	478.8750	478.86017	9.3
$\bar{3}$.3.3 (**7**)	517.8262	−70.15	26.9[b]	517.8951	517.88266	7.8
			trans-Cyclononene Analogues			
$\bar{4}$.$\bar{3}$.3 (**8**)	556.8530	−75.08	38[d]	556.9121	556.91145	0.4
4.$\bar{3}$.3 (**9**)	556.8530	−75.08	38[d]	556.9121	556.91758	−3.4
			Model Compounds			
1-MePyr (**13**)	323.8353	−50.1[e]	*f*	323.9151	323.91275	1.5
N,*N*-DMA (**17**)	285.9478	−54.5[e]	*f*	286.0347	286.03017	2.8

[a] This is the simple sum of full resonance GI_{Benson} (Scheme 2) uncorrected for strain. [b] Obtain $\Delta H_f°$(g) from Pedley (ref 38) and subtract the sum of Benson group increments (ref 36). [c] Obtain $\Delta H_f°$(g) from Lias *et al*. (ref 39) and subtract the sum of Benson group increments (ref 36). [d] Strain energy estimated by calculating the difference in strain energies between the 4.3.3 and 3.3.1 bicyclic alkanes using the SPARTAN molecular mechanics package and adding this to the 7.8 kcal/mol strain energy in the 3.3.1 alkane. [e] Selected experimental data (see Table 2). [f] The strain energies are incorporated in the ΔH_f values used here which are the selected values for **13** and **17** from Table 2. [g] This table shows that use of the Schleyer increments predicts a value about 2.8 kcal/mol too low for *N*,*N*-dimethylacetamide (**17**) and 1.5 kcal/mol too low for 1-methylpyrrolidinone (**13**). The average discrepancy in these two model systems is 2.2 kcal/mol and correction using this number would reduce the RE loss (*e.g.* to 20.8 kcal/mol for the 2.2.2 system, 14.2 kcal/mol for the $3.\bar{2}.2$ system, *etc*.), make **8** "hyperstable" by 1.7 kcal/mol, and increase the "hyperstability" of **9** to 5.6 kcal/mol.

Scheme 3



Scheme 4



then addition of the ca. 6 kcal/mol amine inversion barrier brings this value to ca. 24 kcal/mol.

How do these values relate to the amide rotational barrier? Scheme 1 had earlier depicted the rotational transition state for *N*,*N*-dimethylacetamide (15.8 ± 1.0 kcal/mol). If one assumes that the inversion of the nitrogen depicted in the transition state is also about 6 kcal/mol then the orthogonal structure shown in Scheme 3 is ca. 21−22 kcal/mol less stable than the amide. Further insight can be obtained by employing the G2/MP2 data of Wiberg et al.[33] for the ground state and the lowest-energy-transition state for *N*,*N*-dimethylacetamide and its model compounds. The relevant relationship is depicted in Scheme 4. There are two particularly noteworthy points. The computed rotational barrier (14.1 kcal/mol) is the difference between the conventional resonance enthalpy (MCE, COSNAR, eq 9, etc.) and the enthalpy of the isodesmic equation shown for formation of the unconjugated CO−N bond (N in amide and model amine both pyramidal). This last enthalpy, calculated at −2.8 kcal/mol, is a balance between the bond energies of the two σ bonds broken and the two formed in Scheme 4. It is important to realize that the relationships depicted in eqs 1−7 (MCE, MCGI, and COSNAR), Table 2, and the 18.2 kcal/mol resonance energy derived in eq 9 do not correct for the formation of the CO−N σ bond. If one subtracts 2.8 from 18.2 kcal/mol, the result is 15.4 kcal/mol, which agrees well with the experimental rotational barrier (15.8 ± 1.1 kcal/mol). Of course, correction for the N-inversion barrier would yield 21−22 kcal/mol for the rotational process depicted in Scheme 3.

The bridgehead bicyclic lactams studied here introduce a new issue. For example, in the rather rigid $\bar{2}$.2.2 system the nitrogens of both the lactam and the amine are comparably pyramidal. If the inversion barriers (independent of resonance) are comparable then we return to the 21−22 kcal/mol of resonance energy depicted in Scheme 3. The larger more flexible lactams complicate this further by forcing greater planarity on the bridgehead nitrogens in the lactams than those in the amine.

In summary, the 18.2 kcal/mol resonance energy derived isodesmically can be corrected by 2.8 kcal/mol to correct for the CO−N σ bond in order to yield the enthalpy of activation (ca. 15.4 kcal/mol) for rotation. Correction of the rotational transition state to form a planar, orthogonal nitrogen brings this value to ca. 21−22 kcal/mol. This same value should appear in the 2.2.2 system where both nitrogens are comparably pyramidal rather than both planar. (The value in Table 4 is 23.0 kcal/mol and use of the optional correction noted in Table 4 would change this to 20.8 kcal/mol.)

