# Why Do *N*-Alkylated Anilides Bend Over? The Factors Dictating the Divergent Conformational Preferences of 2° and 3° *N*-Aryl Amides

Gabrielle J. Pros and Aaron J. Bloomfield*

Duquesne University, 600 Forbes Avenue, Pittsburgh, Pennsylvania 15282, United States

S *Supporting Information*

ABSTRACT: The conformational preferences of 28 sterically and electronically diverse *N*-aryl amides were determined using density functional theory (DFT), using the B3LYP functional and 6-31G(d) basis set. For each compound, both the cis and trans conformers were optimized, and the difference in ground state energy calculated. For six of the compounds, the potential energy surface was determined as a function of rotation about the N-aryl bond (by 5° increments) for both cis and trans conformers. A natural bond orbital (NBO) deletion strategy was also employed to determine the extent of the contribution of conjugation to the energies of each of the conformers. By comparing these computational results with previously reported experimental data, an explanation for the divergent conformational preferences of 2° *N*-aryl amides and 3° *N*-alkyl-*N*-aryl amides was formulated. This explanation accounts for the observed relationships of both steric and electronic factors determining the geometry of the optimum conformation, and the magnitude of the energetic difference between cis and trans conformers: except under the most extreme scenarios, 2° amides maintain a trans conformation, and the *N*-bound arene lies in the same plane as the amide unless it has ortho substituents; for 3° *N*-alkyl-*N*-aryl amides in which the alkyl and aryl substituents are connected in a small ring, trans conformations are also favored, for most cases other than formamides, and the arene and amide remain in conjugation; and for 3° *N*-alkyl-*N*-aryl amides in which the alkyl and aryl substituents are not connected in a small ring, allylic strain between the two *N*-bound substituents forces the aryl substituent to rotate out of the plane of the amide, and the trans conformation is destabilized with respect to the cis conformation due to repulsion between the π system of the arene and the lone pairs on the oxygen atom of the carbonyl. The cis conformation is increasingly more stable than the trans conformation as electron density is increased on the arene because the more electron-rich arenes adopt a more orthogonal arrangement, increasing the interaction with the carbonyl oxygen, while simultaneously increasing the magnitude of the repulsion due to the increased electron density in the π system. The trans conformation is favored for 2° amides even when the arene is orthogonal to the amide, in nearly all cases, because the C−N−C bond angle can expend at the expense of the C−N−H bond angles, while this is not favorable for 3° amides.
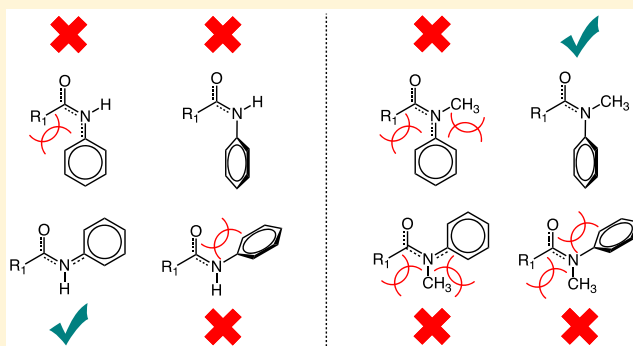
1. INTRODUCTION

In contrast to 2° amides, for which the *trans* conformation is nearly universally favored over the *cis* conformation (as shown in Figures 1 and 2), *N*-al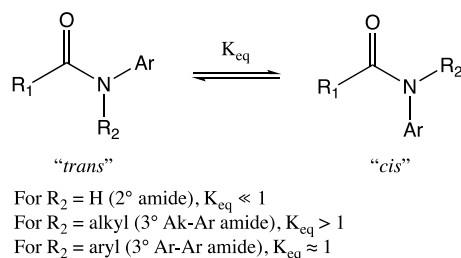kyl-*N*-aryl 3° amides demonstrate the opposite conformational preference. Both experimental and computational results from dozens of independent researchers, together studying hundreds examples of *N*-alkyl-*N*-aryl 3° amides have clearly identified that the *cis* conformation is generally favored over the *trans* conformation by between 0.5 and 5 kcal/mol.[1−7] Multiple studies have even taken advantage of this conformational preference, using 3° amides as *cis* backbones for chelating ligands[8] and macromolecular architecture,[9,10] for preorganization to facilitate synthesis of lactams,[11,12] or for restricting rotation.[13−15] Okamoto et al. synthesized 3° *N*-pyridyl amides and demonstrated that the conformational preference can switch upon the addition of acid[16,17] or in solvents capable of hydrogen bonding.[18]

Figure 1. Conformational preferences of nonlactam amides with aromatic *N*-substituents.

For R₂ = H (2° amide), $K_{eq} \ll 1$
For R₂ = alkyl (3° Ak-Ar amide), $K_{eq} > 1$
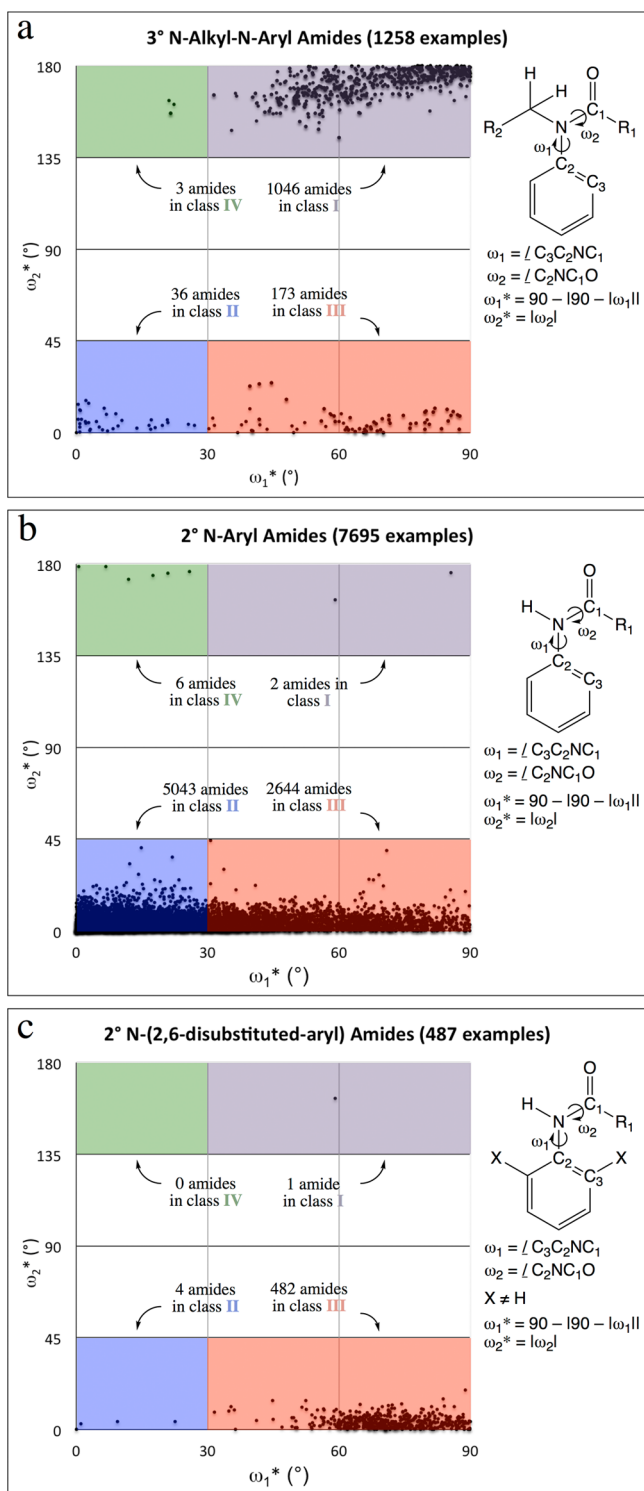For R₂ = aryl (3° Ar-Ar amide), $K_{eq} \approx 1$

