Theoretical Studies on *cis*-Amide Preference in *N*-Methylanilides

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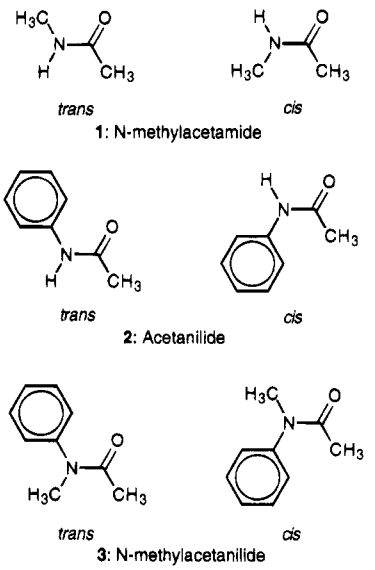
The known general preference of *cis*-amide structure in *N*-methylanilides both in crystal and in solution was studied by *ab initio* molecular orbital (MO) calculations for acetanilide and *N*-methylacetanilide. The *cis* structure was more stable by 3.50 kcal/mol than the *trans* one in *N*-methylacetanilide, whereas the *trans* structure was more stable by 2.15 kcal/mol than the *cis* one in acetanilide at the 6-31G**//4-31G basis set level. In order to examine the reliability of the result, the basis set dependency of the energy difference between *trans*- and *cis*-amide structures was also examined by changing the basis set from 4-31G to 6-31G** in the case of *N*-methylacetamide. The remarkable *cis* preference in *N*-methylanilides seems to be ascribed to destabilization of the *trans* structure due to steric hindrance between the two methyl groups and to electronic repulsion between the carbonyl lone-pair electrons and the phenyl π-electrons in the twisted phenyl orientation.

Introduction

The stereochemistry of the amide bond is an important subject, not only in pure chemistry but also in biological or medicinal chemistry. Since the discussions on amide structure by Pauling in 1948,[1] many experimental and theoretical studies on the *cis*–*trans* stereochemistry of the amide bond have been made.[2] The stereochemistry is sometimes critical in determining the biological activity of amide compounds. The *trans* conformation is more stable in secondary amides (hereafter called N–H amides), and the *cis* conformation is not observed unless there is a special conformational constraint. But, *N*-methylated amino acid residues and also proline residues in peptides occasionally take *cis*-amide structures in the crystalline state.[3] Thus, in amide compounds, the relative stability of *trans*- and *cis*-amide conformation is affected by *N*-methylation, without change of the apparent planar amide structures.

The *cis*-amide structure of *N*-methylacetanilide in the crystal was reported long ago,[4] but it has not attracted much attention. In 1990, we showed that the amide structures of *N*-methylbenzanilide and three derivatives are *cis* in the crystal, whereas those of the corresponding N–H amide compounds are *trans*.[5,6] The same preference for the *cis* structure was also observed in solution. Furthermore, the preference was proved to be general by experiments on *N*-methylanilides with various aliphatic groups at the carbonyl end, such as isopropyl, cyclopropyl, isopropenyl, and *tert*-butyl. All of them adopted the *cis*-amide structure in the crystal.[7] Thus, it was proved that *cis*-amide structure is more stable than the *trans* structure in *N*-methylanilides, whether the substituent group at the carbonyl end is aromatic or aliphatic.

Chart 1



Why is the *trans* preference in N–H anilide reversed to *cis*-anilide preference by *N*-methylation? What is the major factor responsible for the phenomenon? If this phenomenon can be ascribed to an intrinsic property of the molecule, it should be reproducible theoretically for a single molecule *in vacuo*. So, we have attempted to compare the stabilities of *trans*- and *cis*-amide models for N–H and *N*-methyl anilides by using molecular orbital (MO) calculations.

Since amide is a highly polarized group, semiempirical MO methods presently available cannot satisfactorily reproduce its stable structures and relative stability.[8] *Ab initio* MO calculation is essential for the purpose, but the minimal basis set STO-3G is insufficient in precision.[9] A larger basis set, with split-valence orbitals incorporating

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(1) Pauling, L. *The Nature of the Chemical Bond*; Cornell University Press: Ithaca, NY, 1948.

(2) (a) Zabicky, J. *The Chemistry of Amides*; Interscience Publishers: London, 1970. (b) Tsuzuki, S.; Tanabe, K. *J. Cnem. Soc., Perkin Trans. 2* **1991**, 1255. (c) Wang, Q. P.; Benett, A. J.; Brown, R. S.; Santarsiero, B. D. *J. Am. Chem. Soc.* **1991**, *113*, 5757. (d) Wiberg, K. B.; Breneman, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 831.

