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Reliable Determination of Amidicity in Acyclic Amides and Lactams

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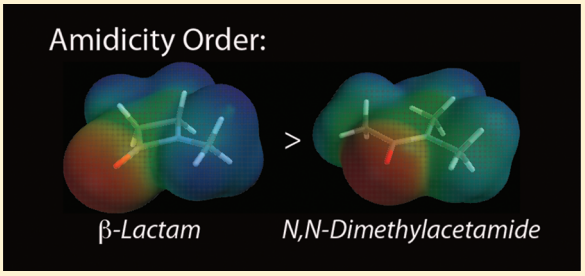
Supporting Information

ABSTRACT: Two independent computational methods have been used for determination of amide resonance stabilization and amidicities relative to *N*,*N*-dimethylacetamide for a wide range of acyclic and cyclic amides. The first method utilizes carbonyl substitution nitrogen atom replacement (COSNAR). The second, new approach involves determination of the difference in amide resonance between *N*,*N*-dimethylacetamide and the target amide using an isodesmic *trans*-amidation process and is calibrated relative to 1-aza-2-adamantanone with zero amidicity and *N*,*N*-dimethylacetamide with 100% amidicity. Results indicate excellent coherence between the methods, which must be regarded as more reliable than a recently reported approach to amidicities based upon enthalpies of hydrogenation. Data for acyclic planar and twisted amides are predictable on the basis of the degrees of pyramidalization at nitrogen and twisting about the *C*−*N* bonds. Monocyclic lactams are predicted to have amidicities at least as high as *N*,*N*-dimethylacetamide, and the *β*-lactam system is planar with greater amide resonance than that of *N*,*N*-dimethylacetamide. Bicyclic penam/em and cepham/em scaffolds lose some amidicity in line with the degree of strain-induced pyramidalization at the bridgehead nitrogen and twist about the amide bond, but the most puckered penem system still retains substantial amidicity equivalent to 73% that of *N*,*N*-dimethylacetamide.



INTRODUCTION

Amide linkages are ubiquitous in proteins, peptides, and natural or synthetic molecules and in most of these they possess, characteristically, a high degree of rigidity on account of resonance between the nitrogen lone pair and the carbonyl.[1] While the resonance hybrids **I** and **II** have been used universally to explain this (Figure 1a), there is a more contemporary view, borne out by structural, electronic, and computational evidence that the resonance overlap is largely between nitrogen and carbon with little charge transfer to oxygen, a mechanism nicely explained by Wiberg's frontier orbital approach in which the HOMO lone pair on nitrogen interacts with the LUMO of the carbonyl, which has little contribution from oxygen (Figure 1b).[2−4] The high π bond character between nitrogen and carbon accounts for the restricted rotation in acyclic amides as well as short *C*−*N* bonds and planarity at nitrogen, as exemplified in archetypal amides such as acetamide or *N*,*N*-dimethylacetamide. The valence bond representation of amide bonds in Figure 1a is completed by a third resonance form, **III**, with no *C*−*N* pi character and on account of positive polarity at carbon and the electronegativity of nitrogen, must be destabilizing.

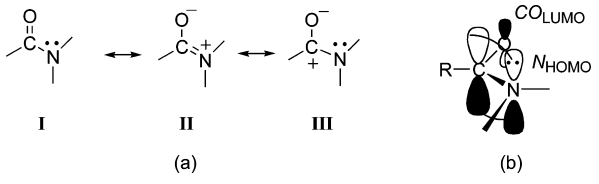


Figure 1. (a) Resonance and (b) HOMO−LUMO interaction in simple amides.

This said, a good number of amides deviate from planarity at nitrogen because of enforced twisting about the *C*−*N* bond,[5−13] which may be due to steric effects (Figure 2a) or cyclic forms that lock the nitrogen lone pair out of alignment with the carbon $2p_z$ orbital (Figure 2b).[5,6,14−22] Reduced conjugation is also found when the amide nitrogen is incorporated either into a small ring or at a bicyclic bridging position, which reduces the angle at nitrogen (Figure 2c).[23−26] In all such cases, there is a partial or even complete disconnection between the nitrogen lone pair and the amide carbonyl, and not only do the nitrogens become pyramidal, but

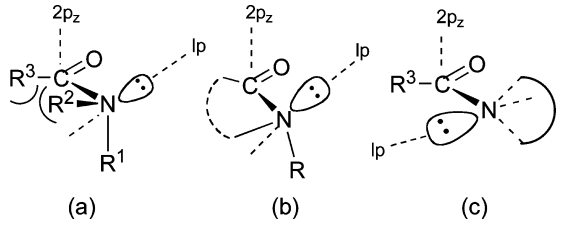


Figure 2. (a) A sterically twisted amide; (b) a twisted lactam; (c) an angularly constrained amide; dashed lines represent axes of the C2p_z orbital and nitrogen lone pairs.

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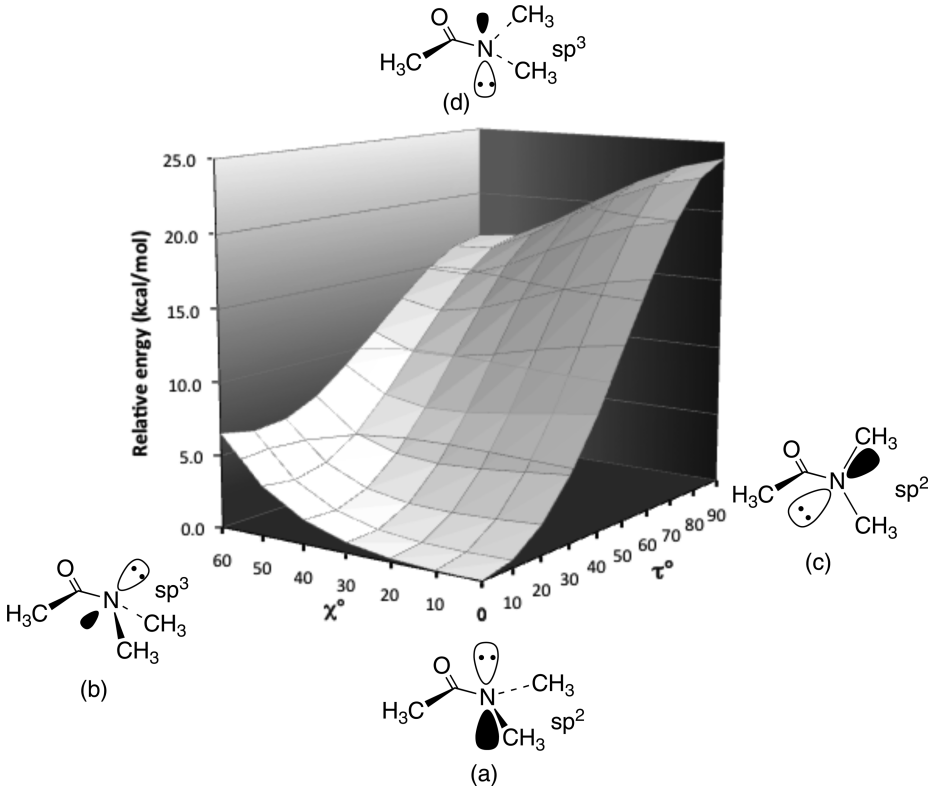


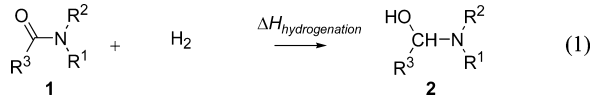
Figure 3. B3LYP/6-31G(d) energy surface for deformation of *N*,*N*-dimethylacetamide **3**. χ and τ are the Winkler–Dunitz pyramidalization and twist parameters in degrees.[34,35] Structures correspond to (a) the planar lowest energy conformer; (b) an untwisted form with sp^3 hybridized nitrogen; (c) a fully twisted form with sp^2 hybridized nitrogen; and (d) a fully twisted form with sp^3 hybridized nitrogen.

also the *C*–*N* bonds tend toward single bond character. There is considerable evidence that strongly twisted amides behave as amino ketones and exhibit enhanced reactivity. In certain cases they are readily hydrolyzed or can even be reduced.[15,27−33]

Interest in twisted and atypical amides has resulted in a need to understand not only the physical and chemical consequences of disconnection between the amide nitrogen lone pair and its carbonyl, but also to calibrate resonance in such amides.