Figure 2. Dihedral angles reported in the Cambridge Crystallographic Database for 3° N-alkyl-N-aryl amides (a), 2° N-aryl amides (b), and 2° N-aryl amides bearing 2,6-disubstituted arenes (c). Class I defined as structures for which $30° < \omega_1^* \leq 90°$ and $135° < \omega_2^* \leq 180°$; Class II defined as structures for which $0° \leq \omega_1^* \leq 30°$ and $0° \leq \omega_2^* \leq 45°$; Class III defined as structures for which $30° < \omega_1^* \leq 90°$ and $0° \leq \omega_2^* \leq 45°$; Class IV defined as structures for which $0° \leq \omega_1^* \leq 30°$ and $135° \leq \omega_2^* \leq 180°$.

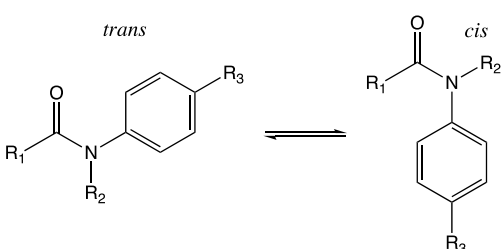Many of the papers discussing the conformation of amides focus solely on acetamide and N-methylacetamide, and those preferences have been well established.[2,3,19,20] There have been significantly fewer studies of more complex systems. Shudo et al.[21,22] explored conformational preferences of N-methylamides in solid state and solution, and the results were in good agreement. They synthesized several polyphenylic amides, and were able to switch from one all cis configuration (cis–cis) to another (cis–cis′) based on temperature, provided that enthalpy was moderate, entropy was large, and they were of the same sign. In a separate work,[23] they described how aryl amides can fluoresce, and found the twisted structures were stabilized in the excited state through charge separation through the arene system, allowing fluorescence. Yamasaki et al.[6] explored the effects of electronically diverse aryl substituents, experimentally comparing conformational equilibria of multiple electron-rich and electron-poor acetanilides and benzanilides. Additionally, Ilieva et al.[24] found a linear relationship between the rotational energy barrier around the amide and various substitutions in the para position. Conformational preferences of 2° amides have been explored, and found a correlation between the configuration and the chemical shift in NMR spectra.[4]

There is less clarity as to why this conformation is preferred. In many cases, especially when the alkyl substituent is a methyl group, it may appear at first glance that purely steric considerations predict the opposite—placing the bulkier aromatic substituent near the oxygen of the amide and the less bulky methyl group near the larger organic portion (R_1 in Figure 1). In some cases,[7,25] the steric strain between the aromatic substituent and R_1 is sufficiently unfavorable to substantially distort the planarity of the amide itself, weakening the N–C bond of the amide and enhancing the rate of solvolysis[7] or allowing insertion of transition metals into the N–C bond.[25]

A few studies over the course of the last 30 years have attempted to provide an explanation for this change in conformational preference.[3–6,19,24,26–28] In particular, a 1995 study by Saito et al.[3] took a theoretical approach to the problem, using ab initio Hartee-Fock modeling with the 4–31G and 6-31G** basis sets to compare the energies of cis and trans conformers of N-methylacetamide, acetanilide (**1a**), and N-methylacetanilide (**1b**). The authors found that both levels of theory were consistent with experimental findings (only N-methylacetanilide preferred the cis conformation), and they proposed that the conformational preference of the 3° amides could be explained by steric strain between the phenyl ring and the N-methyl substituent dominating over conjugation, forcing the phenyl substituent out of the plane of the amide, and that, due to its anisotropic steric profile, the steric repulsion between the orthogonal phenyl ring and acetyl methyl group in the cis conformation is less than the steric repulsion between the two methyl groups in the trans conformation. However, this explanation does not appear to be universally applicable to more complex systems, and does not capture the effects of electronic variations (vide infra).

In this manuscript, we revisit these theoretical studies using density functional theory (DFT), with the B3LYP functional and 6-31G(d) basis set and employing NBO deletion strategies to distinguish between energy differences due to orbital mixing and energy differences due to steric strain. We expand the scope of modeled amides from three to 28, surveying sets of sterically and electronically diverse amides and mapping torsional energy landscapes of six systematically varied amides. Additionally, we survey reported experimental data (both solid state and solution state) of the conformational preferences of