(3) (a) Kojima, T.; Kido, T.; Itoh, H.; Yamane, T.; Ashida, T. *Acta Crystallogr.* **1980**, *B36*, 326. (b) Subramanian, E.; Parthasarathy, R. *Int. J. Pept. Protein Res.* **1989**, 33, 345.

(4) Pedersen, B. F. *Acta Chem. Scand.* **1967**, *21*, 1415.

(5) Itai, A.; Toriumi, Y.; Tomioka, N.; Kagechika, H.; Azumaya, I.; Shudo, K. *Tetrahedron Lett.* **1989**, *30*, 6177.

(6) Toriumi, Y.; Kasuya, A.; Itai, A. *J. Org. Chem.* **1990**, *55*, 259.

(7) Itai, A.; Toriumi, Y.; Saito, S.; Kagechika, H.; Shudo, K. *J. Am. Chem. Soc.* **1992**, *114*, 10649.

(8) Preliminary calculations that we made on *N*-methylacetamide using AM1 and MNDO Hamiltonian implemented in the MOPAC 5.0 program could not reproduce even the relative stability of *cis*- and *trans*-amides. For this reason, we decided to perform *ab initio* MO calculation.

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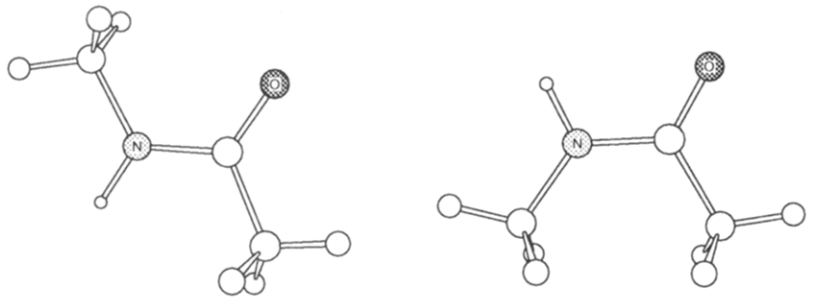


Figure 1. 6-31G** optimized *trans*- and *cis*-amide structures of *N*-methylacetamide (**1**).

polarization functions for both hydrogens and non-hydrogen atoms, should be used for geometry optimization as well as for a single-point calculation. The maximum basis set practically possible for geometry optimization of the anilide derivatives was thought to be the 4-31G basis set, considering our computational resources and results of the preliminary calculations. In order to check the validity of the result based on the 4-31G optimized structure, we first examined the basis set dependency of the optimized geometries and of the relative stability between the *trans*- and *cis*-amide structures by using *N*-methylacetamide (**1**) as a model compound. We used several larger basis sets including 6-31G** for full optimization. The basis set dependencies were examined with reference to the 6-31G** result.

Then, we studied the relative stabilities of *cis*- and *trans*-amide structures of acetanilide (**2**) and *N*-methylacetanilide (**3**). Full optimizations were done at the 4-31G level, and the energies were evaluated by using several larger basis sets including the 6-31G**.

Since the definition of *trans* and *cis* structures of these compounds is ambiguous, especially for **3**, we define them as shown in Chart 1.

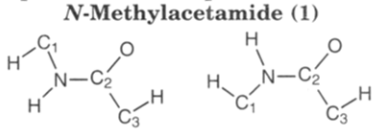
Methods

Ab initio Hartree–Fock calculations were performed for various models of **1, 2**, and **3** by using the Gaussian 86 program.[10] The standard 4-31G, 4-31G*, 4-31G**, and 6-31G** basis sets were used. The geometry optimization was done by the Berny gradient optimization method or the Murtaugh–Sargent method provided in the program.

For each compound, the most stable models for *trans*- and *cis*-amide structures were obtained in the following way. For all three compounds, only either the *trans*- or *cis*-amide structure was found by crystal structure analyses. In order to construct the starting amide structures for the observed amides (*trans*-**1**, *trans*-**2**, and *cis*-**3**), geometrical parameters (bond lengths and bond angles around the amide group) were taken from the reported crystal structures.[11–13] On the other hand, the starting amide structures for the unobserved ones (*cis*-**1**, *cis*-**2**, and *trans*-**3**) were prepared by rotating the amide torsion angles of the corresponding amide models by 180°. As regards the other torsional angles about the N–C(phenyl), N–C(methyl), and C(carbonyl)–C(methyl) bonds, the most stable conformations were searched by single-point calculations at the 4-31G level by rotating these bonds systematically and combinatorially. Torsion angles of these bonds were varied with a 30° step, while other geometrical parameters were fixed. Finally, the most stable conformers of *trans* and *cis* models obtained by this systematic search were fully optimized without any constraints by using the 4-31G basis set. All of the fully optimized structures were confirmed to be the minimum energy structures by frequency calculations (none of imaginary frequency).

