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"Amide Resonance" Correlates with a Breadth of C−N Rotation Barriers

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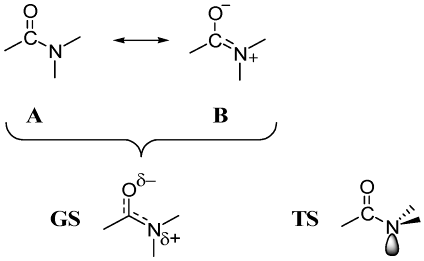
Abstract: Complete basis set calculations (CBS-QB3) were used to compute the CN rotation barriers for acetamide and eight related compounds, including acetamide enolate and O-protonated acetamide. Natural resonance theory analysis was employed to quantify the "amide resonance" contribution to ground-state electronic structures. A range of rotation barriers, spanning nearly 50 kcal/mol, correlates well to the ground-state resonance weights without the need to account for transition-state effects. Use of appropriate model compounds is crucial to gain an understanding of the structural and electronic changes taking place during rotation of the CN bond in acetamide. The disparate changes in bond length (ΔrCO ≪ ΔrCN) are found to be consonant with the resonance model. Similarly, charge differences are consistent with donation from the nitrogen lone pair electrons into the carbonyl π^* orbital. Despite recent attacks on the resonance model, these findings demonstrate it to be a sophisticated and highly predictive tool in the chemist's arsenal.

Introduction

The amide linkage is a key facet in the structure of proteins, peptides, and other biologically important molecules. The amide functional group has traditionally been characterized by a restricted C−N bond rotation, coplanarity of the attached atoms, short C−N bond lengths, red-shifted carbonyl stretching frequencies, relative stability toward nucleophilic attack, and protonation at oxygen rather than nitrogen. These empirical observations are at odds with the amino-carbonyl formulation (**A**) and are traditionally explained by suggesting that the "amide resonance" (**B**) plays an important, albeit lesser, contributing role in the hybrid structure of amides (Scheme 1).[1] According to the resonance rationale, the large C−N rotation barriers in amides (around 15−20 kcal/mol) arise from the partial double bond character resulting from the amide resonance. Resonance form **B** is unable to stabilize the transition state for C−N bond rotation because the nitrogen lone pair is orthogonal to the carbonyl π bond in that structure. In support of this line of reasoning amides having twisted C−N bonds are found to have hydrolysis rates similar to ketones, are more readily protonated at nitrogen rather than oxygen, and have larger ^{17}O chemical shifts.[2]

Wiberg and co-workers[3] challenged this resonance rationale on the basis of results obtained using Bader's atoms in molecules (AIM)[4] analysis. The AIM results were inconsistent with significant contribution from resonance form **B**, showing a higher electron density on nitrogen in the planar ground state than in the transition state. Wiberg and Breneman[5] soon published results showing that the higher electron density on the ground-state nitrogen was not reproduced using other methods of charge analysis, and Perrin[6] criticized the applicability of the AIM population analysis method. Setting aside the AIM results, two major criticisms of the amide resonance remain: (1) In going from formamide's planar ground state to its transition state, the C−N bond lengthens by ~0.08 Å, but

Scheme 1. Amide Resonance Model



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[4] See: Bader, R. F. W.; Matta, C. F. *J. Phys. Chem. A* **2004**, *108*, 8385 and references therein.

[5] (a) Wiberg, K. B.; Breneman, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 831. (b) Breneman, C. M.; Wiberg, K. B. *J. Comput. Chem.* **1990**, *11*, 361.

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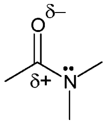
Scheme 2. Polarization Model

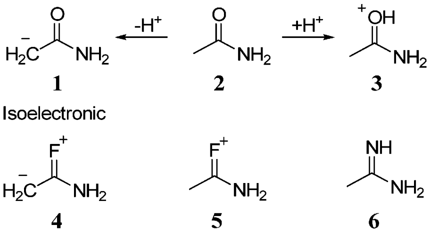


the C−O bond decreases only ~0.01 Å. (2) The charge on oxygen changes less than the charge on nitrogen. A polarization argument was proposed as an alternative explanation for hindered rotation.[7] According to the polarization model, the role of the oxygen is only to polarize the C=O bond to give a positive charge on the carbonyl carbon (Scheme 2). The nitrogen lone pair electrons are stabilized by attraction to the electron-deficient carbon. According to this model, the barrier to rotation is localized to interactions between the carbon and nitrogen atoms, and amides should be considered carbonyl-amines.[8]

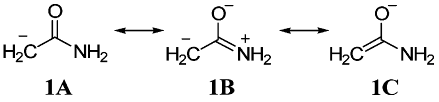
This critique of the amide resonance generated a spate of publications, some agreeing with and refining the polarization model, others defending the amide resonance, and everything in between.[2,6,8,9,10] Recent publications have focused on quantifying the resonance stabilization energy (RSE) for delocalization of the nitrogen lone pair electrons. Ab initio valence bond calculations and two different localization schemes provide very similar values near 25 kcal/mol for the RSE of formamide.[10e,j,k] Although the RSE values are obviously significant, it is still unclear whether this one factor dominates others in controlling the rotation barriers for a series of related molecules.[10e,k]

Pauling estimated the contribution of the amide resonance (**B**) to the overall resonance hybrid as about 40% based on bond lengths of model compounds.[1a] In recent publications, others have sought to use quantum mechanics to assess the extent to which resonance form **B** contributes to the wave function of planar formamide. Glendening and Hrabal[10j] used Weinhold's natural resonance theory (NRT)[11] and found values near 30% while Basch and Hoz[10g] used ab initio valence bond calculations to arrive at a value of 27%. Mo et al. derive a much lower value (13%) when they treat polarized π bonds as separate resonance forms in a valance bond scheme.[10e]