Table 1. Computational Method Validation by Comparison of the Difference in Energy (in kcal/mol) of cis and trans Conformers, Computed at Different Levels of Theory and Found Experimentally

compound	1a	2a	3a	4a	1b	2b	3b	4b
R_1	CH_3	CH_3	CH_3	H	CH_3	CH_3	CH_3	H
R_2	H	H	H	H	CH_3	CH_3	CH_3	CH_3
R_3	H	CF_3	NO_2	H	H	CF_3	NO_2	H
B3LYP/6-31G*	3.06	3.72	4.09	0.95	−2.51	−1.39	−0.65	−2.08
	2.46[a]	3.22[a]	3.66[a]	1.10[a]	−2.76[a]	−1.68[a]	−0.96[a]	−2.09[a]
B3LYP/6-31G* w/PCM	3.86	3.89	4.40	1.05	−1.88	−0.86	−0.02	−1.80
	2.64[a]	3.40[a]	3.95[a]	1.22[a]	−2.14[a]	−0.95[a]	−0.37[a]	−1.70[a]
M062X/jul-cc-pvdz	2.41	2.64	3.07	0.69	−2.23	−1.18	−0.78	−2.26
	1.84[a]	2.63[a]	3.04[a]	0.68[a]	−2.26[a]	−1.22[a]	−0.81[a]	−2.25[a]
M062X/jul-cc-pvdz w/PCM	1.76	2.52	3.03	0.54	−2.20	−0.64	−0.19	−1.71
	1.74[a]	2.50[a]	3.01[a]	0.53[a]	−1.64[a]	−0.67[a]	−0.22[a]	−1.70[a]
MP2/jul-cc-pvdz	1.90	2.12	2.42	0.79	−3.09	−2.04	−1.48	−2.01
MP2/jul-cc-pvdz w/PCM	1.12	1.94	2.26	0.56	−2.41	−1.62	−1.22	−1.52
MP4/jul-cc-pvdz sp[d]	1.54	2.25	2.62	0.82	−2.84	−1.53	−1.11	−2.04
experimental	>2[b]	N/A	N/A	0 < X < 1[b]	−1.35[c]	−0.92[c]	−0.55[c]	N/A

[a]Calculated with Grimme's D3 dispersion corrections.[30] [b]Determined by IR in carbon tetrachloride.[33] [c]Determined by NMR in dichloromethane-d^2 at 213 K (Supporting Information of Yamasaki et al.[6]). [d]Single-point calculation using M062X/jul-cc-pvdz geometry

several thousand amides to guide our analysis and corroborate our findings.

2. THEORETICAL CALCULATIONS

All calculations were performed using the Gaussian 16 program suite.[29] Geometry optimizations were run with the hybrid functional B3LYP and Pople's 6-31G(d) basis set, followed by frequency calculations to ensure all ground states were at a local minimum. Natural bond orbital (NBO) analysis was also carried out, allowing utilization of the $DEL keyword to delete interactions between the amine lone pair and the π-orbitals in the aryl system. Additionally, for selected structures, energetic and geometric results obtained using B3LYP and Pople's 6-31G(d) basis set were compared to both the M06-2X functional and the ab initio MP2 method with Dunning's jul-cc-pvdz basis set. For DFT calculations, Grimme's empirical D3 dispersion corrections were also calculed.[30] Single point MP4 calculations were also performed using the M06-2X/jul-cc-pvdz geometry. Tomasi's polarizable continuum model (pcm)[31] was also employed to model the dielectric constant of dichloromethane. All ground state configurations can be found in the Supporting Information.

3. RESULTS AND DISCUSSION

3.1. Examination of Crystallographic Data. A key piece of the puzzle comes from an evaluation of thousands of reported crystal structures (for more info, see SI) of 3° and 2° (nonlactam) amides bearing aromatic substituents on the nitrogen. It appears that the primary predictor of the cis/trans conformational preference of 3° amides (as defined by ω_2* in Figure 2) is the dihedral angle of the aromatic substituent with respect to the amide (ω_1* in Figure 2). In acyclic cases, allylic

(also known as $A^{1,3}$) strain between the ortho substituents (even H) on the aryl ring and the N-methyl (or alkyl) group appears to force a rotation of the aryl ring out of the plane of the amide, breaking conjugation. When considering 3° N-alkyl-N-aryl amides, 1049 of 1258 (83.4%) compounds crystallize in the cis conformation (ω_2* is within 45° of 180°). Of these, 1046 (>99.5%) structures present with $\omega_1* > 30°$ (defined as Class I). And in 36 of 39 (92.3%) of cases for which $\omega_1* \leq 30°$, the trans conformation is favored (Class II). This class is predominantly composed of amides in which aryl and alkyl substituents are connected, forming a small (<7 atom) ring containing the nitrogen atom of the amide. This small ring enforces the nearly coplanar ω_1*, but does not have an immediately clear direct way to influence ω_2*. Nevertheless, when the aryl ring is close to coplanar with the amide, the cis form appears to be generally disfavored.

Of the 1258 crystal structures of 3° N-alkyl-N-aryl amides analyzed, only about 5% appear in Class III, crystallizing in the trans conformation, while the aryl substituent is also rotated out of plane ($\omega_1* > 30°$). This class appears to be primarily populated with amides containing very sterically demanding R_1 groups, allowing steric considerations to dominate, as well as amides containing fluorinated aromatic rings, for which π-stacking between molecules within the crystal may overcome intramolecular factors. There are only three examples of amides with nearly coplanar aryl substituents and cis conformations (Class IV); however, these appear to be examples of extremely distorted Class I compounds ($\omega_1* > 20°$). No examples of cis amides with $\omega_1* < 20°$ were found.

Of the 7695 crystal structures of 2° (nonlactam) amides with aromatic N-substituents, 5043 (65.5%) appear in Class II, while only six appear in Class IV, and only two were found to
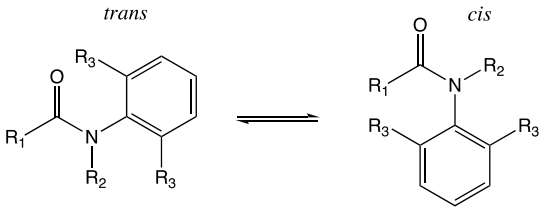
be in Class I, but these appear to be special cases in which the significant portion of heteroatoms in the molecules may well lead to dominant internal (or intermolecular) dipole−dipole interactions. Gas-phase calculations (see the SI) of the molecule reported by Irie et al.[32] do indicate the cis form to be ca. 0.4 kcal/mol more stable than the trans form. Even in cases for which the aromatic substituent on the nitrogen atom of the amide is forced out of plane by steric clashes (as is observed for most 2° amides in which the aryl substituent is a 2,6-disubstituted phenyl ring), the trans preference is not overcome, resulting in a Class III geometry being adopted.