Infrared Frequencies. The stretching frequencies of the carbonyl and (CO)−N bond linkages are considered to provide insights into the role of resonance in the bridgehead lactams.[2,14,15] One would anticipate loss of resonance to reduce the contribution of **10C**, therefore reducing the frequency of the (CO)−N vibration and increasing the frequency of the

Table 5. Comparison of Calculated Infrared Carbonyl Frequencies for Bridgehead Bicyclic Lactams and Model Compounds

lactam	ν_{CO}(uncorr) (cm^{-1})	ν_{CO}(corr) (cm^{-1})	ν_{CO}(exp) (cm^{-1})
$\bar{2}$.2.2 (**1**)	2058	1757	1761 (1755)[c]
3.$\bar{2}$.2 (**2**)	2007	1713	1713 (1711)[c]
$\bar{3}$.2.2 (**3**)	1996	1704	(1705)[c]
3.3.$\bar{2}$ (**4**)	1998	1705	
$\bar{3}$.3.1 (**5**)	1980	1690 (assumed)	1690.5
$\bar{3}$.3.2 (**6**)	1951	1665	(1677)[c]
$\bar{3}$.3.3 (**7**)	1952	1666	
$\bar{4}$.3.3 (**8**)	1923	1641	
4.$\bar{3}$.3 (**9**)	1921	1640	
1-MePyr (**13**)	1974	1685	1698
pyr Azir (**15**)	2171	1853	1843[d]
plan Azir (**16**)	2152	1837	

[a] Assumed the value for the $\bar{3}$.3.1 system, which is midway between the extreme values in the bridgehead bicyclic lactams, to be the standard for correction; correction factor = 0.8535. [b] Taken from ref 46. [c] See ref 14. [d] The experimental value is the an N-alkyl derivative.

Table 6. Frontier Molecular Orbitals for Bridgehead Bicyclic Lactams and Model Compounds (Orbital Energies in au Multiplied by 27.21 to Provide Units in eV)

lactam	E_{HOMO} (eV)	E_{Subjac} (eV)	E_{LUMO} (eV)
trans−Cyclohexene Analogue			
$\bar{2}$.2.2 (**1**)	9.87	11.40	−4.5
trans-Cycloheptene Analogues			
3.$\bar{2}$.2 (**2**)	9.79	11.13	−4.9
$\bar{3}$.2.2 (**3**)	9.79	11.15	−4.8
3.3.$\bar{2}$ (**4**)	9.60	11.03	−4.9
trans-Cyclooctene Analogues			
$\bar{3}$.3.1 (**5**)	9.74	11.05	−5.1
$\bar{3}$.3.2 (**6**)	9.79	10.89	−5.3
$\bar{3}$.3.3 (**7**)	9.50	10.86	−5.1
trans-Cyclononene Analogues			
$\bar{4}$.3.3 (**8**)	9.58	10.82	−5.5
4.$\bar{3}$.3 (**9**)	9.60	10.81	−5.3
Model Compounds			
1-MePyr (**13**)	9.96	10.95	−5.6
pyr Azir (**15**)	10.93	12.48	−4.4
plan Azir (**16**)	11.12	11.27	−5.8
N,*N*-DMA (**17**)	9.97	11.16	−5.6

carbonyl vibration. Unfortunately, the (CO)−N vibration (amide III) is very complex since it is heavily mixed with other C−C and C−H vibrations and is shared by a few vibrational modes. Additional difficulty arises from the differences in the ring strains of the different frameworks being compared. The more strained the framework, the more resistant it is to the framework stretching that incorporates (CO)−N. Correction of this factor is also not obvious. Hence, the (CO)−N vibrational frequencies were not employed.

In contrast, the carbonyl frequency is well isolated and provides significant insight. In Table 5 we list carbonyl frequencies for bridgehead bicyclic lactams and some model compounds. The experimental data agree reasonably well with the corrected data. Since carbonyl frequencies considerably reflect local geometry at carbon in addition to the overall resonance one must compare the lactam with the corresponding ketone.[46] Thus, the $\bar{2}$.2.2 system has its ν_{CO} some 30 cm^{-1} higher than the ketone and aziridinone (pyramidal) is about 21 cm^{-1} higher than cyclopropanone while 1-methylpyrrolidinone is about 52 cm^{-1} lower than the corresponding ketone.[46] The $\bar{3}$.2.2 lactam has a ν_{CO} comparable to that of the ketone.[46]