Figure 3 illustrates the B3LYP/6-31G(d) energy surface for *N*,*N*-dimethylacetamide where the coordinates represent the degree of twist about the *C*–*N* bond and pyramidality at nitrogen (represented by the Winkler–Dunitz τ and χ parameters, respectively; τ represents twist from 0–90° in the lowest energy direction about the *C*–*N* bond, and χ varies between 0° for planar sp^2 hybridized nitrogen to 60° for pure sp^3 hybridized nitrogen).[34,35] Several features are evident upon deformation from the ground state planar structure (Figure 3a). First, twisting about the *C*–*N* bond in *N*,*N*-dimethylacetamide and pyramidalization at nitrogen are concomitant processes. Second, the energy of *N*,*N*-dimethylacetamide is relatively insensitive to modest deviations from planarity at nitrogen. The profile along the χ axis supports Wiberg's earlier calculations demonstrating a very shallow bending deformation energy for formamide.[2,36] At the B3LYP/6-31G(d) level, complete sp^3 hybridization without twist (Figure 3b) results in a loss of only about 6.5 kcal mol^{-1}, about a quarter of the resonance stabilization that is lost through rotation of the lone pair into the plane of the molecule without deformation at nitrogen (Figure 3c) and just over a third of the energy lost upon relaxation and pyramidalization of the completely twisted structure (Figure 3d). Where the nitrogen lone pair is in an sp^3 hybridized orbital, which is coplanar with the carbonyl carbon $2p_z$ orbital, an appreciable degree of resonance is retained. Third, relative to the bending deformation, twist about the *C*–*N* bond raises the energy of *N*,*N*-dimethylacetamide quite rapidly. Finally, the lowest energy pathway between planar *N*,*N*-dimethylacetamide (τ, χ = 0°) and fully relaxed twisted *N*,*N*-dimethylacetamide (τ = 90, χ = 60°) is clearly nonlinear.

While interpolation onto this type of surface based upon the degree of twist and pyramidality in other, similar amides may provide an estimate of their residual resonance, there have been several other molecule-specific approaches. Greenberg has looked at a number of computational methods for determining the resonance energies in various open chain and twisted bicyclic amides. These include "methyl capping", and carbonyl substitution nitrogen atom replacement (COSNAR).[17,18,37] More recently, Csizmadia and co-workers defined a new "amidicity" index, which purports to quantify relative amide character for a wide range of amides.[38−40] Their method utilizes computed enthalpies of hydrogenation of the amide carbonyls (eq 1), which should reflect the degree of amide character; a high degree of resonance stabilization should result in more positive enthalpies of hydrogenation and vice versa.



(1)

In their approach, $\Delta H_{hydrogenation}$ for iconic amides *N*,*N*-dimethylacetamide **3** and fully twisted 1-aza-2-adamantanone **4** were respectively assigned 100 and 0% "amidicity", which they have defined as percentage amide character. The amidicity for other amides was interpolated from their computed

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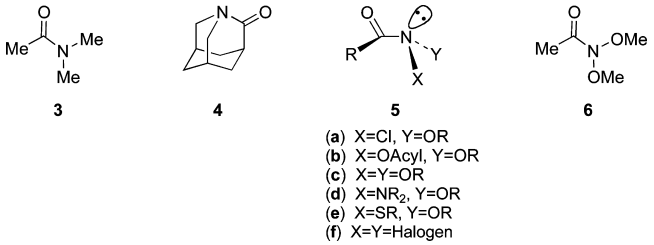
$\Delta H_{hydrogenation}$ using a two-point plot of these extreme amidicities against their enthalpies of hydrogenation. A wide range of amides were examined including small lactam structures.



For a number of years, we have studied anomeric amides **5**, amides bearing two heteroatoms at the amide nitrogen.[41−50] These amides possess highly pyramidalized amide nitrogens on account of the combined electron demand of the two heteroatoms. At the expense of resonance stabilization, the nitrogen rehybridizes from sp^2 toward sp^3 since in this manner the electron demand of the electronegative atoms is better satisfied. Where both atoms attached to nitrogen are either chlorine or oxygen, the pyramidalization is complete. In order to quantify the degree of residual resonance stabilization in these amides, we required an accurate computational means of determining amidicity. Application of the hydrogenation method of Csizmadia was considered less suited to this end for a number of reasons. First, their calculations for aminol hydrogenated products require use of arbitrary nonground state geometries free from secondary interactions such as hydrogen bonding so that the enthalpy change reflects, solely, changes in resonance. While they accomplished this for simple amides by fixing the HOCN dihedral angle in **2** at 180°, the method was considered to be less suited to the complex structures of anomeric amides with additional heteroatoms at nitrogen. Second, it requires full frequency analysis for each amide to compute enthalpic contributions for each molecule **1** and its hydrogen addition product **2**.

We recently described two independent methods, the first a new *trans*-amidation method and the second Greenberg's COSNAR,[17,18,37] which gave nearly identical results for one anomeric amide, *N*,*N*-dimethoxyacetamide.[50] *N*,*N*-Dimethoxyacetamide was computed to have resonance stabilization of about −8.6 kcal mol^{-1} and an amidicity of about 47% that of *N*,*N*-dimethylacetamide.

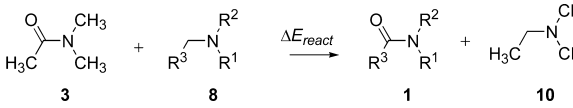
In this paper, we outline in detail these methods and show that they give consistent resonance stabilization energies for a wide range of amides including small lactams where, in our opinion, the results of Csizmadia are in error. The results proffer an interesting finding on β-lactams and model structures for penicillin and cephalosporin antibiotics, which, contrary to popular dogma, have high amidicities.

RESULTS AND DISCUSSION

The COSNAR method determines the stabilization gained through resonance by translocating a carbonyl and an amine nitrogen from **7** and **8** into the same skeleton to give amide **1** and hydrocarbon **9**. Isodesmically, this is reflected in the reaction energy for eq 2, and the method is well suited to systems where strain influences are found, since the strain component is similarly conserved in all elements of the reaction. Amidicity of **1** is determined as a percentage of the COSNAR energy for *N*,*N*-dimethylacetamide.