Scheme 3. Acetamide and Related Molecules with Varying C−N Rotation Barriers



Scheme 4. Resonance Forms for the Enolate of Acetamide



Despite the findings described above, resonance has recently been called a crude tool that is not satisfactory to explain the π interactions in amides.[9a] The purpose of this study is to examine the usefulness of the resonance model as a predictive tool. Whereas the C−N rotation barriers of formamide and thioformamide have been thoroughly studied, we place the acetamide rotation barrier in the context of several other C−N rotation barriers ranging from 2 to 49 kcal/mol (Scheme 3). The extent to which simple considerations of these contributing resonance forms predict the full range of rotation barriers qualitatively and computed resonance contributions correlate quantitatively attests to the enduring utility of the resonance model.

Streitwieser and co-workers showed that after deprotonation at the α C of acetamide, the resulting enolate **1** has a much lower C−N rotation barrier than acetamide **2**.[12] Their computational results were in agreement with NMR measurements for a substituted amide lithium enolate.[13] Any explanation of the rotation barrier in amides should be suitable to explain the lower rotation barriers in amide enolates. It may be argued that his experiment supports the polarization model. Certainly, H_2C^- should be considered more electron-donating than CH_3, and one would think that this would lead to a less positive carbonyl carbon. However, an equally viable rationale can also be made using the resonance model. In addition to resonance forms **A** and **B**, discussed above, an enolate has another resonance form, **C**, which should be the dominant one in this case (Scheme 4). Of the three resonance forms shown, **B** is the only one that should increase the C−N rotation barrier. Evaluation of the three resonance forms of **1** suggests that **1B** contributes the least to the hybrid structure; if **1B** is viewed as a perturbation on the best resonance form, **1C**, it is seen to involve a separation of charge with electron donation from the more electronegative nitrogen atom to the less electronegative carbon atom.

In hopes of considering a broad range of rotation barriers, a molecule related to acetamide **2** was sought with a higher barrier to rotation. O-protonated acetamide **3** is expected to have a higher barrier to C−N rotation.[14] The lower electronegativity of nitrogen allows it to bear the positive charge in **B** more readily than oxygen. To further expand the range of rotation barriers and more fully explore the roles of electronegativity and charge, molecules **4**−**6** were also considered. Structures **4**−**6** are

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(7) (a) Wiberg, K. B.; Hadad, C. M.; Rablen, P. R.; Cioslowski, J. *J. Am. Chem. Soc.* **1992**, *114*, 8644. (b) Wiberg, K. B.; Rablen, P. R. *J. Am. Chem. Soc.* **1993**, *115*, 9234.

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(9) (a) Wiberg, K. B. In *The Amide Linkage: Structural Significance in Chemistry, Biochemistry, and Materials Science*; Greenberg, A., Breneman, C. M., Liebman, J. F., Eds.; Wiley-IEEE: New York, 2002; pp 33−46. (b) Wiberg, K. B.; Rush, D. J. *J. Am. Chem. Soc.* **2001**, *123*, 2038. (c) Wiberg, K. B. *Acc. Chem. Res.* **1999**, *32*, 922. (d) Hadad, C. M.; Rablen, P. R.; Wiberg, K. B. *J. Org. Chem.* **1998**, *63*, 8668. (e) Wiberg, K. B. *J. Chem. Ed.* **1996**, *73*, 1089. (f) Laidig, K. E.; Cameron, L. M. *J. Am. Chem. Soc.* **1996**, *118*, 1737. (g) Wiberg, K. B.; Rablen, P. R.; Rush, D. J.; Keith, T. A. *J. Am. Chem. Soc.* **1995**, *117*, 4261. (h) Wiberg, K. B.; Rablen, P. R. *J. Am. Chem. Soc.* **1995**, *117*, 2201. (i) Knight, E. T.; Allen, L. C. *J. Am. Chem. Soc.* **1995**, *117*, 4401. (j) Laidig, K. E.; Cameron, L. M. *Can. J. Chem.* **1993**, *71*, 872.

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(11) (a) Glendening, E. D.; Weinhold, F. *J. Comput. Chem.* **1998**, *19*, 593. (b) Glendening, E. D.; Weinhold, F. *J. Comput. Chem.* **1998**, *19*, 610. (c) Glendening, E. D.; Badenhoop, J. K.; Weinhold, F. *J. Comput. Chem.* **1998**, *19*, 628.

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isoelectronic with **1**−**3**, respectively, so the same types of electron configurations and orbital interactions are possible.

Despite their similarities, the isoelectronic molecules are sometimes predicted by resonance theory to have considerably different barriers due to the change in charge and electronegativity. The structures shown in Scheme 3 do not necessarily represent the best resonance form for each molecule; instead, the structure shown emphasizes the similarity to amide **2**. For instance, **4** is the neutral isoelectronic analogue of **1** and can be thought of as arising from **1** by converting the carbonyl oxygen into F^+. Naturally, **4** would be better represented by its fluorovinyl amine depiction, $H_2C{=}C(F)NH_2$. The carbonyl carbon in acetamide **2** is polarized even further by converting O into F^+ to give isoelectronic structure **5**. Last, turning **3** into the electronically neutral equivalent, acetamidine **6**, will further probe the role of charge. Using simple rules for evaluating resonance forms,[1c,d] a sophomore organic chemistry student would predict C−N rotation barriers for these molecules in the following order **5** > **3** > **2** > **6** > **1** ≈ **4**. Herein, these molecules will be investigated more quantitatively using high-accuracy complete basis set calculations and employing a natural resonance theory (NRT) analysis.