In the case of **1**, the 4-31G optimized structures were further optimized by stepwise use of the 4-31G** and 6-31G** basis sets. With regard to **2** and **3**, further single-point calculations were performed at the 4-31G*, 4-31G**, and 6-31G** levels based on the 4-31G-optimized geometries.

Table 1. Optimized and Experimental Geometries of *N*-Methylacetamide (1)



	trans				*cis*	
	4-31G	6-31G**	crystal[a]	gas[b]	4-31G	6-31G**
Bond Lengths						
C1–N	1.453	1.446	1.465	1.468	1.451	1.444
N–H	0.990	0.991	–	–	0.993	0.994
N–C2	1.350	1.353	1.290	1.386	1.354	1.357
C2=O	1.224	1.200	1.236	1.224	1.224	1.210
C2–C3	1.505	1.515	1.536	1.520	1.520	1.513
Bond Angles						
C1–N–C2	121.4	121.4	120.5	119.6	127.0	127.4
H–N–C2	119.7	119.4	–	110.0	114.5	113.9
C1–N–H	119.0	119.2	–	–	118.6	118.8
O–C2–N	121.8	122.1	123	121.8	121.1	121.3
N–C2–C3	115.7	115.2	116.5	114.1	117.0	116.7
C3–C2–O	122.5	122.6	–	–	121.9	122.0
Torsion Angles						
H–C1–N–H	0.3	0.3	–	–	0.0	0.0
H–C3–C2–O	0.3	0.3	–	–	0.0	0.0
C1–N–C2–C3	180.0	180.0	–	–	0.0	0.0

[a] Data from ref 11. [b] Data from ref 14.

Results

***N*-Methylacetamide (1).** For *N*-methylacetamide (**1**), models for *trans* and *cis* structures were optimized stepwise by using the 4-31G, 4-31G**, and 6-31G** basis sets. The most stable structures for *trans* and *cis* models finally obtained by the 6-31G** geometry optimization are shown in Figure 1. In both structures, the two methyl groups (*N*-methyl and *C*-methyl) are both at the eclipsed position to the N–H and C=O bonds, respectively.

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(11) Katz, J. L.; Post, B. *Acta Crystallogr.* **1960**, *13*, 624.

(12) (a) Brown, C. J. *Acta Crystallogr.* **1966**, *21*, 442. (b) Wasserman, H. J.; Ryan, R. R.; Layne, S. P. *Acta Crystallogr.* **1985**, *C41*, 783.

(13) The reported values from the crystal structure of *N*-methylacetanilide were not consistent with those of other *N*-methylanilide derivatives.[7] Therefore, we solved the *N*-methylacetanilide structure ourselves (unpublished data).

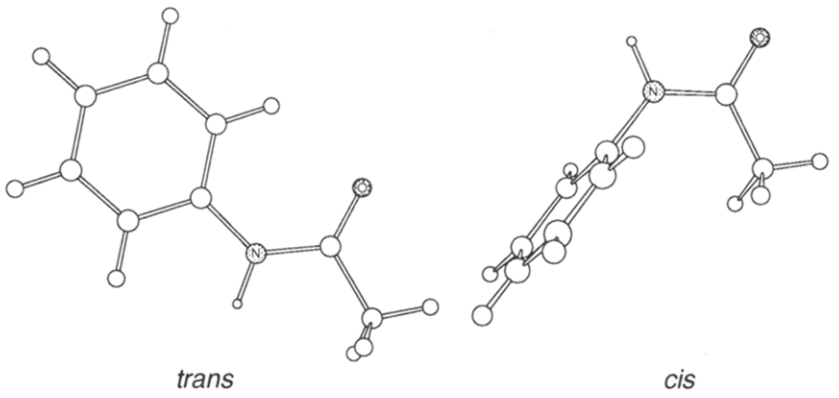


Figure 2. 4-31G optimized *trans*- and *cis*-amide structures of acetanilide (**2**).

Table 2. Total Energy (hartree) and Energy Difference ($\Delta E = E_{trans} - E_{cis}$) (kcal/mol) for *N*−Methylacetamide (1)

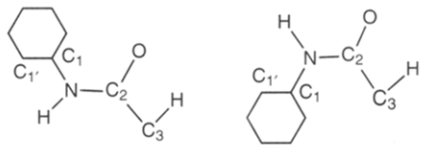
	4-31G//4-31G	4-31G**//4-31G	6-31G**//4-31G	6-31G**//6-31G**
E_{trans}	−246.641 943	−246.780 788	−247.018 566	−247.019 518
E_{cis}	−246.637 819	−246.776 780	−247.014 610	−247.015 601
ΔE (kcal/mol)	−2.59	−2.51	−2.48	−2.46