(2)

Our *trans*-amidation method computes the total destabilization of an amide **1** relative to *N*,*N*-dimethylacetamide **3** using eq 3. The maximum possible loss of resonance can be estimated



(3)

from the destabilization in the case of the fully twisted and strain-free 1-aza-2-adamantanone **4**. For instance, at the B3LYP/6-31G(d) level, this has been computed to be 18.17 kcal mol^{-1}.[50] In straightforward cases where the amide in question **1** is not stabilized or destabilized by other factors, the residual amide resonance, RE, can be determined as $-(18.17 - \Delta E_{react})$ kcal mol^{-1} and should be similar in value to that obtained from eq 2, a COSNAR analysis for the same amide. The percentage amidicity relative to *N*,*N*-dimethylacetamide is then derived from eq 4.

$$100 \times (18.17 - \Delta E_{react})/18.17\% \quad (4)$$

In the *trans*-amdiation method, ΔE_{react} is comprised of a resonance component together with any additional stabilization or destabilization quanta where these manifest themselves in products but not reactants. As depicted in eq 5, such quanta might represent a change in strain energy or a difference in an inductive effect of substituents, and when such factors impact upon the reaction energy, these must be evaluated separately and deducted from ΔE_{react} to reveal the resonance component.[51]

$$\Delta E_{react} = \Delta E_{resonance} + \Delta E_{strain} + \Delta E_{inductive} \quad (5)$$

Together with the common structures *N*,*N*-dimethylacetamide **3** and *N*,*N*-dimethylethylamine **10**, the combination of the *trans*-amidation reaction and COSNAR requires calculation of minimum energy structures of only four new compounds (**7**, **8**, **1**, and **9**) for each amide. In addition, the isodesmic nature of eqs 2 and 3 should avoid the need for calculation of enthalpy contributions through a full frequency analysis of each molecule, since these largely cancel.[18,52]

The resonance energies of *N*,*N*-dimethylacetamide have been determined by both the *trans*-amidation and COSNAR methods at various levels of theory, and the results are presented in Table 1. Values were consistently similar and relatively unchanged at B3LYP with larger basis sets or at MP2 post-Hartree−Fock levels, though the latter presented slightly lower stabilizations with improvement in correlation energy. This, together with the computational efficiency, as well as the relative insensitivity of the DFT calculations to the choice of basis set, indicates that computations at the B3LYP/6-31G(d) level are justified. In addition, the similarity of the results at B3LYP/6-31G(d) with those from a calculation at this level, but incorporating ZPE and enthalpy corrections to the electronic energies confirms the expected cancellation of enthalpy contributions in these isodesmic reactions.

We have obtained B3LYP/6-31G(d) amide resonance energies and amidicities by both the *trans*-amidation and COSNAR methods for the range of amides and lactams **11**−**24**. For a good number of these, amidicities were also computed by

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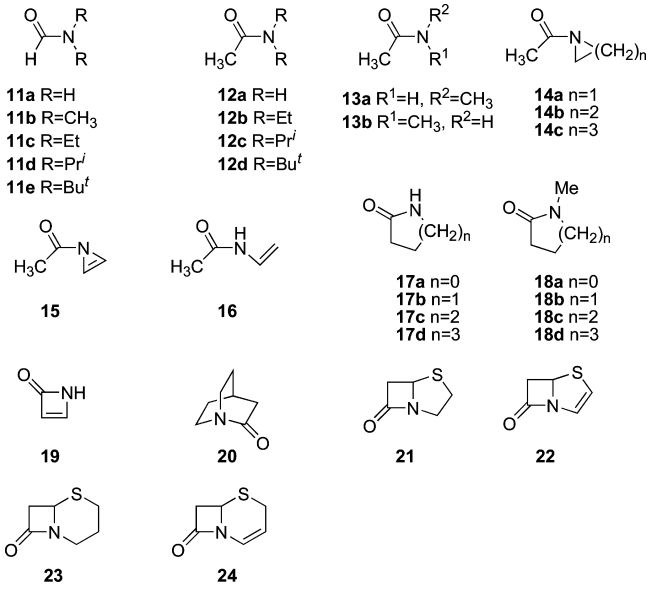
Table 1. *trans*-Amidation and COSNAR Energies (kcal mol^{-1}) for *N,N*-Dimethylacetamide 3 at Various Levels of Theory

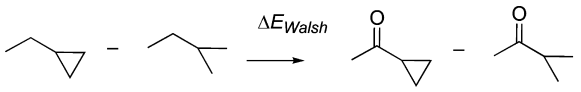
	N,N-dimethylacetamide **3**	
method	RE[a]	ΔE_{COSNAR}[b]
B3LYP/6-31G(d)	−18.17	−18.53
B3LYP/6-31G(d) (freq.)[c]	−18.06	−18.07
B3LYP/6-31G(d,p)	−18.41	−18.78
B3LYP/6-311+G(d,p)	−17.55	−18.15
B3LYP/cc-pVTZ	−17.91	−18.67
MP2/6-31G(d)	−17.63	−17.69
MP2/6-31G(d,p)	−17.59	−17.87
MP2/6-311+G(d,p)	−15.58	−16.36
MP2/cc-pVTZ	−16.97	−17.61
G3/MP2[d]	−16.32	−16.75

[a]Calculated from eq 3 for 1-aza-2-adamantanone; RE = $-\Delta E_{react}$. [b]Calculated from eq 2. [c]Electronic energies inclusive of ZPE and enthalpy corrections for all structures. [d]MP2/6-31G(d) optimized energy with MP2/6-311++G(2df,2p)//MP2/6-31G(d) basis set correction and QCISD(T)/6-31G(d)//MP2/6-31G(d) correlation correction.

Csizmadia and co-workers using their hydrogenation method. Data for all amides in this study are presented in Table 2 together with percentage amidicities by our methods as well as the results for the same amides at B3LYP/6-31G(d) and B3LYP/6-31G(d,p) where given by Csizmadia and co-workers.[38,39]



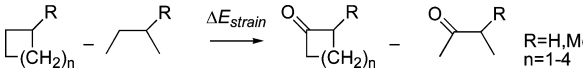
In the case of 3-membered cyclic amines in **14a** and **15**, the COSNAR method underestimates the stabilization energy since the ketone is partially stabilized by conjugation with the Walsh orbitals of the three membered ring, while in the product amide this resonance interaction is largely replaced by lone pair resonance. The optimized structures of the ketone and the amide are illustrated in Figure 4 and demonstrate the change in conformation of the acetyl group; in Figure 4a the methine hydrogen is orthogonal to the carbonyl C $2p_z$ orbital, but in **14a** (Figure 4b) the twist about the *C*−*N* bond is only 19°. We estimated the magnitude of this stabilization in the ketone isodesmically from eq 6 at −3.8 kcal mol^{-1} in the case of **14a** and, from a similar equation, at −2.8 kcal mol^{-1} for the 2-



(6)

azirene derivative **15**. Correcting for this stabilization in the ketone yields a COSNAR reaction energy similar to that from our *trans*-amidation method.

In application of the *trans*-amidation method to lactams, a correction needs to be made for a change in strain when the carbonyl is transferred to the cyclic amine, i.e., one ring carbon is transformed from sp^3 to sp^2 hybridization. We estimated this isodesmically for the *β*-, *γ*-, *δ*-, and *ε*-lactams using eq 7 in

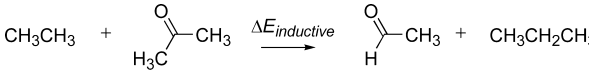


(7)

which the oxygenation of the corresponding cycloalkane is measured relative to oxygenation of butane to butanone (eq 7, R = H) or in the case of *N*-methylated lactams, 2-methylbutane to 3-methylbutanone (eq 7, R = Me).

The strain correction in each case is the sum of the change in angle strain or I-strain (a positive energy change) and total release of strain due to removal of eclipsing interactions or Pitzer strain (a negative energy quantity). Revealingly, for the four- and, to a lesser extent, the five- membered rings where there are strong eclipsing interactions, the introduction of a carbonyl actually leads to a net strain release owing to a staggered conformation about the carbonyl (Table 2). In the case of the six-membered rings, the opening of one carbon from ideal tetrahedral geometry or increase in Pitzer strain leads to a small, net increase in ring strain. When a carbonyl is inserted into cycloheptane, there appears to be an increase in Pitzer strain, but the relief of I-strain results in a small net strain release. For each lactam, the energy change from eq 3 must therefore be adjusted for the strain release or increase, intrinsic in the reaction, by subtracting the ΔE_{strain} to yield the true change in energy owing to loss of resonance.