3.2. Computational Method Validation. Kang[19] and Avalos et al.[4] found B3LYP/6-31G* to be an appropriate level of theory for amides, based on energy and geometry results. However, to ensure this system would be appropriate for a larger substrate scope, benchmark calculations made with B3LYP/6-31G(d) were compared to those obtained using M06-2X (which implicitly captures some dispersion) with a larger basis set (jul-cc-pvdz). Since DFT methods do not explicitly capture dispersion, Grimme's empirical D3 corrections[30] were also employed for a comparison. The ab initio MP2 method, which does explicitly capture dispersion was also tested with jul-cc-pvdz. All results were then compared to experimental results (Table 1). PCM was also used to model the dielectric constant of DCM (used experimentally by Yamasaki et al.), and it was found that in nearly all cases, utilizing PCM had little to no effect on energy differences between conformers. The differences in energy between cis and trans isomers are consistent across all computational methods (and consistent with limited experimental data) insofar as the 2° amides show preference for the trans conformation, while the 3° amides show preference for the cis conformation. In addition to agreement on the computed signs, the magnitudes of the computed energy differences are also similar across computational methods and follow two important experimental observations: the difference in energy between conformers of *p*-substituted-*N*-methylacetanilides increases with greater electron density in the arene (see section 3.4), and the energy difference is substantially greater for acetanilide than for formanilide. It was interesting to note that dispersion corrections had little effect on the differences in energy between cis and trans conformers, and in some cases, the values obtained with the dispersion correction deviate even further from experiment. Because of the general agreement of all levels of theory, with each other and with experimental data, and because the computational cost varied significantly between the methods, B3LYP/6-31G(d) was ultimately selected for all of the following computations (unless explicitly stated otherwise).

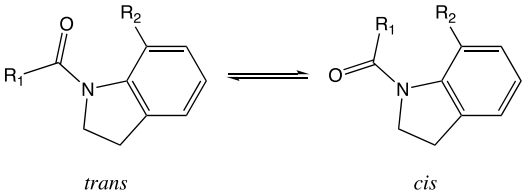**3.3. Computational Analysis of Steric Contributions.** In an attempt to investigate the role of steric strain in these systems, two series of anilides were modeled computationally in both cis and trans conformations. In the first series (Table 2), the three positions on the anilide core were substituted with either H or CH_3, allowing comparisons of formanilides vs acetanilides, 2° vs 3° amides, and phenyl vs 2,6-dimethylphenyl aryl substituents. In the second series (Table 3), all amides are the cyclic 3° amides in which the aliphatic substituent is an ethylene bridge tethered to the ortho position of the aromatic substituent. In the first series, all 2° anilides were more stable in the trans conformation, and all 3° anilides were more stable in the cis conformation. However, in the case of (2,6-dimethylphenyl)formamide (**5a**), the two conformers were

Table 2. Comparison of Computed ω_1^* and $E_{cis} − E_{trans}$ Values for a Series of Related Anilides

R_1	R_2	R_3	compound	ω_1^*	$E_{cis} − E_{trans}$ (kcal/mol)
H	H	H	cis-**4a**	30°	0.95
H	H	H	trans-**4a**	0°	
H	CH_3	H	cis-**4b**	41°	−2.08
H	CH_3	H	trans-**4b**	0°	
CH_3	H	H	cis-**1a**	43°	3.06
CH_3	H	H	trans-**1a**	0°	
CH_3	CH_3	H	cis-**1b**	90°	−2.51
CH_3	CH_3	H	trans-**1b**	45°	
H	H	CH_3	cis-**5a**	60°	0.03
H	H	CH_3	trans-**5a**	60°	
H	CH_3	CH_3	cis-**5b**	90°	−1.57
H	CH_3	CH_3	trans-**5b**	84°	
CH_3	H	CH_3	cis-**6a**	89°	1.19
CH_3	H	CH_3	trans-**6a**	63°	
CH_3	CH_3	CH_3	cis-**6b**	89°	−2.55
CH_3	CH_3	CH_3	trans-**6b**	82°	

Table 3. Comparison of 3° Amides in Which Alkyl and Aryl Substituents Are Tethered in a Small Ring

R_1	R_2	compound	ω_1^*	$E_{cis} − E_{trans}$ (kcal/mol)
H	H	cis-**7**	5°	−0.39
H	H	trans-**7**	5°	
H	CH_3	cis-**8**	27°	−1.44
H	CH_3	trans-**8**	47°	
CH_3	H	cis-**9**	11°	1.17
CH_3	H	trans-**9**	2°	
CH_3	CH_3	cis-**10**	55°	1.32
CH_3	CH_3	trans-**10**	48°	

nearly equal in energy. The differences in energy between the two conformers were larger across the board for acetamides than for formamides, with 2° acetamides more strongly favoring trans than 2° formamides, and 3° acetamides more strongly favoring cis conformations than 3° formamides.