The structural parameters obtained from the 4-31G and 6-31G** optimizations are compared in Table 1, together with the experimental ones. In all basis sets, amide torsion angles for *cis* and *trans* structures are almost equal to 0° and 180°, respectively. Judging from the sum of the bond angles around the amide nitrogen and the carbonyl carbon, the planarity of the amide group appears to be maintained in both structures. When the *trans* and *cis* models are compared, there are remarkable differences in bond angles, but no significant difference is found in bond lengths. The 4-31G optimized *trans* structure is consistent with the results reported by other groups.[14] With regard to the effect of different basis sets on the geometries, deviations of the structural parameters are negligible among the three basis sets. The largest deviations in bond lengths and bond angles between the 4-31G and 6-31G** levels are 0.024 Å (C2=O) and 0.42° (N−C2−C3), respectively. With regard to consistency with the experimental structure, the structural parameters for the *trans* models are in good agreement with those of the experimental structures[15] (which have *trans*-amide both in the crystal and in the gas phase) within the limits of accuracy of the experimental methods.[16]

The total energies for the *trans* and *cis* models and the energy differences between them ($\Delta E = E_{trans} - E_{cis}$) obtained with various basis sets are compared in Table 2. In all the basis sets, the *trans* structure is more stable than the *cis* one, although the energy difference between the two conformers varies slightly depending on the basis set used. The differences are −2.59, −2.51, −2.48, and −2.46 kcal/mol, respectively, for the 4-31G//4-31G, 4-31G**//4-31G, 6-31G**//4-31G, and 6-31G**//6-31G** results, showing a tendency to decrease as the basis set becomes larger. Since the decrease of the energy difference from the 4-31G//4-31G level to the 6-31G**//6-31G** level was only 5%, it was suggested that the basis set dependency of the energy difference is relatively small, compared to that of the total energy itself.

Thus, we have concluded that the 4-31G basis set is adequate for use in geometry optimization for the purpose of examining the relative stability of *trans*- and *cis*-amides.

Table 3. 4-31G Optimized and Experimental Geometries of Acetanilide (2)



	trans		*cis*
	calcd	crystal[a]	calcd
	Bond Lengths		
N−C1	1.409	1.413	1.424
N−H	0.992	1.080	0.995
N−C2	1.360	1.354	1.362
C2=O	1.220	1.219	1.222
C2−C3	1.506	1.495	1.501
	Bond Angles		
C1−N−C2	129.2	127.6	127.3
H−N−C2	116.2	117	114.6
H−N−C1	114.6	115	118.1
N−C2=O	124.0	123.1	120.5
C3−C2−N	114.3	115.4	117.5
C3−C2=O	121.6	121.3	122.0
	Torsion Angles		
C1′−C1−N−H	0.0	17.6	90.1
H−C3−C2−O	0.0	–	0.0
C1−N−C2−C3	180.0	−3.4	0.0

[a] Data from ref 12.

Acetanilide (2). The most stable *trans*- and *cis*-amide models of **2**, which were obtained by systematic bond rotations of N−C(phenyl) and C−C(methyl) bonds, were further optimized without any constraints by using the 4-31G basis set. The most stable *trans* and *cis* structures are shown in Figure 2.

(14) (a) Sugawara *et al.* calculated the relative stabilities of *trans*- and *cis*-amide structures of *N*-methylformamide and *N*-methylacetamide at the 4-31G level in order to confirm their spectroscopic observation. Sugawara, Y.; Hirakawa, A. Y.; Tsuboi, M.; Kato, K.; Morokuma, K. *J. Mol. Spectrosc.* **1986**, *21*, 115. (b) Four stable conformers of *trans*-*N*-methylacetamide were found at the 4-31G* level. Mirkin, N. G.; Krimm, S. *J. Mol. Struct.* **1991**, *242*, 143. (c) Random, L.; Riggs, V. *Aust. J. Chem.* **1982**, *35*, 1071.

(15) (a) Kitano, M.; Fukuyama, T.; Kuchitsu, K. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 384. (b) Kitano, M.; Kuchitsu, K. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3048. (c) Wong, M. W.; Wiberg, K. B. *J. Phys. Chem.* **1992**, *96*, 668.