In the application of eq 3 to formamides **11** as opposed to acetamides or alkylamides, the ΔE_{react} must be modified by the extent to which an *α*-methyl (in acetamides) as opposed to an *α*-hydrogen (in formamides) stabilizes the carbonyl (through inductive or hyperconjugative stabilization of canonical form **III** in Figure 1). This can be computed isodesmically from eq 8, and the destabilization of 7.4 kcal mol^{-1} at B3LYP/6-31G(d) is close to the previously accepted value of about 7 kcal mol^{-1}.[53,54]



(8)

Formamide and *β*-propiolactam are two cases where energy corrections in the *trans*-amidation method are critical in determining correct resonance relative to *N,N*-dimethylacetamide. We have gauged the reliability of B3LYP/6-31G(d) against higher levels of theory, and Table 3 indicates that the inductive destabilization of the acyl hydrogen in formamide **11a**, together with the resultant resonance energies RE and ΔE_{COSNAR}, were largely independent of either basis set or computational method. As predicted, inclusion of enthalpy corrections also led to negligible change in reaction energies. Although as a percentage of corresponding resonance energies for *N,N*-dimethylacetamide (Table 1), the amidicities were

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Table 2. B3LYP/6-31G(d) Reaction Energies (kcal mol^{-1}), Resonance Energies (kcal mol^{-1}) and Amidicities (%) for Structures 3, 4, 11−24

amide	ΔE_{corr} [a]	ΔE_{react} [b]	RE [c]	ΔE_{COSNAR} [d]	amidicity [e] this study [f]	amidicity [e] reported [g]
N,*N*-Dimethylacetamide **3**			−18.17	−18.53	100.0 (100.0)	100.0
1-Aza-2-adamantanone **4**		18.17			0	0
Formamide **11a**	7.39[h]	3.71 [−3.67]	−21.84	−22.54	120.2 (121.7)	92.4 (104.0)
N,*N*-Dimethylformamide **11b**	7.39[h]	2.31 [−5.07]	−23.24	−23.42	127.9 (126.4)	96.8
N,*N*-Diethylformamide **11c**	7.39[h]	0.39 [−7.00]	−25.17	−25.34	138.5 (136.8)	
N,*N*-Diisopropylformamide **11d**	7.39[h]	−1.92 [−9.31]	−27.48	−26.93	151.2 (145.4)	
N,*N*-Di-*tert*-butylformamide **11e**	7.39[h]	3.18 [−4.21]	−22.38	−20.40	123.2 (110.0)	
Acetamide **12a**		−0.25	−18.42	−19.12	101.4 (103.2)	96.1
N,*N*-Diethylacetamide **12b**		−2.60	−20.78	−21.20	114.3 (114.4)	97.6
N,*N*-Diisopropylacetamide **12c**		−3.18	−21.35	−21.15	117.9 (114.2)	98.5
N,*N*-Di-*tert*-butylacetamide **12d**		5.96	−12.21	−11.39	67.2 (61.5)	82.0
(*Z*)-*N*-Methylacetamide **13a**		−1.57	−19.74	−19.78	108.7 (106.8)	101.6 (111.3)
(*E*)-*N*-Methylacetamide **13b**		0.94	−17.23	−17.28	94.8 (93.2)	
N-Acetylaziridine **14a**	−3.8[i]	7.64	−10.53	−7.08 [−10.89]	58.0 (58.8)	57.3 (60.0)
N-Acetylazetidine **14b**		0.48	−17.69	−17.70	97.4 (95.5)	91.5 (102.4)
N-Acetylpyrrolidine **14c**		−1.78	−19.95	−19.69	109.8 (106.3)	106.3
N-Acetyl-2-azirene **15**	−2.8[i]	9.3	−8.88	−6.43 [−9.23]	48.8 (49.8)	
N-Vinylacetamide **16**		−0.34	−18.51	−19.61	101.9 (105.8)	87.7
β-Propiolactam **17a**	−2.19[j]	−3.96 [−1.77]	−19.94	−19.99	109.7 (107.9)	75.7 (82.3)
γ-Butyrolactam **17b**	−2.02[j]	−4.32 [−2.29]	−20.47	−20.52	112.6 (110.7)	115.0 (131.8)
δ-Valerolactam **17c**	1.10[j]	−0.11 [−1.21]	−19.38	−19.43	106.6 (104.9)	90.9 (99.8)
ε-Caprolactam **17d**	−2.04[j]	−3.98 [−1.94]	−20.11	−20.16	110.7 (108.9)	
N-Methyl *β*-propiolactam **18a**	−1.89[j]	−4.96 [−3.07]	−21.24	−21.60	116.9 (116.6)	77.8
N-Methyl *γ*-butyrolactam **18b**	−2.74[j]	−5.14 [−2.39]	−20.56	−20.92	113.2 (112.9)	121.9
N-Methyl *δ*-valerolactam **18c**	0.45[j]	0.51 [0.06]	−18.11	−18.47	99.7 (99.7)	93.3
N-Methyl *ε*-caprolactam **18d**	−2.97[j]	−3.51 [−0.53]	−18.71	−19.06	103.0 (102.9)	
2-Oxo-1*H*-azete **19**	−2.15[j]	15.49 [17.64]	−0.53	0.65	2.9 (−3.5)	25.4 (21.4)
1-Azabicyclo[2.2.2]octan-2-one **20**	−1.62[j]	16.47 [18.09]	−0.08	−0.44	0.4 (2.4)	9.9 (15.8)
1-Aza-7-oxo-4-thiabicyclo[3.2.0]heptane **21**	−0.91[j]	1.39 [2.30]	−15.87	−16.23	87.4 (87.6)	
1-Aza-7-oxo-4-thiabicyclo[3.2.0]hept-2-ene **22**	−1.01[j]	3.90 [4.91]	−13.26	−13.62	73.0 (73.5)	
1-Aza-8-oxo-5-thiabicyclo[4.2.0]octane **23**	−1.67[j]	−5.88 [−4.2]	−22.37	−22.73	123.1 (122.7)	
1-Aza-8-oxo-5-thiabicyclo[4.2.0]oct-2-ene **24**	−0.52[j]	0.43 [0.94]	−17.23	−17.58	94.8 (94.9)	

[a]Energy correction. [b]Calculated from eq 3; corrected values in parentheses. [c]Residual resonance given by RE = −(18.17 − ΔE_{react}). [d]Calculated from eq 2. [e]Amidicities relative to *N*,*N*-dimethylacetamide. [f]Calculated according to eq 4 from *trans*-amidation reaction energies; COSNAR amidicities as a percentage of the stabilization in *N*,*N*-dimethylacetamide (−18.53 kcal mol^{-1}) are given in parentheses. [g]Amidicities reported by Csizmadia and co-workers using enthalpies of hydrogenation; B3LYP/6-31G(g,d) values with B3LYP/6-31G(d) values in parentheses.[38,39] [h]Inductive correction from eq 8. [i]Walsh resonance energy correction calculated from eq 6. [j]Ring strain energy correction calculated from eq 7.

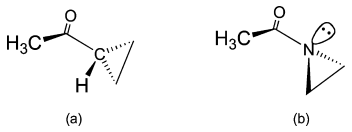

Figure 4. Optimized structures for (a) cyclopropyl methyl ketone and (b) *N*-acetylaziridine **14a**.

slightly higher at the MP2 level, all higher level calculations led to a similar result to that computed from B3LYP/6-31G(d), namely, that formamide **11a** has a higher degree of resonance and higher amidicity than *N*,*N*-dimethylacetamide **3**.

Reaction energies and resonance energies for *β*-propiolactam **17a** computed at different levels of theory are also in relatively good agreement (Table 3). Amidicities from DFT calculations with larger basis sets are in line with the lowest level of theory, but MP2-based methodologies show increasing amidicities with incorporation of correlation energy. From an analysis of strain energies and MP2 optimized geometries at different levels of theory, larger basis sets resulted in more distortion in the cyclobutane ring (Table 3), which becomes less destabilized by Pitzer strain. Accordingly, at the more rigorous levels of theory, the COSNAR stabilization from eq 2 increases, and the ring strain correction for eq 7 decreases in magnitude, resulting in larger RE values. Nonetheless, all calculations accord with a higher amidicity for the *β*-lactam than for *N*,*N*-dimethylacetamide **3**. Cancellation of ZPE and enthalpy contributions was again demonstrated at the B3LYP/6-31G(d) level.