Frontier Molecular Orbitals. Table 6 lists orbital energies for the highest occupied molecular orbital (HOMO) and the first subjacent orbital as well as the lowest unoccupied molecular orbital (LUMO) for each of the bridgehead bicyclic lactams and model compounds studied. The nature of the frontier orbitals in amides, lactams, and distorted lactams has been discussed in line with experimental UV photoelectron spectroscopy (PES) data.[47,48] The most surprising aspect is how little variation there appears to be in the HOMO energy despite quite drastic changes in the overall bonding (e.g. a variation of ca. 20 kcal/mol or nearly 1 eV in resonance energy). For example, the calculated HOMO orbital energy in the orthogonal $\bar{2}$.2.2 system **1** is 9.87 eV while the energy of the HOMO in the fully-resonance stabilized 1-methylpyrrolidinone (**13**) is calculated at 9.96 eV. The reason is that in all of these cases, except the $\bar{2}$.2.2, the HOMO is an essentially nonbonding orbital (allylic ψ_2) with significant localization at nitrogen. For the $\bar{2}$.2.2 system **1** symmetry dictates that there is no mixing of the nonbonding n_N with the carbonyl π system. The result is that overall π overlap in the amide system does little to change the HOMO energy. Qualitatively, it appears that geometry and hybridization at N play the most significant roles.[49,50] Comparison of experimental ionization energies with orbital energy data is problematic since the appropriate comparison should really be with the calculated energy difference between the fully optimized structures of the neutral and the radical cation. Good correlations have been achieved between the orbital energies and the vertical ionization potentials (IP_v)[50] using the assumption of the validity of Koopmans' theorem.[51] However, one must be extremely cautious in these comparisons. First, as noted earlier, neither the adiabatic ionization potential (IP_a) nor the verticle ionization potential (IP_v) really correspond to $-E_{HOMO}$. The best comparisons are likely to occur when the PES ionization bands are similar in shape. However, the nearly planar manxine has an extremely sharp first IP band in contrast to pyramidal amines such as quinuclidine where the bands are significantly broader (e.g. $IP_v - IP_a$ in quinuclidine is 0.5 eV; the corresponding difference in triethylamine is ca. 0.9 eV).[49] The first IP bands in amides are usually quite sharp ($IP_a \approx IP_v$), but distorted amides such as **5** have broader bands.[48] Thus, comparisons between lactams, amides, and model amines are surprisingly complex.

Core Ionization Energies (O_{1S}, N_{1S}, $C_{1S}O$). Core (1S) ionization energies, obtained using X-ray photoelectron spectroscopy (XPS or ESCA), are widely considered to be measures of atomic charge.[52] The N_{1S} ionization energies of nitrogen atoms in aminimides (solid state) were correlated with carbonyl frequencies in a manner explicable using resonance arguments.[53] Similarly, we have found the relatively low N_{1S} ionization energy in 1-azabicyclo [3.3.1] nonan-2-one (**5**), its relatively high O_{1S} ionization energy, and relatively high $C_{1S}O$ ionization energy to be explicable in terms of reduced contribution of canonical structure **10C** in **5** relative to model pyrrolidinones.[54]

Table 7 lists core ionization energies calculated for the bridgehead lactams studied here. We have corrected the O_{1S}, N_{1S}, and $C_{1S}O$ ionization energies (assuming the validity of Koopmans' theorem[51]) by using experimental data[54] for 1-azabicyclo[3.3.1]nonan-2-one (**5**), which is assumed to be representative of the bridgehead lactams studied.

One striking point evident from Table 7 is the sharp separation of data into *trans*-cyclohexene, cycloheptene, cyclooctene, and

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Table 7. Calculated Core Ionization Energies (eV) for Oxygen, Nitrogen, and the Carbonyl Carbon Obtained from Optimized 6-31G* Core Orbital Energies (1 au = 27.21 eV) Corrected To Reproduce Experimental Data[54] for 1-Azabicyclo[3.3.1]nonan-2-one (**5**) with the Assumption of the Validity of Koopmans' Theorem[51]

lactam	O_{1s}[a]	N_{1s}[b]	C_{1s}[c]
	trans-Cyclohexene Analogue		
$\bar{2}$.2.2 (**1**)	537.35	404.75	291.01
	trans-Cycloheptene Analogues		
3.$\bar{2}$.2 (**2**)	536.88	404.83	290.86
$\bar{3}$.2.$\underline{2}$ (**3**)	536.83	404.88	290.86
3.3.$\bar{2}$ (**4**)	536.86	404.75	290.83
	trans-Cyclooctene Analogues		
$\bar{3}$.3.1 (**5**)	536.67 exptl	405.07 exptl	290.81 exptl
$\bar{3}$.3.2 (**6**)	536.41	405.09	290.75
$\bar{3}$.3.3 (**7**)	536.41	404.98	290.78
	trans-Cyclononene Analogues		
$\bar{4}$.$\underline{3}$.3 (**8**)	536.26	405.11	290.68
4.$\bar{3}$.3 (**9**)	536.23	405.17	290.70
	Model Compound		
1-MePyr (**13**)	536.36	405.40	290.78

[a] O_{1s} correction for **5**: $IP_{expt}/IP_{calc} = 536.67/558.49 = 0.9609$. [b] N_{1s} correction for **5**: $IP_{expt}/IP_{calc} = 405.07/423.63 = 0.9561$. [c] C_{1s} correction for **5**: $IP_{expt}/IP_{calc} = 290.81/308.48 = 0.9427$.