(16) The shortening of N−C2 bond length in the crystal structure might be caused by intermolecular hydrogen bond formation between the N−H and C=O groups. It has been found, both theoretically and experimentally, that hydrogen bond formation has a marked effect on N−C2 and C=O bond lengths.[15]

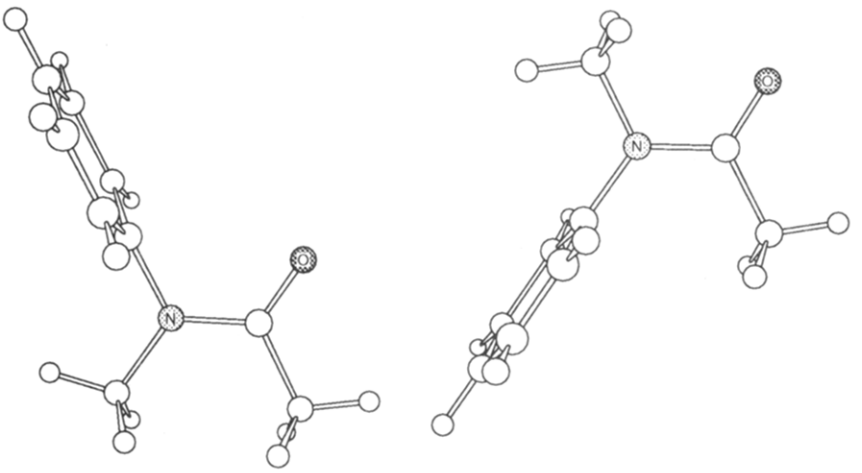
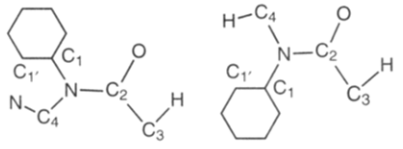


Figure 3. 4-31G optimized *trans*- and *cis*-amide structures of *N*-methylacetanilide (**3**).

Table 4. Total Energy (hartree) and Energy Difference ($\Delta E = E_{trans} - E_{cis}$) (kcal/mol) for Acetanilide (2)

	4-31G//4-31G	4-31G*//4-31G	4-31G**//4-31G	6-31G**//4-31G
E_{trans}	−436.887 514	−437.087 557	−437.106 678	−437.536 938
E_{cis}	−436.883 724	−437.083 961	−437.103 076	−437.533 512
ΔE (kcal/mol)	−2.38	−2.26	−2.26	−2.15

Table 5. 4-31G Optimized and Experimental Geometries of *N*-Methylacetanilide (3)



trans *cis*

	trans calcd	*(trans)″* calcd	*cis* calcd	*cis* crystal[a]
Bond Lengths				
N−C1	1.431	1.433	1.429	1.457
N−C4	1.462	1.463	1.463	1.449
N−C2	1.366	1.373	1.363	1.322
C2=O	1.222	1.224	1.225	1.239
C2−C3	1.506	1.513	1.505	1.505
Bond Angles				
C4−N−C2	122.2	120.0	119.8	120.4
C1−N−C2	120.2	123.9	123.5	122.1
C1−N−C4	117.5	116.0	116.6	117.6
N−C2=O	122.3	123.5	121.7	120.8
C3−C2−N	117.4	119.0	117.6	116.7
C3−C2=O	120.3	117.5	120.7	122.5
Torsion Angles				
C1′−C1−N−C4	55.5	0.0	88.8	87.1
H−C4−N−C1	18.1	60.3	60.1	–
H−C3−C2−O	6.2	0.0	0.0	–
C1−N−C2−C3	177.2	180.0	0.0	0.0

[a] Data from ref 13.

In the most stable *trans*-amide model, the phenyl ring and amide group are coplanar, suggesting favorable conjugation between the two groups, whereas in the most stable *cis*-amide model, the phenyl ring is perpendicular to the amide group. The planarity of the amide group is retained in both models, to the same extent as in **1**. The structural parameters of these two models are shown in Table 3, together with those found in the crystal structure of **2**.

The total energies and energy differences calculated by further single-point calculations at the 4-31G*, 4-31G** and 6-31G** levels based on the 4-31G optimized structures are summarized in Table 4. The *trans*-amide structure is more stable than the *cis* one in all the basis sets. The energy differences ($\Delta E = E_{trans} - E_{cis}$) are −2.38 (4-31G), −2.26 (4-31G*), −2.26 (4-31G**), and −2.15 (6-31G**) kcal/mol, respectively. These values are consistent with the experimental result that *trans*-amide is exclusively observed in the crystal and in solution.

***N*-Methylacetanilide (3).** The most stable *trans*- and *cis*-amide models for **3**, which were searched by systematic rotations of N−C(phenyl), N−C(methyl), and C−C(methyl) bonds, were fully optimized at the 4-31G level. The most stable structures for *trans*- and *cis*-amide models are shown in Figure 3.

The planarity of the amide group is maintained in both models. In the *cis* model, the phenyl ring takes a perpendicular conformation similar to the *cis* model of **2**, whereas in the *trans* model, the phenyl ring makes an angle of about 55° to the amide plane, which is quite different from the *trans* model of **2**. The structural parameters for the optimized *trans* and *cis* models are shown in Table 5, together with those from the crystal structure of **3**.