The trans conformers with phenyl substituents were the only cases in which the aryl substituents were coplanar with the amide π system. It is not surprising that the addition of methyl substituents ortho to the aryl group would induce a rotation from planarity. However, it is noteworthy that all cis conformations were substantially deviated from planar. Even for formamides, where the hydrogen atom of the formyl group is less sterically demanding that of the carbonyl oxygen, the cis conformers deviate by at least 30° from planar, while the trans conformers are completely planar (absent substitution on the
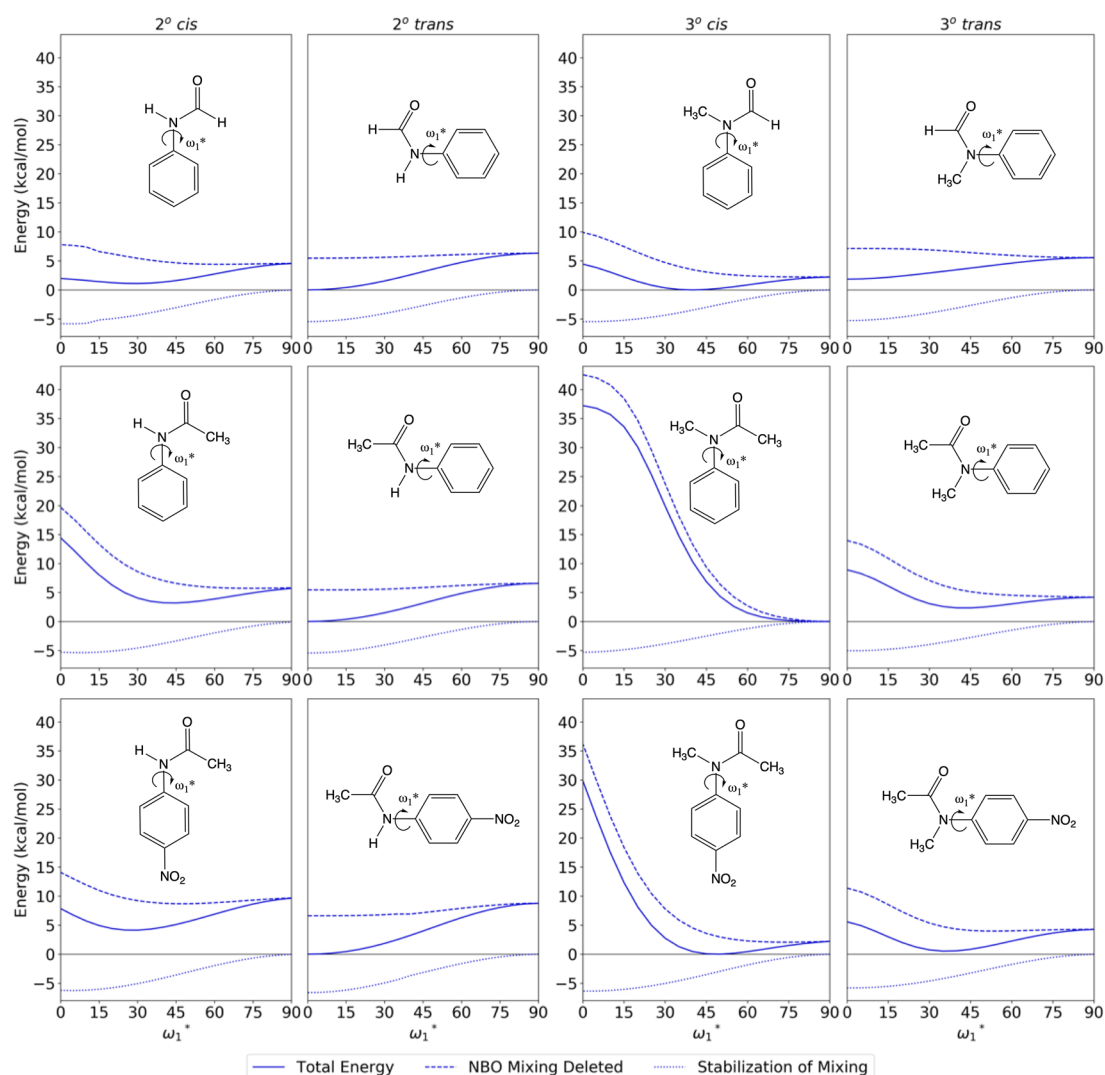
Figure 3. Total energy, stabilization energy due to orbital mixing, and the difference between the two, plotted as a function of ω_1* for cis and trans conformers of formanilide (**4a**), *N*-methyl formanilide (**4b**), acetanilide (**1a**), *N*-methylacetanilide (**1b**), *N*-(*p*-nitrophenyl)acetamide (**3a**), and *N*-methyl-*N*-(*p*-nitrophenyl)acetamide (**3b**).

arene). This trend holds for acetanilide, but both cis and trans conformers of *N*-methylacetanilide are nonplanar.

In the series of cyclic compounds, the degree of coplanarity differed much less between cis and trans conformers. The conformational preference appeared to be dominated by steric repulsion between R_1 and R_2. In both formamides (R_1 = H, which is smaller than O), the more stable conformation placed R_1 and R_2 close to each other. For the acetamides (R_1 = CH$_3$, which is larger than O), the more stable conformation placed R_1 and R_2 far from each other. In all cases, the magnitude of the preference was greater when R_2 was CH$_3$ than when R_2 was H. Because the preference for cis compounds disappears when R_1 increases in size from H to CH$_3$, it is expected that the trans preference for this type of cyclic amide will extend to most cases, and that formamides are the exception to the rule.

Taking the analyses of both series into account as well as the crystallographic data discussed above, it appears that steric considerations of R_1 and the aromatic group are less important in determining the cis/trans preference than the extent of coplanarity (ω_1*) is. There are four interactions that change significantly as a function of ω_1*: Ar-R_1 steric repulsion in the cis conformation, Ar−O steric repulsion in the trans

conformation, Ar-R_2 steric repulsion (which should be the same in both conformations), and the degree of conjugation of Ar with the amide (which should be the same in both conformations).

3.4. Torsional Analysis Using NBO Deletion Strategy. To deconvolute and quantify the contributions of these four factors, scans of ω_1* from 0° to 90° (by 5° increments) were performed with and without NBO deletions of the interaction between the lone pair on nitrogen atom of the amide and the arene π system. This computational approach, accessed by using the $DEL keyword, allows specific orbital−orbital interactions to be artificially forbidden. There is no way to perform an analogous experiment with real molecular systems, and the results are purely theoretical. However, this allows determination of the contributions of these interactions between natural bonding orbitals to the overall energy of a system, or in this case, the difference in energies between conformers.

By comparing potential energy surfaces of both *cis* and *trans* conformers of formanilide (**4a**), *N*-methyl formanilide (**4b**), acetanilide (**1a**), *N*-methylacetanilide (**1b**), *N*-(*p*-nitrophenyl)-acetamide (**3a**), and *N*-methyl-*N*-(*p*-nitrophenyl)acetamide

Table 4. Comparison of the Angles about the Nitrogen Atom of the 2° and 3° Amides Presented in Figure 3, in the trans Conformation with $\omega_1^* = 90°$ and in the cis Conformation with $\omega_1^* = 90°$

"trans"   "cis"

R_1 = H, CH_3 R_2 = H, CH_3 R_3 = Ph, 4-(NO_2)Ph, CH_3
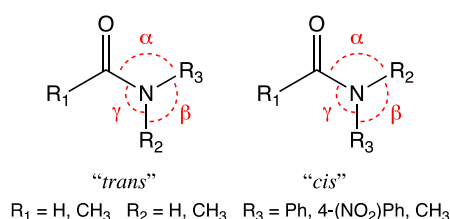
R_1	R_2	R_3	compound	α	β	γ	$\alpha + \beta + \gamma$
H	H	Ph	trans-4a	123.9	118.5	117.4	359.8
			cis-4a	115.5	119.6	124.6	359.7
H	CH_3	Ph	trans-4b	120.2	118.0	121.8	360.0
			cis-4b	120.2	119.0	120.8	360.0
CH_3	H	Ph	trans-1a	123.1	117.7	118.2	359.0
			cis-1a	113.0	118.2	127.3	358.5
CH_3	CH_3	Ph	trans-1b	118.4	115.9	125.6	359.9
			cis-1b	119.4	117.0	123.6	360.0
CH_3	H	4-(NO_2)Ph	trans-3a	121.6	116.8	117.2	355.6
			cis-3a	111.5	116.7	126.2	354.4
CH_3	CH_3	4-(NO_2)Ph	trans-3b	117.6	116.3	125.6	359.5
			cis-3b	119.5	116.9	123.6	360.0
H	H	CH_3	trans-11a	123.0	119.2	117.9	360.1
			cis-11a	115.4	119.3	125.3	360.0
H	CH_3	CH_3	11b	120.0	118.0	122.0	360.0
CH_3	H	CH_3	trans-12a	122.6	118.7	118.8	360.1
			cis-12a	113.2	118.2	127.2	358.6
CH_3	CH_3	CH_3	12b	119.1	115.4	125.5	360.0