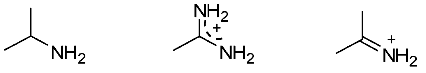
Computational Methods

All conformations of each molecule were optimized in the Gaussian 03W suite of programs[15] at the HF/6-31+G(d,p) level of theory to find the global minimum and lowest-energy transition state. Minima and transition states were confirmed by the number of imaginary frequencies and, for transition states, by observing the related vibrational motion of the imaginary frequency to ensure that it corresponds to C−N rotation. The global minima and low-energy transition structures were reoptimized using the high-accuracy CBS-QB3 method.[16] That compound method optimizes geometries and calculates frequencies at the B3LYP/6-311G(2d,d,p) level. The electron density at this level was analyzed with Weinhold's natural resonance theory (NRT) using the NBO 5.0 program.[17] The NRT algorithm represents the electron density in terms of the idealized resonance forms with weights optimized to minimize the rms deviation from the computed electron density. In all cases, 98 or 99% of the total electron density was explained by Lewis-type resonance forms. For **1**−**6**, at least 90% of the total electron density was accounted for with resonance forms where all of the atoms are bonded together. The remaining 5−9% of the Lewis-type electron density is accounted for with no-bond resonance forms such as the type associated with hyperconjugation. Charges were also analyzed at the B3LYP/6-311G(2d,d,p) level using NPA,[18] ChelpG,[19] and AIM methods[4] as implemented within Gaussian 03W.

Results and Discussion

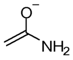
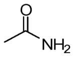
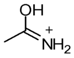
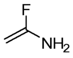
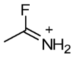
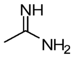
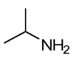
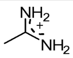
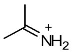
C−N Rotation Barriers and Qualitative Resonance Theory. Rotation barriers for **1**−**6** were computed using the high-accuracy CBS-QB3 method that gives a mean absolute error of less than 1 kcal/mol using the G2 test set.[16] Acetamide **2** has a computed $\Delta G^{\ddagger}$ for C−N bond rotation of 15.4 kcal/mol. In comparison, the experimental gas-phase $\Delta G^{\ddagger}$ for dimethylacetamide is 15.3 kcal/mol.[20] Structures **1**−**6** exhibit an unknown level of CN bonding, ranging from a single to double bond, so model compounds **7**−**9** (Scheme 5) were also studied for comparison to structures with known CN bonding. Isopropyl amine, **7**, is a model system having only a single bond between carbon and nitrogen. Since the amide resonance contains a positive formal charge on nitrogen, the proper comparison for a full double bond is the iminium ion, **9**. Model compound **8** has a nominal bond order of 1.5 between carbon and nitrogen. Table 1 shows the computed CN rotation barriers and geometric parameters for compounds **1**−**9** and their transition structures.

Scheme 5. Model Compounds for C−N Rotation Barrier



7 **8** **9**

Table 1. CBS-QB3 Computed C−N Rotation Barriers and Important Geometric Parameters for **1**−**9**[a]

Structure, #		ΔG‡	rCN	rCO	rCX[b]	X[b]	rCC	Pyramidalization Angle[c]
	**1**		1.479	1.258			1.387	323.5
	1TS		1.523	1.259			1.376	306.0
	1Δ	3.9	+0.044	+0.001			-0.011	-17.5
	**2**		1.367	1.215			1.522	359.9
	2TS		1.459	1.204			1.506	317.3
	2Δ	15.4	+0.092	-0.012			-0.015	-42.5
	**3**		1.303	1.302			1.486	360.0
	3TS		1.390	1.270			1.470	331.6
	3Δ	30.3	+0.087	-0.032			-0.016	-28.5
	**4**		1.382		1.352	F	1.330	341.0
	4TS		1.400		1.372	F	1.323	329.4
	4Δ	1.9	+0.018		+0.019	F	-0.007	-11.6
	**5**		1.291		1.294	F	1.468	360.0
	5TS		1.358		1.286	F	1.443	332.1
	5Δ	40.9	+0.067		-0.008	F	-0.025	-27.9
	**6**		1.385		1.277	N	1.515	346.4
	6TS		1.450		1.265	N	1.509	324.4
	6Δ	9.4	+0.065		-0.011	N	-0.006	-22.1
	**7**		1.472		1.537	C	1.530	325.7
	7TS		1.481		1.532	C	1.534	328.9
	7Δ	2.0	+0.009		-0.006	C	+0.00 4	+3.2
	**8**		1.320		1.320	N	1.496	360.0
	8TS		1.402		1.294	N	1.485	330.1
	8Δ	21.6	+0.082		-0.027	N	-0.011	-29.9
	**9**		1.295		1.485	C	1.485	360.0
	9TS		1.397		1.462	C	1.451	323.0
	9Δ	49.4	+0.101		-0.023	C	-0.034	-37.0

[a] Δ = TS − GS, $\Delta G^{\ddagger}$ in kcal/mol, distances in Å, angles in degrees. The structure shown represents the best resonance form according to NRT analysis. [b] In cases where an oxygen atom is not present, the heavy atom in the same position is designated X. [c] The pyramidalization angle is the sum of all angles around nitrogen (i.e., pyramidalization angle = ∠CNH + ∠CNH′ + ∠HNH).