The values of the total energy and energy difference between *cis*- and *trans*-amide models calculated with the 4-31G, 4-31G*, 4-31G**, and 6-31G** basis sets based on the 4-31G geometry are compared in Table 6. The *cis*-amide structure is more stable than the *trans* one in all the basis sets. Energy differences ($\Delta E = E_{trans} - E_{cis}$)

Table 6. Total Energy (hartree) and Energy Difference ($\Delta E = E_{trans} - E_{cis}$) (kcal/mol) for *N*-Methylacetanilide (3)

	4-31G//4-31G	4-31G*//4-31G	4-31G**//4-31G	6-31G**//4-31G
E_{trans}	−475.845 694	−476.068 116	−476.088 209	−476.556 265
E_{cis}	−475.852 115	−476.073 662	−476.093 952	−476.561 851
ΔE (kcal/mol)	4.03	3.48	3.60	3.50

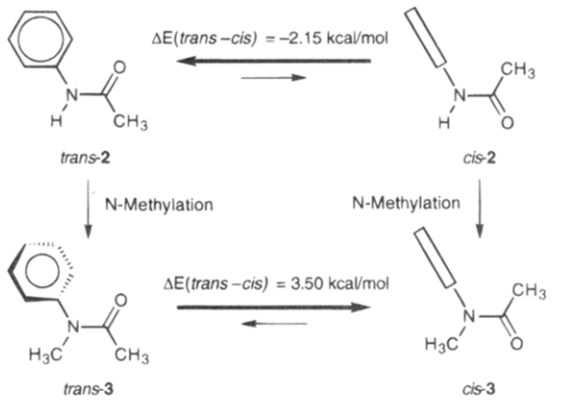
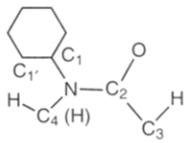


Figure 4. Energetic and conformational features of the most stable models of *trans*- and *cis*-amides for **2** and **3.**

Table 7. 4-31G Optimized Geometries of *Trans* Planar Acetanilide (*trans*-2(90)) and *Trans* Perpendicular *N*-Methylacetanilide (*trans*-3(0))



	trans-**2**(90)	*trans*-**3**(0)
	Bond Lengths	
N–C1	1.428	1.433
N–C4(H)	0.992	1.463
N–C2	1.361	1.373
C2=O	1.218	1.224
C2–C3	1.505	1.513
	Bond Angles	
C4(H)–N–C2	118.6	120.0
C1–N–C2	123.8	123.9
C1–N–C4(H)	117.6	116.0
N–C2=O	122.9	123.5
C3–C2–N	114.8	119.0
C3–C2=O	122.3	117.5
	Torsion Angles	
C1′–C1–N–C4(H)	88.8	0.0
H–C4(H)–N–C1	–	60.3
H–C3–C2–O	0.0	0.0
C1–N–C2–C3	180.0	180.0

are 4.03 (4-31G), 3.48 (4-31G*), 3.60 (4-31G**), and 3.50 (6-31G**) kcal/mol, respectively. These values are consistent with experimental observations that all *N*-methylanilide derivatives adopt the *cis*-amide structure in the crystal and also in solution. Similarly to the results of **2**, addition of a polarization function on heavy atoms decreased the energy difference, whereas that on hydrogen atoms had only a little effect.

Discussion

We have succeeded in reproducing qualitatively the *cis*-amide preference in **3** by *ab initio* MO calculation and have shown that the *cis* preference is an inherent property of *N*-methylanilides. As a result of calculations based on systematic conformational search by single-point calculations and full optimization by using the split-valence basis set, we were able to construct plausible model structures and elucidate reliably the energetic relationship between the two amide conformers. In **2**, the *trans*-amide was more stable than the *cis*-amide by 2.15 kcal/mol, whereas in **3**, the *cis*-amide was more stable than the *trans*-amide by 3.50 kcal/mol at the 6-31G**//4-31G level. The reliability of these results was supported by the results of calculations on **1** with various basis sets from 4-31G to 6-31G** level, and we concluded that the 6-31G** energies based on the 4-31G optimized geometry were satisfactorily reliable for the purpose of examining the relative stabilities of *cis*- and *trans*-amide structures.