(3b) (Figure 3), with and without NBO deletions, the stabilization due to orbital mixing can clearly be seen as a function of ω_1^*. As expected, the maximum stabilization energy occurs at $\omega_1^* = 0°$ in all cases, ranging from −5.0 kcal/mol for phenyl-substituted amides to −6.6 kcal/mol for the electron-deficient *p*-nitrophenyl-substituted amides, and tapers to 0 kcal/mol at $\omega_1^* = 90°$, when the orbitals are orthogonal. There is essentially no difference in these stabilization curves when comparing cis and trans, 2° and 3°, or formyl and acetyl amides—only by changing the electronic character of the *p*-substituent is there a notable change in this curve. This makes sense when considering delocalization of the amide's π electrons: the amide is a π-donor and intuitively should be more stabilized by conjugation with a π-acceptor. That this effect is essentially the same in all cases, suggests that it is not the determining factor, however the slight changes related to electronic character may contribute to the experimentally observed relationship between the magnitude of the cis preference in 3° anilides (see section 3.5).

For *trans*-2° amides, the energy of the conformers appears to be determined almost purely by the stabilization of orbital mixing, with no significant contribution from steric repulsion or any other effects, as demonstrated by the nearly flat lines observed when NBO mixing is deleted. This finding appears at first to be in contrast with Saito et al.,[3] in which repulsion between the arene π system and lone pairs of the carbonyl oxygen was assumed to be an important interaction for 2° anilides when $\omega_1^* = 90°$. It is possible that the repulsion between the arene π system and lone pairs is almost perfectly balanced by steric interactions between the ortho hydrogens on the arene with the carbonyl oxygen atom and nitrogen-bound hydrogen atom. This interpretation is supported by comparing the difference in energies between cis and trans

conformers at $\omega_1^* = 90°$ (−1.77 kcal/mol, − 0.87 kcal/mol, and +0.88 kcal/mol for **4a**, **1a**, and **3a**, respectively). **3a**, which would have the least electron density in its arene π system, is calculated to prefer the trans form at $\omega_1^* = 90°$, while **4a** and **1a** favor the cis form at $\omega_1^* = 90°$. (see section 3.5 for further discussion).

For *cis*-2° amides, there appears to be one or more slightly destabilizing effects that together are greater in magnitude than the orbital mixing stabilization, being most destabilizing at $\omega_1^* = 0°$ and least destabilizing at $\omega_1^* = 90°$. Therefore, the overall energy is minimized at an intermediate value of ω_1^*, in the neighborhood of 30°. In the cases of the acetanilides, this destabilizing interaction would apparently be ascribed to steric interactions between the phenyl ring and the methyl fragment of the acetyl group, however, this effect is also observed in the formanilide case, for which steric interactions with the oxygen in the trans conformation is expected to be greater than steric interactions with the formyl hydrogen in the *cis* conformation. This may be due to a destabilizing electrostatic interaction between the formyl hydrogen and the nearest aromatic hydrogen. In the trans configuration, the same phenylic hydrogen interacts with the partially negative carbonyl oxygen, which allows the molecule to stay planar. There is some experimental support for this finding: while *cis*-**4a** has not been crystallized alone, the analogous *N*-(*p*-tolyl)formamide has been crystallized in the *cis* conformation, and displays an ω_1^* value of 32°.[34]

For *trans*-3° amides, the relationship between stabilizing energy of orbital mixing is the same as for *trans*-2° amides, but there is significant steric repulsion between the *N*-methyl substituent and the ortho hydrogens on the phenyl ring, which is maximized at $\omega_1^* = 0°$ (ca. + 10 kcal/mol), and minimized at $\omega_1^* = 90°$. In the *cis* conformers, this effect is compounded

by additional steric interactions with the methyl group of the acetamide (+35−40 kcal/mol at $\omega_1{}^* = 0°$).

3.5. Comparison of the Steric Interactions in Systems with Orthogonal Arene and Amide Systems. Analysis of the difference in energy between cis and trans conformers in which the aryl substituent is set to be orthogonal ($\omega_1{}^* = 90°$) indicates that even for 2° anilides **4a** and **1a**, the cis forms are favored when $\omega_1{}^* = 90°$ (−1.77 kcal/mol for **4a** and −0.87 kcal/mol for **1a**). In contrast, the trans conformers are favored over cis for *N*-methylformamide (**11a**, + 0.84 kcal/mol) and *N*-methylacetamide (**12a**, +2.39 kcal/mol). Because the energy preference is opposite for anilides ($\omega_1{}^* = 90°$) and for methylamides, it appears that the R_3-O repulsion is greater when R_3 is aromatic than methyl. And because the magnitude of the *cis* preference of **4b** and **1b** is greater than the magnitude of the trans preference for **11a** and **12a**, it appears that repulsive interactions of the *N*-methyl substituent (R_2) with O and R_1 is likely only a small part of the preference for **4b** and **1b**.

Additionally, there is a significant difference between 2° and 3° amides in which the aryl substituent is orthogonal ($\omega_1{}^* = 90°$): in the case of 2° amides, the magnitude of difference in energy (cis−trans) is less than 2 kcal/mol (−1.77 kcal/mol, −0.87 kcal/mol, and +0.88 kcal/mol for **4a**, **1a**, and **3a**, respectively), while for 3° amides, the magnitude of this difference in energy exceeds 2 kcal/mol, and all values are negative (−3.33, − 4.17, and −2.06 kcal/mol for **4b**, **1b**, and **3b**, respectively).

Thus, it appears that the repulsion between lone pairs of the oxygen atom in the carbonyl and the π orbitals of the aromatic system for amides in the trans conformer at $\omega_1{}^* = 90°$ are not equivalent for 2° and 3° amides. This finding is in stark contrast to the analysis performed by Saito et al.,[3] in which this repulsion was assumed to be equivalent for 2° and 3° amides with the same dihedral angles.