The calculated barriers for the model compounds **7**−**9** are 2, 22, and 49 kcal/mol, respectively. The experimental barriers for amides in general and the computed barrier for acetamide (15 kcal/mol) are consistent with a resonance hybrid having a CN bond order less than that in **8** (nominally 1.5). Deprotonation of acetamide to give **1** lowers the barrier to 4 kcal/mol—nearly to the point of a single bond. This is consistent with experiment[13] and with the proposition that the principal resonance forms, **1C**

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(20) (a) LeMaster, C. B.; True, N. S. *J. Phys. Chem.* **1989**, *93*, 1307. (b) Ross, B. D.; True, N. S.; Matson, G. B. *J. Phys. Chem.* **1984**, *88*, 2675. (c) Ross, B. D.; True, N. S. *J. Am. Chem. Soc.* **1984**, *106*, 2451. (d) Feigel, M. *J. Phys. Chem.* **1983**, *87*, 3054. (e) Feigel, M. *J. Chem. Soc., Chem. Commun.* **1980**, 456.

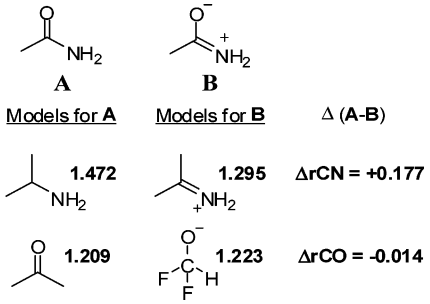
and **1A**, have only single bonds to nitrogen. Protonation of acetamide at oxygen results in **3**, having a rotation barrier (30 kcal/mol) between that of model compounds **8** and **9**. This is consistent with the resonance form **3B** playing a more important role than **3A** and should be expected on the basis of the preference to place a positive formal charge on nitrogen rather than oxygen.

The extent to which electronegativity and charge influence the barriers to rotation was probed using the isoelectronic series **4**−**6**. The same orbital interactions are possible, but alterations of the charge and electronegativity may result in substantially different barriers. Fluorovinyl amine, **4**, is isoelectronic with enolate **1** and has a similar rotation barrier. The change in charge and electronegativity is not expected to alter the primary resonance form **C** but should destabilize **A** relative to **C**. Since neither **A** nor **C** has a double-bonded nitrogen, it is understandable that the barrier remains close to that of isopropyl amine, **7**. Structure **5** is isoelectronic with acetamide **2**, but its barrier is dramatically higher (41 kcal/mol). Whereas the amide resonance **B** is a lesser contributor to the hybrid in **2**, the analogous fluoroiminium ion structure, $CH_3(F)C{=}NH_2^+$, in **5** is clearly dominant, resulting in a barrier nearly as large as the iminium ion model compound **9**. Structure **6** is isoelectronic with **3** but has a substantially reduced rotation barrier (9 kcal/mol). The high barrier in **3** may be attributed to the preference to put the positive charge on nitrogen rather than oxygen. By changing OH^+ to NH, the formal charge is eliminated and so too is the presumed preference for the amide resonance **B**.

Assuming that the contribution from the amide resonance with a CN double bond is what causes high rotation barriers, one would predict the following qualitative ordering: **9** > **5** > **3** > **8** > **2** > **6** > **1** ≈ **4** ≈ **7**. The computed barriers reproduce this trend very well. A simple qualitative model that effectively predicts C−N rotation barriers over such a broad range should not be so readily dismissed.

Geometric Changes. Despite the qualitative predictions that are possible utilizing resonance theory, there remain serious questions regarding the change in geometry upon rotation. For formamide, Wiberg and others report a C−N bond lengthening of ~0.08 Å in going from the planar ground state to the transition state but a disproportionate C−O bond contraction of only ~0.01 Å. Our results with acetamide are similar (ΔrCN = +0.092, ΔrCO = −0.012), and inspection of Table 1 shows the phenomenon to be general for similar molecules with restricted rotation. Nominally, a change from single to double bond order is expected to result in similar distance changes for the CN and CO bonds. The difference between the CN single bond in isopropyl amine (rCN = 1.472 Å) and the double bond in $(CH_3)_2C{=}NH$ (rCN = 1.272 Å) is 0.200 Å. The difference between the double bond in acetone (rCO = 1.209 Å) and a single bond in dimethyl ether (rCO = 1.411 Å) is 0.202 Å. However, the computed bond lengths for **8** and its transition structure serve as a counterexample to the notion that change in formal bond order should be proportional to change in bond length. By symmetry the two resonance forms, **8A** and **8B**, must contribute equally in the ground state, and thus the expected CN bond order is 1.5. In the rotated transition state one NH_2 is unable to participate in π bonding so the bond orders should diverge—one CN bond order increasing from 1.5 to 2 and the other decreasing from 1.5 to 1. Although the changes in bond order are expected to be of equal magnitude, the bond elongation in the former is *3 times* the bond contraction in the latter. Clearly, the common-sense *assumption* that bond length changes should mirror each other does not stand up to further scrutiny. By extension, that same assumption should not be interpreted as a criticism of the amide resonance. Instead, it is possible that the bond length changes can be understood by taking a closer look at the models used to interpret them.[21]

Scheme 6. Model Compounds for CN and CO Bond Lengths in the Hypothetical Structures **A** and **B**