cyclononene sets. This appears to be another validation of the amide/olefin analogy. One notes that the $\bar{2}$.2.2 lactam, which should lack a contribution from **10C**, has the lowest N_{1S} (i.e., least positive N), the highest O_{1S} (least negative O), and the highest $C_{1S}O$ (most positive carbonyl carbon) although there is a natural tendency toward lower ionization energies with increasing molecular size.[52]

Protonation of Bridgehead Lactams. The proton affinities of lactams and their variation with distortion were discussed briefly in an earlier paper.[20] Unstrained lactams and amides are well-known to be much weaker bases than the corresponding amines in solution and in the gas phase (e.g. the gas-phase PA of dimethylethylamine is ca. 12 kcal/mol greater than that of *N*,*N*-dimethylacetamide[39]). Although basis sets much more extended than 6-31G* are necessary to provide precise agreement with experiment,[55] the 6-31G* basis set does a reasonable job and should do particularly well in comparisons in the series since these are isodesmic in nature.[42] It is widely agreed that protonation of amides in the gas phase as well as in solution is thermodynamically favored at oxygen. For example, an earlier MP2/6-31G*//4-31G study found that the PA for O-protonation of formamide is ca. 11.5 kcal/mol more favored than N-protonation.[56] In fact, an X-ray crystallographic structure of dimethylacetamide hydrochloride clearly shows O-protonation (anti to N).[57]

Table 8 provides E_T^{6-31G*} values as well as values corrected thermally (including ZPE) for N- and O-protonation in addition to selected geometric parameters. The O-protonated structures were all taken as anti to N (as in the crystallographic structure noted above) except the $\bar{2}$.2.2 system which was syn to N as noted earlier.[20] Geometries displayed in Table 8 indicate shorter C═N than C═O bonds in moderate-sized bridgehead lactams but longer C−N bonds where resonance stabilization is small.

N-protonation lengthens the C−N bond appreciably. It was previously noted that the resonance energies of O-protonated amides are in the range 35−45 kcal/mol—virtually double those of the corresponding unstrained amides.[20] O-protonation tends to decrease χ_N and τ in order to enhance resonance stabilization. It is striking how significantly the twist angles decrease on the O-protonated species. For example, in Table 8 one notes that the twist angle τ is only 34.1° in O-protonated 3.$\bar{2}$.2 while it is 70.1° in the N-protonated ion. The driving force is of course the substantial gain in resonance upon O-protonation. Similarly, one notes very significant movements of nitrogen toward planarity in the O-protonated species and, of course, toward pyramidalization in the N-protonated species (compare Tables 1 and 8).

Table 9 lists proton affinities (uncorrected and corrected for ZPE and thermal contributions) and compares the difference between N- and O-protonation. The absolute values of PA decrease by ca. 9 kcal/mol upon this correction but the energy differences are very similar. The experimental PA for *N*,*N*-dimethylacetamide (216.2 kcal/mol[39]) agrees reasonably well with the corrected PA at O (218 kcal/mol). O-protonation is favored over N-protonation by 11.8 kcal/mol in agreement with the earlier-cited study on formamide.[56] Interestingly, the computed difference in 1-methylpyrrolidinone is 14.8 kcal/mol, due almost entirely to the reduced proton affinity of 1-methylpyrrolidinone at N. These data should not, unfortunately, be experimentally accessible since protonation will occur totally on oxygen. Nevertheless, the ca. 3 kcal/mol disparity between the N-protonation values for 1-methylpyrrolidinone and *N*,*N*-dimethylacetamide is an independent validation of the 3−5 kcal/mol anomalous stabilization (i.e. reduced strain) in the 5-membered lactam. The computed value for O-protonation (corrected) for 1-methylpyrrolidinone (218.5 kcal/mol) is in reasonable agreement with experiment (216.8 kcal/mol).[39] In passing, it is interesting to note that N-protonation of aziridinone (pyramidal) appears to be 3−4 kcal/mol more favorable than O-protonation. This conclusion must be viewed with some caution. Full optimization of the N-protonated aziridinone ring opens the ion. We assumed a reasonable OC−N bond length of 1.55 Å in the N-protonated ring and surprisingly found it to be a local minimum.[58]