After inclusion of appropriate energy corrections for Walsh orbital conjugation, strain, and inductive contributions, the B3LYP/6-31G(d) computed resonance stabilizations by the *trans*-amidation method are in excellent agreement with those from the COSNAR method (RE = 1.008 × ΔE_{COSNAR} − 0.035, r^2 = 0.991) and derived amidicities are accordingly very similar from both methods (Table 2). Available amidicities according to Csizmadia are similar in only a handful of structures, and considering the excellent agreement between our two methods, determination of amidicities by our *trans*-amidation or Greenberg's COSNAR protocols would appear to be more reliable.

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Table 3. Reaction Energies (kcal mol^{-1}), Resonance Energies (kcal mol^{-1}) and Amidicities (%) for Formamide 11a and β-Propiolactam 17a at Various Levels of Theory

	formamide **11a**				β-propiolactam **17a**			
method	$\Delta E_{inductive}$ [a]	ΔE_{react} [b]	RE [c]	ΔE_{COSNAR} [d]	ΔE_{strain} [e]	ΔE_{react} [b]	RE [f]	ΔE_{COSNAR} [d]
B3LYP/6-31G(d)[g]	7.39	3.71	−21.84 (120.2)	−22.54 (121.7)	−2.19 (10.1°)	−3.96	−19.94 (109.7)	−19.99 (107.9)
B3LYP/6-31G(d) (freq.)[h]	7.62	3.30	−22.39 (123.9)	−22.47 (124.3)	−2.03	−4.25	−20.28 (112.3)	−19.71 (109.1)
B3LYP/6-31G(d,p)	7.46	3.70	−22.17 (120.4)	−22.80 (121.4)	−1.66 (18.2°)	−3.95	−20.71 (112.4)	−20.67 (110.1)
B3LYP/6-311+G(d,p)	7.22	3.02	−21.75 (123.9)	−22.17 (122.2)	−1.97 (17.8°)	−4.30	−19.88 (113.3)	−20.07 (110.6)
B3LYP/cc-pVTZ	7.29	3.12	−22.08 (123.3)	−22.81 (122.1)	−1.41 (18.1°)	−4.17	−20.68 (115.5)	−21.29 (114.0)
MP2/6-31G(d)	7.14	2.83	−21.97 (124.4)	22.43 (126.8)	−0.49 (21.6°)	−3.66	−20.84 (118.0)	20.55 (116.1)
MP2/6-31G(d,p)	6.87	2.78	−21.68 (123.3)	−22.46 (125.7)	−0.50 (22.2°)	−3.72	−20.81 (118.3)	−20.79 (116.3)
MP2/6-311+G(d,p)	6.43	1.86	−20.15 (129.3)	21.06 (128.7)	−0.80 (22.7°)	−4.29	−19.07 (122.4)	−19.70 (120.4)
MP2/cc-pVTZ	6.74	2.23	−21.48 (126.6)	22.28 (126.5)	−0.75 (22.4°)	−4.50	−20.80 (122.6)	−21.04 (119.4)
G3/MP2[i]	6.77	2.77	−20.33 (124.6)	−20.61 (123.1)	−1.07 (21.6°)	−4.30	−19.50 (119.8)	−19.47 (116.3)

[a]Calculated from eq 8. [b]Calculated from eq 3 [c]Calculated from from corresponding RE for *N,N*-dimethylacetamide in Table 1; corrected for inductive destabilization; amidicities in parentheses. [d]Calculated from eq 2; amidicities in parentheses. [e]Calculated from eq 7; twist angle in parentheses. [f]Calculated from corresponding RE for *N,N*-dimethylacetamide in Table 1; corrected for change in ring strain. [g]From Table 2. [h]Reaction energies inclusive of ZPE and enthalpy corrections for all structures. [i]MP2/6-31G(d) optimized energy with MP2/6-311++G(2df,2p)//MP2/6-31G(d) basis set correction and QCISD(T)/6-31G(d)//MP2/6-31G(d) correlation correction.

Table 4 gives *C*−*N* and *C*−*O* bond lengths, H_α−C(O)−N/C_α−C(O)−N bond angles, as well as Winkler−Dunitz pyramidality and twist indices for formamides **11** and acetamides **12** and **13**. In their ground states, formamides **11a** to **11e** and acetamides **3**, **12a**−**c**, and **13a** are computed to be virtually planar at nitrogen with negligible twist about their *C*−*N* bonds. For the full series, there is no inverse correlation between the *C*−*N* and *C*−*O* bond lengths. The formamides **11a** to **11d** with the shortest *C*−*N* bonds actually have the shortest carbonyl bond lengths, while *N,N*-di-*tert*-butylacetamide **12d**, which has the longest *C*−*N* bond, has a shorter *C*−*O* bond than most other acetamides in the series.

Table 4. *C*−*N* and *C*−*O* Bond Lengths, H_α−C(O)−N/C_α−C(O)−N Angles (φ) at the Carbonyl, Pyramidality (χ), and Twist Indices (τ) in B3LYP/6-31G(d)-Optimized Structures of Amides 3, 11−13

	C−N (Å)	C−O (Å)	φ (deg)	χ (deg)	τ (deg)
Formamide **11a**	1.362	1.216	111.9	0.0	0.0
N,N-Dimethylformamide **11b**	1.366	1.220	111.8	0.0	0.0
N,N-Diethylformamide **11c**	1.363	1.222	112.3	2.4	0.3
N,N-Diisopropylformamide **11d**	1.364	1.223	112.0	0.0	0.0
N,N-Di-*tert*-butylformamide **11e**	1.374	1.227	113.7	0.0	0.0
Acetamide **12a**	1.370	1.221	114.6	4.1	−0.5
(*Z*)-*N*-Methylacetamide **13a**	1.369	1.225	115.2	1.7	0.0
(*E*)-*N*-Methylacetamide **13b**	1.374	1.224	116.5	15.8	−2.4
N,N-Dimethylacetamide **3**	1.378	1.227	117.6	4.6	−0.5
N,N-Diethylacetamide **12b**	1.375	1.229	117.8	1.1	−0.9
N,N-Diisopropylacetamide **12c**	1.375	1.230	118.8	0.1	−0.3
N,N-Di-*tert*-butylacetamide **12d**	1.402	1.225	119.4	15.4	43.8

From analysis of *C*−*N* bond lengths and H_α−C(O)−N angles, the steric demands of α-hydrogen of formamides **11a**−**11d** are clearly similar. However, relative to formamide, *N,N*-dimethylation in **11b** increases the amidicity by about 4% in line with an inductive effect of the nitrogen methyl groups. Intuitively, electron donation to nitrogen by positively inductive alkyl groups should raise the energy of the lone pair resulting a better $n_N - \pi^*_{CO}$ interaction. The computed resonance in formamide **11a** is similar to the thermodynamic value (−21.8 kcal mol^{-1}) based on experimental heats of formation.[55] *N,N*-Dimethylformamide has an experimental rotational barrier 2−3 kcal mol^{-1} higher in energy than formamide in solution,[56] and in general, formamides have a higher amide rotational barrier than acetamides both in the gas phase and in solution,[57,58] and while ground state steric effects play a role, a large portion of these barriers is attributable to the resonance. The relative values for formamide and acetamide as well as *N,N*-dimethylformamide and *N,N*-dimethylacetamide in Table 2 are clearly realistic. With **11b**−**d** increasing alkyl size at nitrogen from methyl to ethyl and isopropyl results in greater amidicities in line with the increasing inductive effect, but *N,N*-di-*tert*-butylformamide **11e** breaks this trend. Though computed to be planar, steric hindrance results in a larger H_α−C(O)−N angle and a very long *C*−*N* bond length, which reduces overlap and resonance. Here steric effects overshadow the inductive effect.