Whereas the bonding in resonance form **A** of acetamide should be well represented by the "normal" C═O bond in acetone and the "normal" C−N bond in isopropyl amine, the bonds in resonance form **B** are atypical due to their ionic nature (Scheme 6). Investigation of the $C{=}N^+$ bond distance in the iminium ion **9** shows a bond length of 1.295 Å, about 2% longer than that in the neutral imine. Accounting for the charge on oxygen proved to be even more important because the $C{-}O^-$ bond in **B** is poorly approximated by the neutral model compound, dimethyl ether. Methoxide ion has a much shorter bond distance (rCO = 1.304 Å) than its neutral counterparts and, in fact, is slightly closer to the double bond distance in acetone than it is to the single bond distance in dimethyl ether. This decreased bond distance has been partly attributed to a Coulombic attraction between the carbon nucleus and the negative charge on oxygen.[22] Figure 1 shows the computed CO bond distances for a series of fluorine-substituted methoxide ions, $F_nCH_{(3-n)}O^-$; the bond distance decreases as the charge on carbon becomes more positive to the point where trifluoromethoxide has a CO bond distance comparable to the double bond in acetone. Experimental and theoretical investigations into the anomalous CO bond distance in trifluoromethoxide attribute the phenomenon to Coulombic attraction (ionic bonding) and negative hyperconjugation,[22,23] both of which are possible in the hypothetical structure **B**. The best model compound for **B** is difluoromethoxide (rCO = 1.223 Å) because the charge on carbon is closest for this molecule.[24] Using the improved models for the bond lengths in the hypothetical structure **B**, one should *expect* unequal bond length changes upon rotation in amides.[25] During CN bond rotation in acetamide, the approximately 8

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(21) In 1955, Wheland warned, "They do require us, however, always to bear in mind that resonance has meaning only with reference to a particular method of approximating the actual situation, and constantly to be on guard lest we assign to the various contributing structures a physical significance which they do not in fact possess."[1b]

(22) (a) Rablen, P. R. *J. Am. Chem. Soc.* **2000**, *122*, 357. (b) Wiberg, K. B. *J. Am. Chem. Soc.* **1990**, *112*, 3379.

(23) (a) Reed, A. E.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1990**, *112*, 1434. (b) Farnham, W. B.; Smart, B. E.; Middleton, W. J.; Calabrese, J. C.; Dixon, D. A. *J. Am. Chem. Soc.* **1985**, *107*, 4565.

(24) Interpolation of the curve in Figure 1 using the actual atomic charge in acetamide leads to a slightly longer model bond length of 1.227 Å.

(25) For additional reasons why ΔrCO might be smaller than expected, see refs 10i,j.

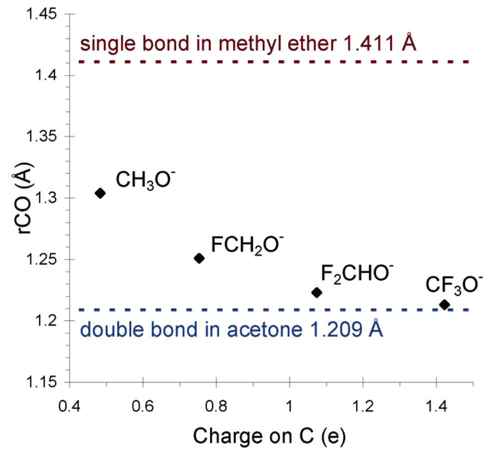

Figure 1. CBS-QB3-computed carbon−oxygen bond distances in reference compounds (dimethyl ether and acetone) and in fluorinated methoxide ions as a function of charge on carbon. Charge is based on an average of NPA, ChelpG, and AIM charges.

times larger increase in CN bond length (ΔrCN = +0.092 Å) compared to the decrease in CO bond length (ΔrCO = −0.012 Å) is shown to be completely consistent with the hypothesis that this change is due to the elimination of resonance form **B** in the transition state. According to the model compounds in Scheme 6, the expected change is an order of magnitude larger for the CN bond change than the CO bond change.

Table 1 shows the important geometric parameters for the ground state, the rotational transition state, and the difference between them. All of the molecules with restricted rotation share certain geometric similarities: strongly pyramidalized nitrogen atoms in the transition state, a significant lengthening of the CN bond upon rotation, and a smaller decrease in the CO (or CX) bond. Consistent with the importance of the amide resonance, the ground states of molecules with barriers of at least 15 kcal/mol are characterized by geometries where the NH_2 fragment is coplanar with the heavy atoms of the molecule.

Charge. While the concept of partial atomic charge has been indispensable to the understanding of chemical reactivity and the development of molecular modeling, its definition and quantitative measure is fraught with difficulties of a theoretical and practical nature.[6,26] The partitioning of electrons among atoms may be considered arbitrary and ill-defined. Mulliken analysis is the most commonly employed and, perhaps, least respected method of population analysis due to its known dependence on basis set. We employed three different methods of population analysis: the natural population analysis (NPA)[18] method of Weinhold, a wave function-based method that solves many of the problems of the Mulliken analysis; the ChelpG method[19] that fits the electrostatic potential; and Bader's atoms in molecules (AIM)[4] approach that divides atomic basins by the "zero-flux" surface of the electron density.