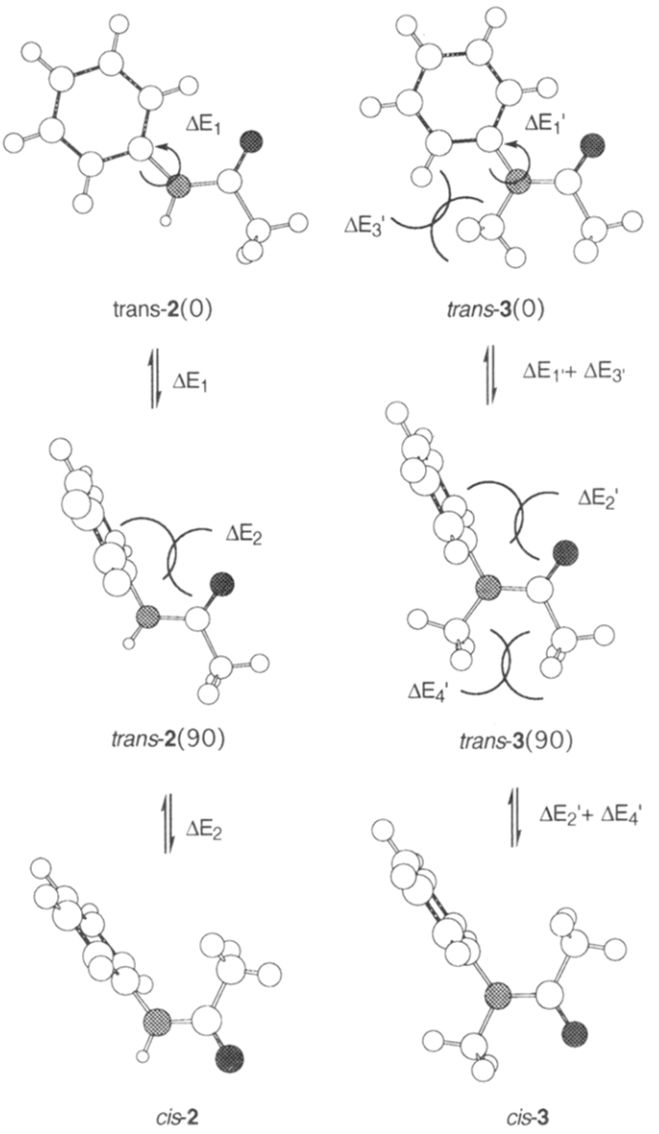


Figure 5. Energy relationships of conformers of **2** and **3.**

Energetic and conformational features of the most stable models of *trans*- and *cis*-amides for **2** and **3** are summarized schematically in Figure 4. Comparing the *trans* models of the two compounds, **2** adopts a conforma-

Table 8. Total Energy (hartree) and Energy Difference ($\Delta E = E(90) - E(0)$ (kcal/mol)) for *Trans* Planar Acetanilide (*trans*-2(90)) and *Trans* Perpendicular *N*-Methylacetanilide (*trans*-3(0))

	4-31G//4-31G	4-31G*//4-31G	4-31G**//4-31G	6-31G**//4-31G
$E_{trans\text{-}2(90)}$	−436.882 580	−437.083 080	−437.102 130	−437.532 694
$E_{trans\text{-}3(0)}$	−475.840 774	−476.061 845	−476.082 062	−476.550 136
$\Delta E_{trans\text{-}2(90)-trans\text{-}2(0)}$	3.10	2.81	2.85	2.66
$\Delta E_{trans\text{-}3(90)-trans\text{-}3(0)}$	−3.10	−3.92	−3.84	−3.85

tion with the amide and phenyl planes coplanar (*trans*-**2**), whereas **3** adopts a conformation with these planes twisted about 55° (*trans*-**3**). This means that the *trans* coplanar conformation of **2**, which is favorable for conjugation of the phenyl and amide groups, is destabilized by the *N*-methylation and is forced to adopt the twisted conformation. On the other hand, in the *cis* models of both compounds (*cis*-**2** and *cis*-**3**), the amide plane and the phenyl ring are perpendicular to each other. This means that the *cis*-amide structure of **2**, in which conjugative stabilization between the phenyl ring and the amide group is not present from the beginning, is not destabilized any further by the *N*-methylation.

On the basis of the above results, the remarkable *cis* preference in *N*-methylanilides seems to be ascribed to destabilization of the *trans* structure (*trans*-**3**) due to steric hindrance between the two methyl groups and to electronic repulsion between the carbonyl lone-pair electrons and the phenyl π-electrons in the twisted phenyl orientation.

In order to discuss the steric effect (the repulsion between the *N*-methyl group and the phenyl ring and the repulsion between the *N*-methyl and *C*-methyl groups) and the electronic effect (π-conjugation and π-repulsion) in detail, we performed structure optimization of the "*trans* perpendicular acetanilide (*trans*-**2**(90))" and "*trans* planar *N*-methylacetanilide (*trans*-**3**(0))". (The values in parentheses are torsional angles of the aromatic ring, which were fixed during structure optimization.) The resulting structural parameters and their energies are summarized in Tables 7 and 8.