Conceptually, one can compare the experimental PA[39] values for 1-methylpyrrolidine (228.7 kcal/mol), cyclopentanone (198.9 kcal/mol), and 1-methylpyrrolidinone (216.8 kcal/mol, O-protonation) to understand that amines have PA values typically 25−30 kcal/mol higher than ketones in the gas phase while unstrained amides or lactams, which protonate on oxygen, are typically 20 kcal/mol more basic (higher PA values) than ketones. The extra 20−25 kcal/mol of resonance in the O-protonated amide (relative to the neutral) is responsible for this effect. Indeed, Table 9 indicates that N-protonation is favored by ca. 23 kcal/mol over O-protonation in the $\bar{2}$.2.2 system (**1**). The natural amine vs ketone difference is almost restored in this "amino ketone". Inductive effects also undoubtedly play a role in the proton affinity at nitrogen. Thus the PA of quinuclidine (233.1 kcal/mol)[39] is ca. 11 kcal/mol higher than that of 3-quinuclidone (221.9 kcal/mol)[39] which has the carbonyl on C3 rather than C2 as in **1**. From Table 9 it is apparent that the PA at nitrogen in **1** is about 4 kcal/mol higher relative to the slightly less pyramidal N in the 3.$\bar{2}$.2 framework (**2**) and fully 22 kcal/mol higher than for *N*,*N*-dimethylacetamide. In contrast, the absence of resonance stabilization in the O-protonated $\bar{2}$.2.2 system lowers the PA at O by 12 kcal/mol relative to *N*,*N*-dimethylacetamide or 1-methylpyrrolidinone. It is clear that as the bridgehead N atoms approach planarity in rigid bicyclic systems PA values have a tendency to decrease due to the strain in the 4-coordinate nitrogen. These strain effects, previously noted in protonated manxine,[49] are nonetheless outweighed by the ability of larger systems to disperse charge and hence PA at nitrogen is larger in **7** than it is in 1-methylpyrrolidinone.

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Table 8. Optimized (6-31G*) E_T (without and with zero point energy and thermal corrections) and Selected Geometric Parameters[28] for N- and O-Protonated Amides and Lactams (NH^+ and OH^+, respectively)[a]

protonated lactam	$-E_T$ (au)	corr $-E_T$ (au)	$r_{C=O}$ (Å)	r_{CO-N} (Å)	χ_N (deg)	χ_{CO} (deg)	τ (deg)
			trans-Cyclohexene Analogue				
$\bar{2}$.2.2 (**1**NH^+)	401.16261	400.95079	1.167	1.504	57.6	0.0	89.9
(**1**OH^+)	401.12425	400.91451	1.255	1.366	63.0	4.2	79.8
			trans-Cycloheptene Analogues				
3.$\bar{2}$.2 (**2**NH^+)	440.19546	439.95129	1.169	1.506	49.4	0.2	70.2
(**2**OH^+)	440.17654	439.93359	1.287	1.300	41.1	15.4	34.1
$\bar{3}$.2.2 (**3**NH^+)	440.19286	439.94832	1.169	1.518	60.6	0.1	58.4
(**3**OH^+)	440.17699	439.93375	1.299	1.290	45.5	16.6	31.4
3.3.$\bar{2}$ (**4**NH^+)	479.22146	478.94477	1.171	1.506	41.9	0.2	71.5
(**4**OH^+)	479.20493	478.92953	1.289	1.297	31.8	17.1	37.3
			trans-Cyclooctene Analogues				
$\bar{3}$.3.1 (**5**NH^+)	440.20027	439.95627	1.168	1.520	54.3	1.6	37.1
(**5**OH^+)	440.19729	439.95406	1.292	1.290	40.8	10.2	18.9
$\bar{3}$.3.2 (**6**NH^+)	479.21660	478.93975	1.168	1.534	45.2	1.8	29.0
(**6**OH^+)	479.22697	478.95098	1.297	1.286	35.5	10.6	18.1
$\bar{3}$.3.3 (**7**NH^+)	518.24577	517.93671	1.172	1.518	42.8	1.0	52.4
(**7**OH^+)	518.25023	517.94236	1.298	1.287	16.0	15.1	30.2
			Model Compounds				
1-MePyr (**13**NH^+)	324.25195	324.08117	1.162	1.534	51.4	0.4	12.3
(**13**OH^+)	324.27537	324.10476	1.291	1.279	3.7	1.4	0.3
N,*N*-DMA (**17**NH^+)	286.37377	286.21158	1.166	1.524	56.3	0.0	89.9
(**17**OH^+)	286.39245	286.23046	1.298	1.283	0.5	0.6	1.8

[a] All of the O-protonated species are assumed to be *anti* to N except for the $\bar{2}$.2.2 system where it is *syn* to N.[20]

Table 9. Calculated Proton Affinities (PA, in kcal/mol) Uncorrected and Corrected for ZPE and Thermal Corrections (See Ref 60, Abboud *et al*., for PA Values at O and N of Smaller Lactams and Amides in Which Correlation Effects and Corrections for Basis Set Superposition Errors Are Included and Comparisons Made with Experimental PA Data)