Comparison of the cis−trans energy differences of **4a** vs **1a** ($\Delta\Delta E = 0.90$ kcal/mol) and **4b** vs **1b** ($\Delta\Delta E = 0.84$ kcal/mol) at $\omega_1{}^* = 90°$ indicate that there is a difference in the steric interactions of the aryl substituent and R_1 in the cis conformation, but that this difference is less significant than the differences between 2° vs 3°, and also less than cis vs trans for any of the given compounds. Thus, R_3-O interactions in *trans* conformations appear to contribute more to *cis*−trans differences than Ar-R_1 cis interactions.

To explain the difference between 2° and 3° amides at $\omega_1{}^* = 90°$, steric interactions between the geminal aryl and methyl substituents is again invoked. Analysis of the bond angles about the nitrogen atom, as shown in Table 4, appears to provide an intuitive explanation. The nitrogen atom is almost perfectly planar for all amides in Table 4, as indicated by the sum of the bond angles being equal to or within 1.5° of 360.0°), so the expansion or contraction of any one of these angles is necessarily balanced by contraction or expansion of the other two angles.

In *trans*-anilides, repulsion between the electron density of the π system of the aryl substituent and the lone pairs on the oxygen of the carbonyl forces α to increase beyond the ideal 120° geometry of the sp^2-hybridized nitrogen atom, causing the angle between the two *N*-substituents (β) to decrease. For 2° anilides, the small hydrogen atom allows α to expand at the expense of β, while the bulkier alkyl substituents present in the 3° anilides reduces the extent to which this repulsion can be accommodated. For all *trans*-2° amides shown in Table 4,

including *N*-methylformamide (**11a**) and *N*-methylacetamide (**12a**), the angle (α), defined by the *ipso* carbon of the aromatic substituent, the nitrogen, and the carbon of the carbonyl, is substantially larger (3.0−4.7°) for 2° amides than corresponding 3° amides.

This analysis also provides some insight as to why the *cis* preference of 3° acetanilides is greater than that of 3° formanilides (−2.51 kcal/mol for **1b** vs −2.08 kcal/mol for **4b**): minimal steric repulsion between R_1 and R_2 in the case of *trans*-formanilides allows α and β to expand at the expense of γ, while *trans*-acetanilides with significant steric repulsion between R_1 and R_2 do not allow for this relaxation, thereby increasing steric interactions between R_2 and R_3 (and therefore R_3 and O). Similarly, for cis cases, O-R_2 repulsion propagates to crowd the system, which is better accommodated by formanilide systems due to decreased R_1-R_3 interactions, which propagate. Unfortunately, because cis and trans conformers differ in multiple ways, it is difficult to compare α and γ values.

The angle (β) between the two noncarbonyl substituents on the nitrogen atom (R_2 and R_3) is useful for comparing steric strain between cis and trans conformers because the interaction between R_3 and R_2 is equivalent in both conformers (in contrast with angles α and γ, which are difficult to compare between conformers because the interactions R_1-R_3, O-R_3, R_1-R_2, and O-R_2 interactions are all nonequivalent). In all cases shown in Table 4, except for **3a** and **11a**, β is smaller for trans conformers than for their corresponding *cis* conformers by 0.5−1.1°, indicating that trans conformers have an overall increase in the steric strain across the amide (combined repulsion from the O-R_3 and R_1-R_2 interactions in the trans conformer is greater than combined repulsion from the O-R_2 and R_1-R_3 interactions in the cis conformer).

In the case of **11a**, β is actually 0.1° larger in the trans conformation. This is a special case because all of the substituents involved are small and interact very little in either conformation. That the difference in β between *cis*-**4a** and *trans*-**4a** is so much larger than observed for **11a** conformers indicates that the R_3-O interaction in *trans*-**4a** (R_3 = Ph) is more destabilizing than the R_3-O interaction in *trans*-**11a** (R_3 = CH_3). In the case of **3a**, β is also 0.1° larger in the trans conformation than in the cis conformation. This supports the notion that π system-lone pair interactions play a dominant role, as the electron deficient arene is expected to be least repelled (electron-deficient **3b** also has the smallest decrease in β of all 3° amides when comparing cis and trans conformers).

Formanilides **4a** and **4b** were found to have very similar changes in β, indicating little difference in the steric profile of the conformers of 2° and 3° formamides. However, for **1a** and **1b**, in which R_1 is larger, the steric crowding of the whole system increases. Because **1b** is more crowded than both **1a** and **4b**, the R_3-O interaction in *trans*-**1b** is more significant that for **1a** or **4b**. And, because **1b** has the largest change in β, and because this change of β is more significant for **1a** vs **4a** (R_3 = Ph) than for **11a** vs **12a** (R_3 = CH_3), can be deduced that these R_3-O repulsions in the trans conformer are dominant over R_3-R_1 and R_2-O repulsions in the *cis*. This analysis is another line of evidence that contradicts the findings of Saito et al. which indicated that R_1-R_2 interactions are dominant.

3.6. Computational Analysis of Arene Electronics. Given the differences between the phenyl and *p*-nitrophenyl compounds observed above, and the fact that the electronic character of the arene has previously been reported to have a significant influence on experimentally determined *cis-trans*

energy differences of 3° amides,[6] this analysis should be extended to a range of electronically distinct amides.

Solution-phase ^{1}H NMR analysis[6] of a dozen N-methylated acetanilides with differing substituents on the phenyl ring, for which the energy difference was small enough to observe the equilibrium between both conformers, indicates a very strong linear correlation ($R^2 > 0.95$) between the Hammett parameter (σ)[35] of the aromatic substituent, and the difference in energy between the cis and trans conformers.[6] The more electron-rich the aryl substituent, the stronger the preference for the cis conformation, with a linear relationship defined by

$$\Delta G°(\text{kcal/mol}) = -1.40 + 1.01\sigma$$

In cases for which both N-substituents on the 3° amide are aromatic, the more electron-rich one preferentially rotates out of plane, and sits cis to R_1, while the less electron-rich one remains conjugated to the amide, and sits trans to R_1. The energy differences for these N,N-diaryl amides less dramatic, but still significant. For instance, for N-(p-methoxyphenyl)-N-(p-nitrophenyl)acetamide, the free energy difference between the two conformers was found experimentally to be only 1.1 kcal/mol (vs 1.5 kcal/mol for N-methyl-N-(p-methoxyphenyl)-acetamide).