In the case of secondary and tertiary acetamides **3**, **12b** and **12c**, **13a** and **13b**, amidicities in Table 2 can also be rationalized on the basis that resonance is dictated by a balance between a steric interaction between the α-methyl group and nitrogen substituents, which lengthens *C*−*N* bonds and reduces pi overlap, and inductive enhancement of resonance owing to alkyl substitution at nitrogen. C_α−C(O)−N angles in Table 4 show that acetamide **12a** and the more stable (*Z*)-*N*-methylacetamide **13a** have a similar deformation due to a common *syn* relationship between the α-methyl and NH. Amidicity increases in **13a** because of the inductive effect of one methyl at nitrogen. The *N*-methyl in the higher energy (*E*)-form of *N*-methylacetamide **13b** must have a similar inductive enhancement to that in **13a**, but steric hindrance between the *syn* methyls results in a stretched *C*−*N* bond relative to **13a** and a degree of pyramidalization at nitrogen (Table 4). This results in a significant 13% reduction in amidicity, which from Figure 3 is probably mostly accounted for by bond stretching since deformation at nitrogen of 15° is likely to produce a marginal increase in energy.

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N,*N*-Dimethylacetamide **3**, *N*,*N*-diethyl- and *N*,*N*-diisopropylacetamide, **12b** and **12c**, are similarly affected by *syn* alkyl groups at the carbonyl and on nitrogen. An increasing steric effect, as evidenced by the angles at carbon (Table 4), is overshadowed by the increase in inductive stabilization, which probably accounts for the contraction in the C−N bond length and higher amidicities in the *N*,*N*-diethyl- and *N*,*N*-diisopropylacetamides **12b** and **12c**. A recent QM/MM study using MP2:MM3, which partitions the rotational barriers of *N*,*N*-dimethyl-, *N*,*N*-diisopropyl-, and *N*,*N*-di-*tert*-butylformamides and acetamides into electronic and steric components, supports the role of alkyl substitution in resonance enhancement.[58] The electronic component, which must relate to the degree of resonance that is lost upon rotation away from the planar ground state, increased with size of the alkyl substituent. In line with our results, the highest electronic barriers were found for *N*,*N*-diisopropylformamide **11d** and *N*,*N*-diisopropylacetamide **12c** (see footnote[59]).

In its lowest energy form, *N*,*N*-di-*tert*-butylacetamide **12d** is found to possess a slightly pyramidal nitrogen (χ = 15°) but is strongly twisted (τ = 44°) to offset a strong steric interaction. A nearly identical twist angle was computed in two recent studies.[58,60] This results in diminished resonance overlap, which manifests itself in a much longer C−N bond (Table 4). From Figure 3, the degree of pyramidalization would likely lead to little energy change, but a similar twist in *N*,*N*-dimethylacetamide would raise energy by some 10 kcal mol^{-1} leaving a residual resonance energy of about −8 kcal mol^{-1} and an amidicity of 45%. The higher stabilization of −12.2 and −11.4 kcal mol^{-1} for **12d** can be ascribed to the inductive effect of the *tert*-butyl groups. The radically reduced resonance energy is supported by very low computed barriers for isomerization in **12d**. At the B3LYP/6-31+G(d) level, Mujika and co-workers determined a ΔG_{rot} of only 3.4 kcal mol^{-1}, while the hybrid QM/MM method of Demachy et al. gave a ΔE_{rot} of only 2.2 kcal mol^{-1}. In their study, a low electronic component to the barrier of 8.7 kcal mol^{-1}, presumably due to loss of limited resonance, was offset by a reduction in steric strain of −6.5 kcal mol^{-1}. The absence of an experimentally determined rotational barrier for **12d** is therefore not surprising.[58]

Both methods performed similarly for *N*-acetylated cyclic amines **14a**−**c**. In the global minimum energy structure for the aziridine derivative (**14a**), the lone pair is still largely conjugated with the carbonyl, but the ring size ensures that the nitrogen is strongly pyramidal with the lone pair in an sp^3 hybrid orbital (τ = 19.2°, χ = 104°). From Figure 3, the loss of resonance due to complete pyramidalization of the amide nitrogen in *N*,*N*-dimethylacetamide, without twisting, is estimated at about 6.5 kcal mol^{-1},[50] and the reduction in resonance stabilization of about 7.6 kcal mol^{-1} determined in this study is only slightly greater, reflecting some additional loss due to twisting. *N*-Acetylazetidine (**14b**) is largely untwisted, and the nitrogen is only moderately puckered (τ = −2.4°, χ = 26°), leading to a small reduction in amidicity. *N*-Acetylpyrrolidine (**14c**) (τ =0.55°, χ = 2°) is untwisted and nearly planar, and not surprisingly, amidicity in this case is similar to that of the *N*,*N*-diethylacetamide **12b**.

N-Acetyl-2-azirene **15** (τ = −47°and χ = 126°) is the most pyramidal of all the amides in this study, but it is significantly twisted, and its lone pair is not as conjugated as in the aziridine analogue **14a**. Although in the COSNAR method we have estimated a loss of Walsh conjugative stabilization around −2.8 kcal mol^{-1} upon formation of the amide, it is probably overestimated, as with a 47° twist some of this stabilization is probably retained in the amide. The COSNAR energy is therefore likely to be slightly overestimated. In the open chain analogue, *N*-ethenylacetamide **16**, the results indicate that there is very little delocalization of the nitrogen amide lone pair onto the vinylic group in the gas phase. Delocalization would invoke unfavorable ammonium ion character at the amide nitrogen, which would destabilize the carbonyl through resonance form **III** (Figure 1). Wiberg has shown that even in vinylamine any resonance interaction would at best be weak, and in the case of **16**, resonance would be less likely.[4] Structural and electronic factors support this view. In the optimized structure for **16**, the double bond is virtually the same in length (1.336 Å) as that in simple 1-pentene (1.334 Å) or pent-4-en-2-one (1.334 Å) and shorter than the double bond in *N*-ethylvinylamine (1.341 Å) (all used in the COSNAR calculation). Correspondingly, the methine carbon−nitrogen bond in **16** is 1.396 Å and longer than that of the amine by 0.006 Å. In addition, analysis of Mulliken group charges shows that the terminal $=CH_2$ group of the amide bears significantly less negative charge (−0.122) than that of *N*-ethylvinylamine (−0.154).

It should be noted that our amidicities for formamides **11a** and **11b** and acetamides **12b**, **12c**, and **13a** are somewhat higher than those reported by Mucsi and co-workers at the B3LYP/6-31G(d,p) level.[38,39] In contrast to our results, they also calculated a lower amide character for formamide (93.4%) and *N*,*N*-dimethylformamide (96.8%) than found for acetamide (96.1%) and *N*,*N*-dimethylacetamide (100%). While they reported a higher amidicity (104%) for formamide relative to acetamide at the B3LYP/6-31G(d) level,[38,39] here, and for other amides in Table 2 in common with Csizmadia's study,[38] we can only compare our amidicities with their values determined at the similar B3LYP/6-31G(d,p) level since all their tabulated data based upon B3LYP/6-31G(d) calculations are incorrect (see footnote[61]). Their method did not predict inductive enhancement in the cases of diethyl and diisopropyl substitution, while their amidicity for *N*,*N*-di-*tert*-butylacetamide **12d** (82%) was significantly higher than our values (67 and 62%). The hydrogenation method also predicts weak amide resonance in *N*-vinylacetamide **16**, which implies strong resonance between the amide nitrogen and the vinyl group. Structural data does not support this. In the case of *N*-acetylated cyclic amines **14a**−**c**, though our values were all larger than Csizmadia's, all three methods performed similarly.