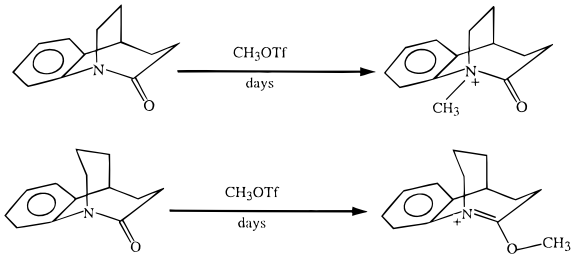
	uncorrected (ZPE/thermal) (kcal/mol)			corrected (ZPE/thermal) (kcal/mol)		
lactam	PA at N	PA at O	diff	PA at N	PA at O	diff
			trans-Cyclohexene Analogue			
$\bar{2}$.2.2 (**1**)	238.8	214.7	24.1	228.9	206.2	22.8
			trans-Cycloheptene Analogues			
3.$\bar{2}$.2 (**2**)	232.8	222.5	10.2	224.7	213.6	11.1
$\bar{3}$.2.2 (**3**)	233.3	223.3	10.0	223.6	214.4	9.1
3.3.$\bar{2}$ (**4**)	234.5	224.2	10.4	224.7	215.1	9.6
			trans-Cyclooctene Analogues			
$\bar{3}$.3.1 (**5**)	228.4	226.5	1.9	219.0	217.6	1.4
$\bar{3}$.3.2 (**6**)	223.7	230.2	−6.5	214.1	221.2	−7.1
$\bar{3}$.3.3 (**7**)	227.9	230.7	−2.8	218.1	221.6	−3.5
			Model Compounds			
1-MePyr (**13**)	212.9	227.5	−14.7	203.7	218.5	−14.8
Pyr Azir (**15**)	205.0[a]	201.3	3.7	196.3[a]	192.6	3.8
N,*N*-DMA (**17**)	215.6	227.5	−11.7	206.5	218.3	−11.8

[a] N-Protonated Aziridinone Calculated with Fixed OC−N of 1.55 Å, since the structure ring opens during optimization (see ref 58).

The N- versus O-protonation "crossover" points appear to be in the geometry regions defined by the $\bar{3}$.3.1, $\bar{3}$.3.2, and $\bar{3}$.3.3 structures. Since the geometry variations are discontinuous (constrained by the bicyclic frameworks) and since differences in molecular size confound the issue slightly, the intrinsic amide group structural requirements for N- versus O-protonation "crossover" are not fully defined. Obviously, the effects of solvent will also be important and one would anticipate slight favoring of solvation of the O-protonation form due in part to steric accessibility of the basic atom to solvent. These data suggest that the $\bar{3}$.3.1 molecule would be an interesting system for experimental protonation studies.

Some insight into the question of N- vs. O-protonation has been provided by Brown and Wang (Scheme 5).[59a,b] Their observations are in line with our predictions of N-protonation of the $\bar{3}$.2.2 system and O-protonation of the $\bar{3}$.3.2 system. Brown is careful to note that it is not clear whether these very slow reactions are under kinetic or thermodynamic control. Our predictions, of course, relate to thermodynamic parameters. Werstiuk, Brown, and Wang have also examined N- vs O-protonation of bridgehead lactams using semiempirical theory.[59b]

Scheme 5



Conclusions

The properties of the bridgehead bicyclic lactams fall rather neatly into classes based upon the *trans*-cycloalkene analogy. For example, the CO−N bond in the $\bar{2}$.2.2 system, a *trans*-cyclohexene analogue, is calculated to be 1.433 Å, while the 3.$\bar{2}$.2, $\bar{3}$.2.2, and 3.3.$\bar{2}$ systems, which are all *trans*-cycloheptene analogues, have CO−N bond lengths close to 1.400 Å. Losses in resonance energy also follow this pattern. The $\bar{2}$.2.2 system, which lacks resonance by symmetry, "loses" 23.0 kcal/mol of resonance energy (see Table 4) compared to a hypothetical model maintaining full resonance and the ring strain of the 2.2.2 framework. Another way of thinking about resonance is to consider the isodesmic approaches of eqs 1−7. The data in Table 2 suggest resonance energies on the order of 18 kcal/mol for this comparison of unstrained amides with separated amines and ketones. Correction of this value by ca. 2.8 kcal/mol for formation of the CO−N σ bond leads to a value comparable to the CO−N rotational barrier (gas phase) of *N*,*N*-

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dimethylacetamide (ca. 15 kcal/mol). If one "planarizes" the transition state by adding the 6 kcal/mol N inversion barrier, resonance stabilization is ca. 21 kcal/mol. This value corresponds roughly to the above calculated value for the rigid $\bar{2}$.2.2 system where N in both the lactam and the amine are comparably pyramidal if one employs the ca. 2 kcal/mol correction in Table 4.

We note that 1-methylpyrrolidinone appears to have about 3−5 kcal/mol of "extra stability" via the isodesmic approaches described in this paper. This is not due to an anomalously strong resonance stabilization but rather to unusually low strain in the lactam as a result of fewer nonbonded repulsions than in the model compounds. This is also apparent in the calculated proton affinity at N of this compound which is about 3 kcal/mol lower than those calculated for the model compounds.