By comparing corresponding conformers of **2** and **3** as shown in Figure 5, the relative energies of the steric and the electronic effects might be discussed separately. The energy differences (6-31G**//4-31G) between pairs of conformers are as follows.

$$\Delta E_{trans\text{-}2(90)-trans\text{-}2(0)} = \Delta E_1 = +2.66 \text{ kcal/mol}$$

$$\Delta E_{cis\text{-}2-trans\text{-}2(90)} = \Delta E_2 = -0.51 \text{ kcal/mol}$$

$$\Delta E_{trans\text{-}3(90)-trans\text{-}3(0)} = \Delta E_{1'} + \Delta E_{3'} = -3.85 \text{ kcal/mol}$$

$$\Delta E_{cis\text{-}3-trans\text{-}3(90)} = \Delta E_{2'} + \Delta E_{4'} = -3.50 \text{ kcal/mol}$$

Roughly speaking, we can regard $\Delta E_{trans\text{-}2(90)-trans\text{-}2(0)}$ as reflecting the loss of π-conjugation (ΔE_1), $\Delta E_{cis\text{-}2-trans\text{-}2(90)}$ as reflecting the electronic repulsion between π and oxygen lone pair (ΔE_2), $\Delta E_{trans\text{-}3(90)-trans\text{-}3(0)}$ as reflecting the sum of the steric repulsion (*N*-methyl group and phenyl ring) and the loss of π-conjugation ($\Delta E_{1'} + \Delta E_{3'}$), and $\Delta E_{cis\text{-}3-trans\text{-}3(90)}$ as reflecting the sum of the steric repulsion (*N*-methyl and *C*-methyl groups) and the electronic repulsion ($\Delta E_{2'} + \Delta E_{4'}$). We assume that the energies of the loss of π-conjugation (ΔE_1, $\Delta E_{1'}$) and π-lone pair repulsion (ΔE_2, $\Delta E_{2'}$) have the nearly same values in **2** and **3**.

$\Delta E_1 \approx \Delta E_{1'}$; loss of π-conjugation

$\Delta E_2 \approx \Delta E_{2'}$; electronic repulsion between π-electrons and oxygen long pair

Under this assumption, the energy ($\Delta E_{3'}$) of the steric repulsion between the *C*-methyl group and the phenyl ring and the energy ($\Delta E_{4'}$) of the steric repulsion between the *C*-methyl and *N*-methyl groups can be calculated. Interestingly, $\Delta E_{4'}$ is nearly equal to the energy difference between *cis*-**1** and *trans*-**1**.

$\Delta E_{3'} = 6.51$ kcal/mol; steric repulsion between *N*-Me and phenyl ring

$\Delta E_{4'} = 2.99$ kcal/mol; steric repulsion between *N*-Me and *C*-Me

The *N*-methylation of acetanilide causes steric hindrance ($\Delta E_{3'}$) to the phenyl group. This hindrance is not compensated by the π-conjugation ($\Delta E_{1'}$), ($|\Delta E_{3'}| > |\Delta E_{1'}|$) and forces the phenyl ring to rotate to the *trans* twisted conformation. In this *trans* conformation, there are two repulsions: the steric ($\Delta E_{4'}$) and the electronic ($\Delta E_{2'}$). Mainly owing to this steric repulsion ($\Delta E_{4'} >> \Delta E_{2'}$), the *cis* conformer is the most stable one.

The reason why the *cis*-amide preference is more distinct in *N*-methylanilide derivatives than in ordinary *N*-methylamides can be explained as follows. Generally, the phenyl group is thought to be a very bulky group that offers severe steric hindrance to neighboring groups. But, due to its anisotropic bulkiness, the phenyl ring can be less bulky than a methyl group when it lies at right angles to the amide plane. So, the steric hindrance brought about by *N*-methylation causes the rotation of the phenyl ring to the perpendicular position at the cost of loss of conjugation between the phenyl ring and the amide group. Consequently, *N*-methylation controls the amide conformation through favoring the rotation of the *N*-phenyl plane in anilides. On the other hand, in ordinary amides such as peptides, which have substituent groups with one or two hydrogen atoms on the neighboring carbon at the amino end, *N*-methylation does not introduce enough steric hindrance to affect the amide conformation, but essentially only diminishes the energetic difference between *trans*- and *cis*-amide conformation. The *trans*-amide structure is still a little more favorable than the *cis*-amide one in general.

Further investigation on the characteristic behavior of *N*-methylanilides, particularly on the height of the energy barrier of *trans*−*cis* interconversion, is in progress. Further examination of *cis*-amide preference in related systems will also be conducted, both theoretically and crystallographically.

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