Results for the β-, γ-, and δ-lactam series contrast markedly to those of Csizmadia. Bond lengths, pyramidality and twist indices for all monocyclic lactams are presented in Table 5. β-Lactams **17a** and **18a** are essentially planar and, after

Table 5. C−N and C−O Bond Lengths, Winkler−Dunitz Pyramidality (χ), and Twist Indices (τ) in B3LYP/6-31G(d) Optimized Structures of Lactams 17 and 18

	C−N (Å)	C−O (Å)	χ (deg)	τ (deg)
β-Propiolactam **17a**	1.376	1.208	1	0
γ-Butyrolactam **17b**	1.374	1.218	16	2
δ-Valerolactam **17c**	1.372	1.225	16	4
ε-Caprolactam **17d**	1.371	1.226	1	1
N-Methyl β-propiolactam **18a**	1.376	1.211	0	0
N-Methyl γ-butyrolactam **18b**	1.374	1.221	11	−2
N-Methyl δ-valerolactam **18c**	1.377	1.227	12	2
N-Methyl ε-caprolactam **18d**	1.375	1.228	3	1

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compensation for the net strain release upon introducing a carbonyl into the azetidine ring, are computed by both the *trans*-amidation method, as well as by the strain independent COSNAR method, to gain amidicity relative to *N*,*N*-dimethylacetamide. At B3LYP/6-31G(d) the effect is magnified in the *N*-methylated case **18a** where an amidicity of 117% is computed. This result undermines the oft-mistaken view that β-lactams possess amide linkages that are weakened by pyramidalization of the nitrogen atom or by strain in the four-membered ring. A recent computational approach using the G3/B3LYP method gives an even higher amide resonance energy for **17a** of some 21.6 kcal mol^{-1},[62] which supports our result. It therefore seems that our amidicities for β-lactams are much more appropriate than the low amidicities determined by Csizmadia for the unsubstituted and *N*-methylated β-lactams (75.7 and 77.8% for **17a** and **18a**, respectively[38]), which appear to be in error (see footnote[63]).

Optimized geometries support this computed amidicity. The *C*−*N* bond in β-lactams **17a** and **18a** are virtually the same as that in the secondary amide (*E*)-*N*-methylacetamide **13b** and tertiary amides *N*,*N*-dimethylacetamide **3**, *N*,*N*-diethylacetamide **12b** and *N*,*N*-diisopropylacetamide **12c** (Table 5, Table 4). Boyd has analyzed crystal structures for the bulk of monocyclic β-lactam structures and found that many possess *C*−*N* bond lengths in this range.[64]

Our results suggest that the amide character in the lactam series **17** is largely independent of ring size, again a result different from Csizmadia's outcome. While the amidicities of the γ-lactams **17b** and **18b** are similarly high in both series in accord with their results, the much lower amidicity recorded by Csizmadia's method for δ-lactams **17c** and **18c**, which they attributed to greater twisting in the six-membered ring, was not found by either of our methods. Data in Table 5 show that the degree of twist in all the lactam structures is computed to be trivial. γ- and δ-lactams present with some pyramidality at nitrogen, but as outlined in the introduction, this small deviation from the plane is likely to lead to very little loss of resonance. Not surprisingly, **17c** and **18c** afforded similar amide character to *N*,*N*-dimethylacetamide **3**. In addition, the *C*−*N* bond lengths in **17** and certainly in **18** are not very different across all four lactams, suggesting no major influence of ring size. While in series **17**, there appears to be an inverse relationship between the *C*−*N* and *C*−*O* bond lengths, this is not evident in the methylated lactam series **18**. In addition, there is no correlation between *C*−*O* bond lengths and amidicity since the carbonyls in γ-lactam **17b** and β-lactam **18a**, which have highest amidicities, are not long in relation to the others in the series.

It is clear that, at the very least, the β-lactam system can be regarded as bearing an amide bond with similar strength to that of *N*,*N*-dimethylacetamide **3**. As demonstrated by results in Table 3, more rigorous computational methods actually increase the resonance energies and amidicities of β-propiolactam **17a**. Arguments basing reactivity of β-lactams antibiotics on a highly reactive ring structure owing to diminished resonance are incorrect. Importantly, where β-lactams are concerned, Csizmadia's reactivity arguments based upon relative amidicities are questionable.[38−40]

After introduction of a strain correction analogous to that needed for β-lactams, 2-oxo-1*H*-azete **19** was computed to have very low amidicity consistent with the antiaromatic character imposed by resonance overlap. Though a much higher value of 25% was found, Csizmadia's hydrogenation method gave a similar qualitative outcome.

Like 1-aza-2-adamantanone **4**, elusive quinuclidone **20**, which on account of its instability could only be synthesized as its tetrafluoroborate salt quite recently,[19] has no amide character. In this rigid structure, the *trans*-amidation method requires a strain energy offset since transfer of a carbonyl to quinuclidine in the *trans*-amidation method decreases Pitzer strain. A strain release of 1.62 kcal mol^{-1}, obtained from an isodesmic reaction using bicyclo[2.2.2]octane as cycloalkane by analogy with eq 7, resulted in a near zero resonance energy from this method. The residual resonance of −0.44 kcal mol^{-1} by COSNAR is of the same order as that obtained earlier at the 6-31G(d) level by Greenberg (−0.9 kcal mol^{-1}).[37] Analysis of the ground state B3LYP/6-31G(d) structures for **20** and **4** shows complete twist (τ = 90°) and a near optimum pyramidality (χ = 60.9°) in the case of **4**, whereas **20**, while similarly pyramidal at nitrogen (χ = 62.2°), has 7° less twist about the *C*−*N* bond (τ = 82.7°), which is clearly to relieve Pitzer strain.

Fused β-lactams are the pharmacophores of very many antibiotics, penicillins and cephalosporins being the main classes in common usage today. These acylate a serine side chain in the enzymes transpeptidases that are responsible for cross-linking peptidoglycans in bacterial cell walls.[65,66] Numerous, often fallacious arguments have been posted for the acylating activity of the β-lactam moiety in penam and cephem structures, one of which is that the β-lactam structure possesses a weakened amide bond. This has been attributed to pyramidality at the bridgehead nitrogen and/or twisting about the amide *C*−*N* bond or simply by strain in the four-membered ring, which is undoubtedly more prevalent in the fused bicyclic systems.[65−67] Compounding the situation, some monocyclic β-lactams (as well as γ- and δ-lactams) also exhibit antibiotic activity, and distortion arguments in this case are clearly incorrect, since not only do structures show that the β-lactam ring is mostly planar,[64] but results herein and elsewhere[62] indicate that the degree of resonance is similar to that in *N*,*N*-dimethylacetamide. Clear-cut correlations between activity and structure are difficult on account of the adsorption, metabolism, and protein binding considerations controlling biological outcomes. The methods outlined in this paper allow analysis of this amide character relative to *N*,*N*-dimethylacetamide, and the results for model penam **21**, penem **22**, cepham **23**, and cephem **24** scaffolds are presented in Table 2 and Figure 5.