Atomic charges calculated by these methods gave disparate results, often differing from each other by 0.3*e* and sometimes by as much as 0.8*e*. For the purposes of this study, the atomic charges were less important than the change in atomic charge upon rotation of the CN bond. Although this result yielded better agreement between the three methods, the deviations were still large (typically differing by around 0.1*e*). Despite the lack of quantitative agreement between the methods, there exists a rather coherent qualitative description of the charge effects observed upon rotation.[27] The change in atomic charge upon rotation, Δq, is given in Table 2 as an average for the three population analysis methods employed here. For all molecules exhibiting hindered rotation, the NH_2 moiety is more negative in the transition state than the ground state. This and the change in charges on C and X are consistent with a ground-state effect in which there is donation from the NH_2 lone pair electrons into the C═X π* orbital. In contrast, those few molecules that exhibit free CN rotation (<4 kcal/mol) differ from the rest in that their Δq(CX) values are of the opposite sign.

Table 2. Change in Charge Δq (TS − GS) for **1**−**9** in Order of Decreasing CN Rotation Barrier

molecule	NH_2	C	X[a]	CX	barrier[b]
9	−0.204	+0.257	−0.039	+0.218	49.4
5	−0.197	+0.212	−0.001	+0.211	40.9
3	−0.201	+0.158	+0.070	+0.228	30.3
8	−0.125	+0.025	+0.152	+0.176	21.6
2	−0.073	+0.047	+0.015	+0.062	15.4
6	−0.094	+0.062	+0.056	+0.118	9.4
1	−0.025	+0.056	−0.152	−0.096	3.9
7	−0.013	+0.024	−0.025	−0.001	2.0
4	−0.068	+0.033	−0.068	−0.035	1.9

[a] Carbonyl oxygen or equivalent moiety. [b] CBS-QB3-computed barrier in kcal/mol.

The results found in Table 2 seem to substantiate the remaining criticism of amide resonance theory: $|\Delta q(\mathrm{O})| < |\Delta q(\mathrm{N})|$. On the basis of the formal charges in **B** one might expect that Δq(O) should be equal in magnitude to Δq(N), but there are several reasons why they might differ. The orbital explanation is that the C═O π* orbital has the reverse polarization of the π orbital, meaning that it has a larger lobe on carbon than oxygen. Therefore, donation into this orbital from the nitrogen lone pair increases the ground-state electron density on carbon more than oxygen.[9e,10g,i,j] There is also a complimentary explanation that does not rely upon orbital arguments. It is naïve to think that atomic charges should closely mirror formal charges because electronegativity differences strongly influence the expected atomic charge. According to resonance form **B** the π electrons should be polarized from nitrogen toward oxygen. Electronegativity differences will influence both the σ and π electrons, being most evident in the σ distribution. The σ electrons should be polarized in the opposite manner to those in the π system due to the increased electronegativity of N^+ and the electropositivity of O^- in resonance form **B**. Although the σ effect will tend to ameliorate the π effect, there is no reason to believe that it will do so equally for nitrogen and oxygen. In fact, using the model compounds in Scheme 6 we find that the difference in charge between the NH_2 in isopropyl amine **7** and iminium **9** is more than 60% larger than the difference in charge on oxygen between acetone and difluoromethoxide.

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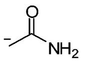
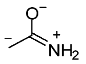
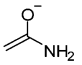
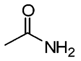
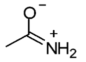
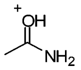
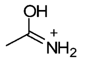
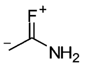
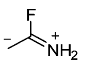
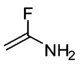
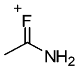
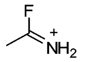
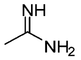
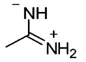
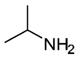
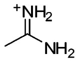
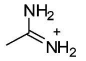
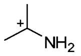
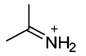
(26) (a) Martin, F.; Zipse, H. *J. Comput. Chem.* **2005**, *26*, 97. (b) Pacios, L. F.; Gomez, P. C. *J. Mol. Struct. (THEOCHEM)* **2001**, *544*, 237. (c) Sigfridsson, E.; Ryde, U. *J. Comput. Chem.* **1998**, *19*, 377. (d) Wiberg, K. B.; Rablen, P. R. *J. Comput. Chem.* **1993**, *14*, 1504.

(27) NPA, ChelpG, and AIM charges are in the Supporting Information in Tables S2, S3, and S4. A notable exception to the coherent qualitative agreement between the methods is found for the change in AIM charges for acetamide (**2**). Whereas the AIM method shows negative values for Δq(N) and positive values for Δq(CX) in all five of the other molecules with significant rotation barriers, it inexplicably presents the opposite pattern for acetamide. Wiberg and Breneman have attributed this discrepancy to the anisotropic definition of atomic basins in AIM.[5] Similar results for formamide were the genesis of the current controversy.[3]

Table 3. Natural Resonance Theory Results for **1**−**9**

#		resonance weights[a] A	%	B	%	C	%
1	GS		39		3		49
	TS		35		0		54
2	GS		62		28		
	TS		85		2		
3	GS		34		58		
	TS		82		2		
4	GS		4		7		82
	TS		4		1		85
5	GS		23		67		
	TS		77		4		
6	GS		71		20		
	TS		87		1		
7	GS		91				
	TS		92				
8	GS		46		46		
	TS		85		1		
9	GS				86		
	TS		71		0		

[a] Weights of all bonded resonance forms. See ref 11 and Computational Methods for details.

Natural Resonance Theory Analysis. Qualitative resonance analysis of the ground-state structures **1**−**9** successfully predicts the CBS-QB3 computed rotation barriers, but a quantitative measure would be much more convincing. NRT analysis provides weights for each Lewis structure. The percent weight of each resonance contributor (**A**, **B**, and **C**) is presented in Table 3 for both ground and transition states. No-bond resonance forms such as those associated with hyperconjugation are omitted for clarity and make up the difference from the total Lewis weight.