We have applied the hyperstability concept, previously employed by Schleyer and co-workers to rationalize the low enthalpies of hydrogenation for medium-sized bridgehead bicyclic alkenes. When one employs isodesmic logic [e.g. methyl capping or comparison with bicyclic ketones and bridgehead amines (i.e. COSNAR)], hyperstability results for the 4.3.3 system. The apparent 3−4 kcal/mol of hyperstability in the 4.$\bar{3}$.3 system is really a manifestation of the higher strain of the model system rather than any "tightening" of the bonding in the amide linkage. This is also true for the hyperstable bridgehead olefins. It is not that the olefinic linkage is unnaturally short or strong but that there is more strain in the saturated systems.

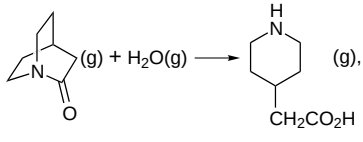
The concept of hyperstability in bridgehead bicyclic alkenes is, nevertheless, of significant practical utility since addition to the double bond is *the* characteristic olefin reaction. Enthalpies of hydrogenation are experimentally accessible and, since the transition state for hydrogenation involves the start of the saturation of the double bond, resistance to hydrogenation should also have a kinetic component.

In contrast to the olefins, the characteristic amide reaction is nucleophilic acyl substitution. Hyperstability is not in immediate evidence for this *net* reaction. For example, let us examine the hypothetical gas-phase hydrolysis reaction depicted in eq 10. The enthalpy of hydrolysis is calculated using published thermochemical data to be +4.4 kcal/mol. It may not be generally known that gas-phase hydrolysis of simple amides is

$$CH_3CON(CH_3)_2(g) + H_2O(g) \rightarrow CH_3COOH(g) + HN(CH_3)_2(g), \quad \Delta H_r^\circ = +4.4 \text{ kcal/mol} \quad (10)$$

endothermic. In solution, the formation of ionic products and the difference in solvation energies of the reactants and products is apparently the driving force for hydrolysis.

In Table 10 we list ΔH_f°(g) values for the bridgehead lactams using eqs 8 along with the calculated gas-phase enthalpies of hydrolysis. Not surprisingly, gas-phase hydrolysis of the $\bar{2}$.2.2 lactam **1** is exothermic by 27−28 kcal/mol (eq 11). This ca.



(g), $\Delta H_r^\circ = -27.5$ kcal/mol (11)

30 kcal/mol difference relative to *N*,*N*-dimethylacetamide is due to the loss of resonance as well as the strain in **1** which total about 30 kcal/mol and is probably an underestimate since the product will probably have internal hydrogen bonding. Table 10 indicates that hydrolysis of the 4.$\bar{3}$.3 lactam ("hyperstable" by the isodesmic approaches noted earlier, e.g. see Table 4) is similarly at least 16−17 kcal/mol more exothermic than that of

Table 10. Calculated ΔH_f°(g) for Bridgehead Bicyclic Lactams Using the Form of Eq 8 Wherein Optimized E_T(6-31G*) Data from Table 1 (Uncorrected for ZPE and Thermal Energies) and the Sum of "Schleyer" Increments[44] Are Employed[b]

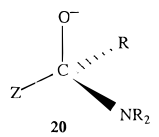
	ΔH_f°(g) (kcal/mol)	$\Delta H^\circ_{hydrolysis}$(g)[a] (kcal/mol)
trans-Cyclohexene Analogue		
$\bar{2}$.2.1 (**1**)	−22.7	−27.5
trans-Cycloheptene Analogues		
3.$\bar{2}$.2 (**2**)	−30.9	−17.8
$\bar{3}$.2.$\bar{2}$ (**3**)	−30.4	−24.7
3.3.$\bar{2}$ (**4**)	−30.3	−19.8
trans-Cyclooctene Analogues		
$\bar{3}$.3.1 (**5**)	−40.0	−15.0
$\bar{3}$.3.2 (**6**)	−38.1	−15.5
$\bar{3}$.3.3 (**7**)	−35.4	−19.7
trans-Cyclononene Analogues		
$\bar{4}$.$\bar{3}$.3 (**8**)	−36.7	−23.3
4.$\bar{3}$.3 (**9**)	−40.5	−16.6
Model Compounds		
1-methylpyrrolidinone[b] (**13**)	−48.6	+1.2
N,*N*-dimethylacetamide[b] (**17**)	−51.7	+2.3

[a] Benson parameters[36] were used to estimate ΔH_f°(g) of products. [b] The calculated gas-phase enthalpies of hydrolysis (*e.g.* eqs 10 and 11) are also listed. Use of the 2.2 kcal/mol correction noted in the heading of Table 4 would make the ΔH_f°(g) values more negative and make the $\Delta H^\circ_{hydrolysis}$ values less negative by this value.