This relationship between the conformational preferences of substituted acetanilides and the Hammett parameters of the substituents also manifests in computed gas-phase energies (Figure 4). As expected, all six of the 2° anilides were found to
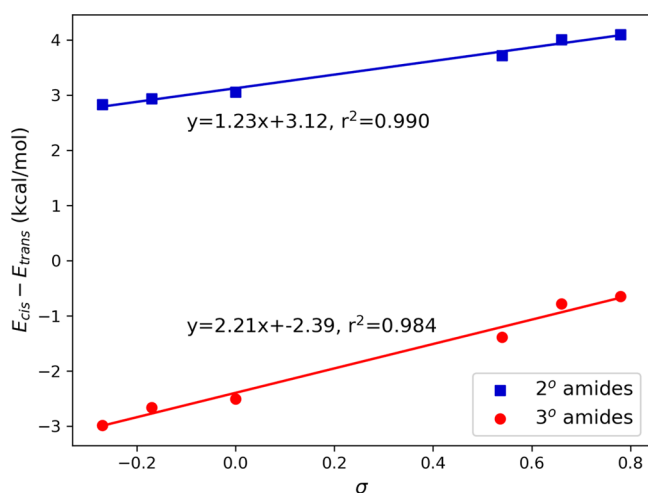

Figure 4. Computed energy differences between cis and trans conformers of a series of p-substituted acetanilides and N-methylacetanilides, compared to the Hammett parameter (σ) of the p-substituent: OCH_3 (**13**), CH_3 (**14**), H (**1**), CF_3 (**2**), CN (**15**), and NO_2 (**3**).

be more stable in the trans conformation, while their corresponding 3° N-methyl analogs were found to be more stable in the cis conformation. The cis–trans energy differences followed the same general trend for both 2° and 3° acetanilides (the more electron-deficient the arene, the more stable the trans conformation). In both cases, the correlation is quite strong ($R^2 > 0.98$), though the slope was found to be much steeper for the 3° acetanilides. This difference in slope can be explained by considering the influence of N-methylation on α (Table 4)—increased electron density in the π system of the aryl substituent has a greater influence on the cis–trans energy difference in 3° amides than in 2° amides due to the proximity

of the π system and oxygen lone pairs that is enforced by the bulky alkyl substituent. (Note that the slope and intercept for 3° compounds deviate from what was found via NMR by Yamasaki et al.,[6] however, they both exhibited the same general trend. The difference can be attributed to differences between gas phase and solution phase chemistry.)

For this series of p-substituted 2° acetanilides, the trans conformers optimize to have a nearly perfectly planar geometry ($\omega_1^* < 2.0°$), with the π system of the arene in near-perfect conjugation with that of the amide. When in the cis configuration, the optimum geometries of the 2° acetanilides showed a significant rotation of the arene out of plane, due to steric strain between the arene and the methyl group of the acetyl. The rotation is more extreme for more electron-rich arenes—up to 51° for p-OCH_3 (cis-**13a**), the most electron-rich of those modeled, while the least electron-rich arenes retained a greater degree of planarity, as little as 31° for both p-NO_2 (cis-**3a**) and p-CN (cis-**15a**). This is consistent with the competition between conjugation and steric strain noted in section 3.4, for which there is an increased stabilization of conjugation for more electron-poor arenes.

In the cases of the 3° acetanilides, for which the N-methyl substituent imposes steric strain on the arene, even the trans conformers showed significant deviation from planarity, spanning from 38° for the electron-withdrawing p-NO_2 (trans-**3b**) to 46° for the electron-donating p-OCH_3 (trans-**13b**). In the cis conformers, the electron-rich arenes p-OCH_3 (cis-**13b**), p-OAc (cis-**16b**), p-CH_3 (cis-**14b**), and unsubstituted (cis-**1b**), are almost completely perpendicular, while increasingly electron-poor arenes lie increasingly closer to planar, with the extreme example of p-NO_2 (cis-**3b**) deviating from planar by only 51°.

Thus, the addition of electron-donating substituents to the arene contributes to the destabilization of trans conformers in two ways: increased electron density in the aryl substituent decreases the penalty for loss of conjugation, allowing the arene to rotate further out of the plane of the amide, which in turn orients the π system more toward the lone pairs of the oxygen atom, and the magnitude of the repulsion increases with greater electron density in that π system.

4. CONCLUSIONS

The conformational preferences of anilides appear to be determined primarily by a complex interplay of steric and orbital delocalization effects. For 2° anilides, with minimal steric limitations, orbital delocalization dominates, strongly favoring the coplanar geometry, for which the trans Class II geometry is favored over the cis Class IV geometry due to the greater steric bulk of the substituents on the carbonyl side of the amide compared to the steric bulk of the carbonyl (except for formanilides). For 2° anilides with sterically demanding aryl substituents (such as 2,6-disubstituted arenes), orbital delocalization can be overcome, allowing the aryl substituent to rotate out of plane. Even for these noncoplanar arrangements, the trans Class III geometry is more stable than the cis Class I geometry because of the dramatic disparity in the size of the arene and hydrogen substituents, and the fact that the arene can tilt away from the carbonyl oxygen, toward the small hydrogen.

In contrast, for 3° N-alkyl-N-aryl amides, steric strain between the alkyl and aryl substituents is sufficient to rotate the aryl substituent out of conjugation with the amide, resulting in either the cis Class I or trans Class III

conformations, the latter of which would place the electron density of the aryl substituent in close proximity to that of the lone pairs on the carbonyl oxygen atom, resulting in repulsion. Finally, this repulsion is magnified for 3° amides because the steric bulk of the alkyl substituent prevents the aryl substituent from tilting away from the lone pairs, as can occur with 2° amides. This final effect is responsible for the dramatic disparity between the abundance of examples of Class III structures for 2° N-aryl amides and 3° N-alkyl-N-aryl amides.

■ ASSOCIATED CONTENT

ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jpca.9b04555.

> Supplementary figures, coordinates of all optimized structures referred to in the manuscript, and tabular presentation of data for all figures that appear in the manuscript (PDF)

■ AUTHOR INFORMATION

ORCID ⓘ
Aaron J. Bloomfield: 0000-0001-9805-2308

Author Contributions
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes
The authors declare no competing financial interest.

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■ ABBREVIATIONS

DFT, density functional theory; NBO, natural bond order

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■ NOTE ADDED AFTER ASAP PUBLICATION

Due to a production error, this paper published ASAP on August 26, 2019, with a graphic missing from Table 2 and the wrong graphic in Table 3. The corrected version was reposted on September 5, 2019.