The results in Table 3 confirm all of the qualitative arguments presented earlier. It is also clear that the capacity for resonance form **B** to contribute to the transition structure is greatly diminished if not eliminated. Our value of 28% for the contribution of **B** in the hybrid structure of acetamide is similar to the values obtained for amides by Glendening and Hrabal[10j] as well as those by Basch and Hoz.[10g]

Since both **A** and **C** have CN single bonds, one would expect the contribution of **B** in the ground state to be a determining factor for the rotation barrier according to the amide resonance theory. A plot of computed barrier versus percent weight of amide resonance **B** (Figure 2) shows an excellent correlation ($r^2 = 0.98$) with a mean absolute deviation (MAD) of only 2 kcal/mol from the line of best fit. The fit seems even more remarkable because this simplistic model accounts for only one ground-state resonance form and yet it correlates so well to a variety of structural types and a broad range of barrier heights. Certainly other factors such as the extent of nitrogen rehybridization or hyperconjugation, must influence the rotation barrier (vide infra), but the net result of such effects is likely to be similar enough in **1**−**9** to contribute only about 2 kcal/mol variation.

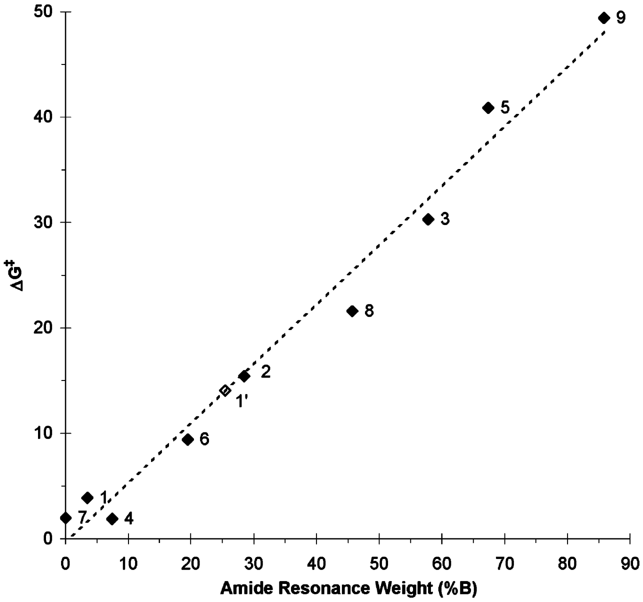
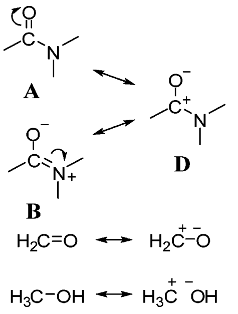


Figure 2. CBS-QB3-calculated CN rotation barriers and NRT resonance weights for amide resonance **B** in **1**−**9**. Line of best fit to **1**−**9**, $r^2 = 0.98$, MAD = 2 kcal/mol. Open diamond, **1′** (vide infra), is not used for fit.

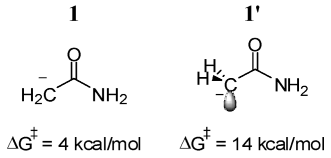
Scheme 7. Ionic Resonance Forms



Much has been made over the inclusion of ionic resonance **D** (Scheme 7).[7,9c−e,h,10c−e,g,k,12] In the tradition of most organic chemistry textbooks, resonance forms involving heterolysis of π bonds (e.g., formaldehyde in Scheme 7) are shown explicitly while those involving σ bonds are not (e.g., methanol in Scheme 7).[1d,e] NRT does not directly calculate the weights of ionic structures, such as $H_2C^+-O^-$ in formaldehyde, because it treats polar bonds (both σ and π) with a single resonance form that varies smoothly between the limits of ionic and covalent bonding.[11] Instead, such a structure is subsumed in one polar−covalent structure for π bonds ($H_2C{=}O$) and σ bonds (H_3C-OH). Using the percent ionic character reported in the NRT analysis, one may estimate the weight of structure **D** as well as new values for **A** and **B** (which formerly subsumed **D**). Doing so gives weights for acetamide of 50%, 23%, and 18% for **A**, **B**, and **D**, respectively. Using resonance weights recomputed in this manner does not improve the correlation seen in Figure 2.

Polarization Model. Before concluding that the amide resonance model is the most important factor controlling the CN rotation barriers for **1**−**9**, one should see how well competing models fare. According to the polarization model, CN rotation barriers in amides are due to polarization of the

Scheme 8. Twisted Acetamide Enolate, **1′**



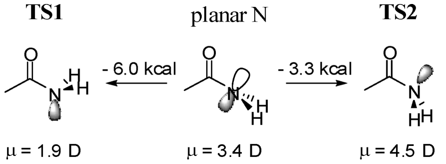
carbonyl group, as in $C^{+}-O^{-}$, leading to Coulombic interactions.[7b] Qualitatively, this model is hard to distinguish from the resonance model because they both predict higher CN rotation barriers for $CH_3C(=X)NH_2$ when X is more electronegative. Two computationally quantifiable results might be used to measure the extent of polarization: (1) the weight of resonance form **D** and (2) the atomic charge on carbon. Neither quantitative measure provided any decent correlation for **1**−**9** (r^2 of 0.1 and 0.4, respectively) and improved only moderately by excluding the model compounds ($r^2 < 0.6$ for **1**−**6**).