N,*N*-dimethylacetamide. This reflects the decrease in strain in transforming a 4.3.3 bicyclic network to a cyclononane system. This is a strong thermodynamic driving force, and "hyperstability" does not appear to be useful in this thermodynamic context. However, if one were to examine ring opening reactions of bridgehead olefins which totally cleaved the olefinic linkage, the hyperstability concept would also lose its significance.

We can now attempt a comparison of π distortion energies in a bridgehead amide and the corresponding bridgehead alkene. The experimental ΔH_f° value for bicyclo[3.3.1]non-1(2)-ene (**12**) is 7.4 kcal/mol (4.5 and 10.2 kcal/mol more stable than its isomers bicyclo[4.2.1]non-1(2)-ene and bicyclo[4.2.1]non-1(8)-ene, respectively).[61] We first assume the ring strains in both amide **5** and alkene **12** to be that of the alkane (7.8 kcal/mol, see Table 4). Comparison of the sum of Benson group increments modified by ring strain yields a value of −7.5 kcal/mol for **12** which is 14.9 kcal/mol lower than the experimental value. Similarly, if we compute the sum of the Benson group increments for **5** (using the full amide resonance increments, see Scheme 2) and the ring strain we obtain an estimate of −52.5 kcal/mol which is 12.5 kcal/mol lower than the calculated ΔH_f°(g) in Table 10.

What then might be the practical chemical utility of the "hyperstable lactam" concept beyond interesting academic discussions of isodesmic models of resonance? The answer appears to lie in actual processes that disrupt resonance while keeping the ring intact. Protonation at nitrogen could be one such measure. However, the larger bridgehead lactams protonate at oxygen. The more significant point is that the 4-coordinate intermediates en route to nucleophilic substitution (e.g. **20**) saturate the carbonyl carbon thus removing resonance



20

while keeping the ring system intact and, in some cases, possibly increasing strain. (Since structure **20** will have both C and the

adjacent N in the sp^3 hybridization state rather than sp^2 as in planar amides, this aspect will mimic the change upon hydrogenation of olefinic carbon atoms.) Moreover, whereas the 4-coordinate intermediate in an acyclic or simple monocyclic lactam can allow the nitrogen to "relax" to a pyramidal structure, the constraints imposed by the bicyclic frameworks such as 4.3.3 do not permit this "relaxation" thus adding to the destabilization of the intermediate. If this were to be true then added stability for 4.$\bar{3}$.3 should be apparent relative to four-coordinate intermediates similar to **20** and, presumably, the transition states leading to them. In this case, the hyperstability of a lactam such as 4.$\bar{3}$.3 could possibly manifest itself in a slower hydrolysis rate relative to *N*,*N*-dimethylacetamide despite the fact that its hydrolysis is far more exothermic.

The calculations, when uniformly corrected, nicely reproduce the known trends in carbonyl frequencies of the bridgehead lactams where higher frequencies (corrected for ring size) reflect reduced resonance stabilization. The E_{HOMO} values vary surprisingly little for a range of related systems which vary by roughly 20 kcal/mol (ca. 0.8 eV) in resonance stabilization. The reason is that the HOMO is a nonbonding orbital primarily localized on nitrogen (totally so for the $\bar{2}$.2.2 system due to symmetry) and variations in energy are primarily due to local geometry and hybridization at nitrogen rather than π overlap. In contrast, the LUMO energies vary significantly due to changes in overlap in this antibonding orbital. The core (O_{1S}, N_{1S}, and $C_{1S}O$) orbital energies reflect the *trans*-cycloalkene paradigm and appear to be sensitive probes of resonance stabilization in amides. Dipole moments may reflect increases in resonance. Thus, for the $\bar{2}$.2.2 system the dipole moment is calculated to be 4.34 D and this is 0.5 D higher than the 4.$\bar{3}$.3 system. However, the calculated changes are not very large and the relationship between resonance and dipole moment is not straightforward in these systems.

Unstrained amides and lactams protonate on oxygen due to the enhanced resonance in the O-protonated structure as well as the loss of resonance in the N-protonated structure which combine to overwhelm (by 11−12 kcal/mol) the greater intrinsic basicity (25−30 kcal/mol) of amines relative to ketones. In contrast, the $\bar{2}$.2.2 system favors N-protonation by ca. 24 kcal/mol since it is an "amino ketone". N- to-O-protonation crossover appears to occur around the geometries exhibited by the $\bar{3}$.3.1, $\bar{3}$.3.3, and $\bar{3}$.3.2 structures. Movement toward planarization at nitrogen decreases the PA at this position and concomitant increases in π overlap as the systems increase in size enhance PA at oxygen. Obviously, solvent effects will play a significant role in this balance. The experimental observation by Brown and Wang of N-methylation of a $\bar{3}$.2.2 derivative and O-methylation of a $\bar{3}$.3.2 derivative supports the calculational predictions, although these workers are cautious in noting that it is not clear whether this slow reaction is under kinetic or thermodynamic control.

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