In all four structures, a unique strain correction was required for the *trans*-amidation method since, once again, the introduction of a carbonyl into the four-membered ring invokes more Pitzer strain release than is generated by increased angular strain in the lactam ring. The correspondence between both methods is excellent, and the resonance energies here, as well as the optimized structures, are largely in accord with a recent computational study by Novak and Chua.[62] Structures were consistent with crystallographic data for antibiotics in these classes.[69−72]

The order of amidicity is cepham/em > penam/em, which accords with greatly reduced pyramidality and reduced twist in the cepham/em system (χ = 23/26°, τ = 7/12°, respectively) relative to the penam/em structure (χ = 54/56°, τ = 18/23°, respectively). As demonstrated by Figure 3, the relatively low degree of deformation at nitrogen and small twist angles in the cepham/em system should lead to little increase in energy. Not surprisingly, the cepham structure with the least pyramidality at nitrogen and twist about the *C*−*N* bond and fused to the least

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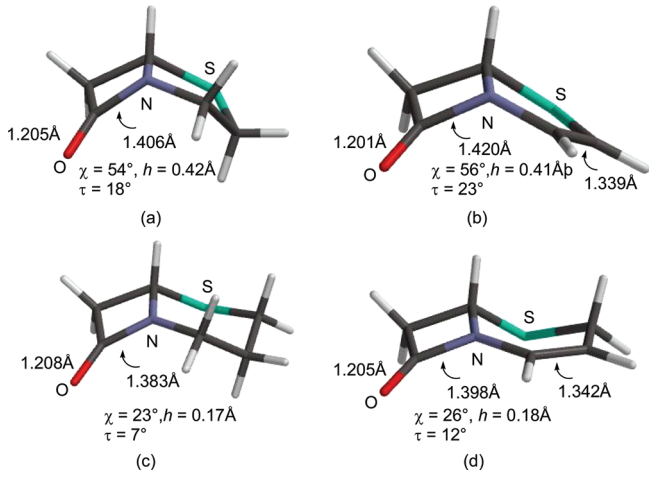

Figure 5. B3LYP/6-31G(d)-optimized structures of (a) a penam **21**; (b) a penem **22**; (c) a cepham **23**; and (d) a cephem **24** antibiotic scaffold. χ and τ are the Winkler–Dunitz pramidality and twist indices,[34,35] and h, the height of nitrogen above the plane of the three atoms to which it is attached, is the Woodward index.[64,68]

rigid six-membered ring structure has similar amidicity to *N*-methyl-β-lactam **18a**. In the case of the penam/penem system, the near complete pyramidalization at nitrogen and, to a lesser extent, the twist about the *C*–*N* bond results in a significant reduction in amidicity, which is more pronounced in the case of the more pyramidal and twisted penem skeleton **22**. For the best part, the reduced amidicities for **24**, **22**, and **21** can be accounted for by the increase in twist and pyramidalization. However, it is clear that amide resonance, even in penems is significant.

In all four structures there is strain in the β-lactam ring. However, the contemporary understanding is that reaction with transpeptidases is a two-step process with initial, rate limiting addition of a serine hydroxyl group to form a tetrahedral intermediate followed by fast ring-opening. Since the ring strain is retained in the transition state for the addition step, this plays a diminished role in their biological activity.[62,65−67,70,73] However, the reaction of the serine side chain of β-lactam-binding proteins at the carbonyl, in the first step to functionalization, clearly disrupts amidicity, which consequently should play a significant role in the biological activity β-lactam antibiotics. Nonetheless, the picture is unclear since, while activity correlates with a high degree of pyramidality at nitrogen as measured through the Woodward h-index (h = 0.25–0.50),[64,68] low h-values in cepham/em systems correlate with activity where there is suitable stereochemistry of carboxylate on the 2-position.[69,72] This study has demonstrated that the classes of β-lactam antibiotics span some 9 kcal mol^{-1} in resonance stabilization, ranging from between 73 and 123% that of *N*,*N*-dimethylacetamide. Since correlations of reactivity with factors such as pyramidality, and hence amidicity alone, are poor, this supports the view that the transport, metabolism, and target binding characteristics of β-lactam antibiotics must play the dominant role in the activity of β-lactam antibiotics.[65,66]

Interestingly, these results indicate that the loss of amidicity, even in the highly pyramidal penam and penem scaffolds, is not excessive, which accounts for the stability of β-lactam antibiotics to adventitious side reactions in the transport of β-lactam antibiotics to their target enzymes.

CONCLUSION

Two independent methods for evaluating residual resonance in amides have been outlined. Both the *trans*-amidation and COSNAR approaches provide a reliable means of determining resonance energies and amidicities relative to *N*,*N*-dimethylacetamide. The employment of calculations at a modest DFT level and without enthalpy terms is facilitated by the isodesmic nature of the approaches, but it is important in the *trans*-amidation method that the additional factors that impact upon the energies of the product amide are fully understood and their influence estimated correctly. Formamides require a compensation of 7 kcal mol^{-1} for the differing effects of an α-methyl as opposed to an α-hydrogen. In the case of the lactams, through the employment of suitable model isodesmic reactions, we have evaluated the mostly favorable changes in ring strain that occur upon the introduction of a carbonyl into a cyclic amine. After adjustment for these effects, resonance energies and therefore amidicities are nearly identical to the strain independent COSNAR method. Similarly, detailed analysis of optimized ground state structures are needed in the COSNAR approach where factors impact differently upon the reactants or products. This is exemplified by the differing contribution of Walsh orbital stabilization of the carbonyl in methyl cyclopropyl ketone and in *N*-acetylaziridine **14a**.

The amidicities have been compared with those obtained by Csizmadia for a similar set of amides using variations in enthalpy of hydrogenation of the amides. In certain cases there are major differences, most notably in the case of formamides and lactams where we computed a stronger amide character. While we determined that β-lactams possess more amide character than *N*,*N*-dimethylacetamide, they determined an amidicity well below that of *N*,*N*-dimethylacetamide. We have identified errors in their approach, which account for this major discrepancy.[61,63] Since amidicities from both of our approaches correlate almost exactly, we consider that the methods employed herein are more reliable than that of Csizmadia and co-workers.

Monocylic β-lactams are computed to be planar at nitrogen but bicyclic systems in the penam/em and cepham/em scaffolds have varying degrees of twist about the lactam *C*–*N* bond and pyramidalization at the nitrogen, which, with the exception of the cepham system, result in reduced amidicities relative to *N*,*N*-dimethylacetamide. The strongly pyramidal penam/em systems lose, respectively, some 5.4 and 8 kcal mol^{-1} of resonance relative to *N*-methyl-β-propiolactam (~21.6 kcal mol^{-1}), largely through pyramidalization but with a limited contribution from twist about the *C*–*N* bond. However, even in the penem motif with the greatest loss of resonance, the lactam system retains some 13 kcal mol^{-1} of stabilization owing to lone pair conjugation.

As noted above, where there are other significant factors leading to destabilization or stabilization of the amide relative to *N*,*N*-dimethylacetamide, these must be offset in the *trans*-amidation method to reveal the true effect upon resonance stabilization. As well as diminishing the resonance, *N*,*N*-bisheteroatom-substitution in **5** leads to an inductive destabilization of the carbonyl relative to *N*,*N*-dimethylacetamide; our recent determination of the amidicity of *N*,*N*-dimethoxyacetamide **6** required that the additional inductive destabilization due to dioxyl substitution be taken into account.[50] Using methods outlined in this paper, we are currently determining accurate amidicities for a wide range of

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N-heteroatom- and *N*,*N*-bisheteroatom-substituted (anomeric) amides.

EXPERIMENTAL SECTION

Computational Details. B3LYP and MP2 calculations with various basis sets were carried out using SPARTAN 08,[74] SPARTAN 10,[75] or Gaussian '03.[76] Energies of global minima of structures for use in isodesmic eqs 2, 3, 6−8 were computed directly without ZPE and enthalpy corrections. Frequency calculations at B3LYP/6-31G(d) were used to determine the enthalpy corrections to ground state electronic energies in application of eqs 2, 3, 7, and 8 to **3**, **4**, **11a**, and **17a**, as well as for computation of the enthalpy of hydrogenation of *N*,*N*-dimethylacetamide **3**, and 1-aza-2-adamantanone **4**. The energy surface for deformation of *N*,*N*-dimethylacetamide (Figure 3) was calculated using Gaussian '03.[76]

ASSOCIATED CONTENT

Supporting Information

Section A: Geometries, B3LYP and MP2 energies of structures **3**, **4**, **11**−**24** and computed ΔE_{COSNAR}, ΔE_{react}, and ΔE_{corr}. Section B: Check of B3LYP/6-31G(d) enthalpy of hydrogenation data for **3** and **4**. Section C: B3LYP/6-31G(d) energy data for *N*,*N*-dimethylacetamide **3** used to construct Figure 3. Section D: The full reference for Gaussian 03. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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