A qualitative example that demonstrates the superior predictive power of the resonance model over the polarization model is provided by examining enolate **1**. Whereas acetamide **2** has a computed CN rotation barrier of 15 kcal/mol, deprotonation at the α carbon reduces that barrier to 4 kcal/mol. According to the polarization model, the small barrier in **1** can be attributed to the donation of electron density from the methylene anion toward the carbonyl, thereby reducing the positive charge on the carbonyl carbon. According to the resonance model, the importance of resonance contributor **B** is greatly diminished because of the introduction of a new resonance form, **C**, that arises when the α carbon is deprotonated. Form **B** does not compete effectively with **C** because it involves electron transfer from nitrogen to carbon as well as charge separation. However, if **C** were somehow eliminated, the relative merits of **A** and **B** should be comparable to that found for **2**. A computational experiment can test this hypothesis. Twisting about the CC bond to the point where the methylene anion orbital is orthogonal to the carbonyl π bond eliminates **C** as a reasonable resonance contributor (Scheme 8). One might predict, utilizing the polarization model, that the CN rotation barrier in the twisted structure **1′** would be close to that in **1**. In contrast, the resonance model clearly predicts a much larger barrier comparable to that in acetamide because similar factors govern the relative merits of **A** and **B** in **1′** and **2**. The computed CN rotation barrier in **1′** is 14 kcal/mol, nearly the same as that in acetamide **2**. The weights for **A** and **B** in **1′** are 60% and 25%, respectively; a close match to that found for **2** and within 0.1 kcal/mol of the line of best fit in Figure 2.

Transition-State Effects. The surprisingly good correlation seen in Figure 2 implies that the CN rotation barriers in **1**−**9** can be predicted based on ground-state effects alone, specifically, the weight of resonance contributor **B**. There is substantial evidence, however, that transition-state effects are important in the overall barrier for amides. Rehybridization and other effects stabilize the transition state, but such effects, in the aggregate, are likely to be quite similar for the molecules studied here. If these transition-state effects were more dramatic or varied from molecule to molecule, we would expect a much larger MAD than the 2 kcal/mol found for the data in Figure 2.

Due to the large geometric changes associated with CN rotation, the most obvious stabilizing effect in the transition state is rehybridization at nitrogen. Table 1 shows that nitrogen is significantly pyramidalized in all transition states but planar in most of the ground-state geometries. A planar acetamide transition structure[28] can pyramidalize in two directions, leading to two possible transition structures (Scheme 9).[29] Although pyramidalization in one direction leads to a 6.0 kcal/mol stabilization, it leads to only 3.3 kcal/mol stabilization in the other direction. The lower value is very similar to that found for isopropyl amine (2.8 kcal/mol). Thus, the rehybridization itself is likely to be responsible for a stabilization of only about 3 kcal/mol. It is probable that dipolar effects may be responsible for the difference between TS1 and TS2 since orientation of the lone pair anti to the carbonyl results in a significantly reduced dipole moment.[30]

Scheme 9. Pyramidalization of Acetamide Rotational Transition States



A second-order perturbation analysis of the natural bonding orbitals shows that, although CN rotation disrupts the amide resonance [$n(N) \rightarrow \pi^*(CO)$], it introduces a smaller stabilizing interaction [$n(N) \rightarrow \sigma^*(CO)$] of 9.6 kcal/mol. Negative hyperconjugation is shown to be, therefore, of the right magnitude to explain the bulk of the difference between vertical RSE values (25 kcal/mol) and rotation barriers (15 kcal/mol) for amides. Even larger hyperconjugative effects are possible with more electronegative substituents. In the extreme case of fluorovinyl amine (**4**), the CN rotation barrier is vanishingly small because the ground-state stabilization due to nitrogen lone pair donation into the C=C fragment is matched by the $n(N) \rightarrow \sigma^*(CF)$ interaction in the transition structure (19.5 kcal/mol). In fact, this interaction is large enough that our initial, uncorrelated level of theory found the C_s-symmetric transition structure to be a shallow minimum. The case of fluorovinyl amine helps explain how there can be a sizable ground-state RSE even in the absence of a significant rotation barrier.

Conclusion

For acetamide and related compounds, most of the nearly 50 kcal/mol variation in their CN rotation barriers is found to be due to stabilization from amide resonance **B** in the ground state. Although several effects stabilize the transition structure, chiefly hyperconjugation, taking them into account is not necessary to explain the bulk of the variation. The apparent discrepancies reported for amide transition structures, in which the CN bond elongates much more than the CO bond contracts, are found to be entirely consistent with appropriate model compounds for resonance **B**. Similarly, the change in charge is consistent with donation from the nitrogen lone pair into the carbonyl π^* orbital. Finally, the resonance explanation for high CN rotation barriers

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(28) The structure with a twisted, planar nitrogen is a second-order saddle point. The two imaginary frequencies represent pyramidalization at nitrogen and CN rotation.

(29) TS1 was the favored transition structure in most cases (**1**, **2**, **4**, **5**, **7**, and **9**). Notable exceptions were those where the electronegative atom, X, bears a proton (**3**, **6**, and **8**). In those cases, TS2 was the favored structure. It is interesting to note that barriers for these molecules lie below the line of best fit in Figure 2 and use of TS1 moves the barrier closer to the line in each case.

(30) See ref 9g for a discussion regarding the polarity differences between the transition states and differential solvation in polar solvents.

is sufficient and quantitatively more consistent than the competing polarization model.

Supporting Information Available: The complete citation for reference 15 as well as CBS-QB3 ground-state geometries, transition structures, absolute energies, and population analyses for **1**−**9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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