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# Theory Supplemented by Experiment. Electronic Effects on the Rotational Stability of the Amide Group in *p*-Substituted Acetanilides

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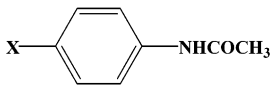
The electronic effect of polar substituents on the barrier of internal rotation around the amide carbon−nitrogen bond in a series of 10 *p*-substituted acetanilides is studied by applying density functional theory at the B3LYP/6-31G(d,p) level. The theoretical results are supplemented by experimental data on the amide C═O and N−H stretching mode frequency shifts. It is shown that computations at the theoretical level employed provide a valuable approach in studying the factors determining the conformational stability of the studied series of compounds. It is found that an excellent linear dependence between the barriers of rotation and frequency shifts exists. It is concluded that the variations of the amide C═O stretching mode frequency can be used for quantitative characterization of the amide group conformational flexibility in the studied series of acetanilides.

## Introduction

The aim of the present study is to analyze the electronic effects of polar substituents transferred through an aromatic ring on the barrier of internal rotation around the amide C−N bond in a series of acetanilides. There is a continuing interest in the conformational stability of the CO−NH grouping in different molecular environments. The interest is determined by the central role of the amide group for the conformational properties of proteins and polypeptides as well as of a great number of low molecular weight organic compounds. Recent developments in chemistry research underline an increasing role of computational chemistry methods in the study of molecular structure and mechanisms of chemical reactions. The ever-increasing accuracy of computational results offers entirely new opportunities for assessing the role of various intramolecular factors on the reactivity and conformational stability of functional groups. These avenues were employed in the present study to analyze the effect of polar substituents on the rotational stability of the amide group in a series of 10 *p*-substituted acetanilides (Scheme 1).

A considerable proportion of experimental and theoretical studies on the structure and energetics of rotation of secondary amides have been focused on the molecule of *N*-methylacetamide. It represents the simplest model molecule for studies on the properties of isolated peptide linkage. In many of these works the cis/trans equilibrium referring to the orientation of the C═O and N−H groups with respect to the amide C−N bond is treated.[1−6] Many studies deal with hydrogen bonding[7−12] and vibrational properties[8−10,13] of the molecule. In a recent study, Kang[6] reinvestigated the rotational isomerism of *N*-methylacetamide by applying ab initio MO and density functional theory (DFT) at HF, MP2, and B3LYP levels with a number of different quality basis sets. The author found that the B3LYP/6-31G(d,p) level of theory provides results in very good correspondence with experiment for geometry parameters, dipole moment, and population of conformers.

**SCHEME 1**




X = H, $CH_3$, OH, $OCH_3$, $OC_2H_5$, $NH_2$, Cl, COOH, $NO_2$, $SO_2NH_2$

Saito et al.[14] in a comparative theoretical study analyzed the differences in structure and conformational stability of *N*-methylacetamide, acetanilide, and *N*-methylacetanilide by applying ab initio MO methods at the HF level with 4-31G, 4-31G(d), 6-31G, and 6-31G(d,p)

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basis sets. The results indicate that the preferred conformation in *N*-methylacetamide and acetanilide is trans, while in *N*-methylacetanilide the cis form is thermodynamically favored. The *trans*-amide structure has been found to be more stable than the *cis*-amide form by 2.2 kcal/mol at the HF/6-31G(d,p) level of computation. The influence of *o*-methyl substituents in the aromatic ring on the rotational isomerism of derivatives of formanilide and acetanilide has also been studied by ab initio MO computations and IR spectroscopy.[15] The crystal structure of acetanilide has been reported.[16] The theoretical results obtained[14,15] are in accordance with the experimental data showing that the *trans*-amide form is found in crystal[16] and in solution.[15]

In a recent review, Wiberg[17] analyzed the changes in electron distribution on the rotational barriers in amides, thioamides, and carboxylic acids and showed that these distributions can provide clues to the origin of barriers.

In the present study, density functional theory computations were applied in determining rotational barriers, fully optimized geometries, and vibrational frequencies of the series of *p*-substituted acetanilides. The theoretical data obtained were supplemented with experimental measurements of the frequencies of the C═O and N−H stretching modes for the CO−NH group in the IR spectra of the compounds. Literature data reveal that N−H stretching frequency can be successfully used in characterizing the cis/trans conformational isomerism in secondary amides.[18] On the other hand, the carbonyl stretching mode frequency is, very possibly, the most sensitive experimental probe for assessing the effect of substituents on the electronic structure of the amide group.

## Computations and Experiments

The *p*-substituted acetanilides were synthesized by known methods via amidation of acetic acid or acetic anhydride with the respective *p*-substituted anilines.[19] The IR spectra of the compounds were obtained in chloroform solution. The NH and CO stretching mode frequencies were measured with an accuracy of $\pm 1$ cm$^{-1}$.

Becke-style three-parameter density functional theory with the Lee−Yang−Parr correlation functional (B3LYP)[20,21] and the 6-31G(d,p)[22] basis set was applied to determine the energies of stable rotameric forms and barrier heights for transition states between cis and trans conformers of the studied compounds. Full geometry optimization was carried out for the cis and trans rotameric forms. Transition states for rotation around the amide C−N bond were fully optimized at the B3LYP/6-31G(d,p) level by traditional transition state optimization using Berny's algorithm,[23] and all structures were further characterized by analytic computations of harmonic frequencies at the same level/basis set. All computations were carried out with the Gaussian 98 program package.[24]

## Results and Discussion

**Rotational Barriers.** The cis/trans isomerism in amides is linked to the hindered rotation around the central C−N bond (Figure 1). The strong resonance between the nitrogen lone pair and the carbonyl bond determines the partially double-bond character of the C−N bond and the stabilization of the two rotameric forms. Spectroscopically, the cis and trans conformations are easily detected by inspecting the position of the N−H stretching mode frequency in the IR spectra. The more stable trans conformer has an N−H stretching band situated at a frequency about 20−30 cm$^{-1}$ higher than that of the cis form.[15,25]

The degree of resonance interaction between the N−H and C═O groups determines the hindered rotation around the carbon−nitrogen bond and influences the conformational stability of the compounds. Therefore, polar substituents linked through a conjugated system to the amide grouping are expected to influence the conformational isomerism of amides. The *p*-substituted acetanilides, the subject of the present study, represent a suitable model system for studying the role of electronic effects on the properties of the amide group. The substituents in the para position in the aromatic ring are quite distant from the acetamido grouping and, therefore, other interferences such as steric interactions or direct field effects are not expected to have any significant role.

As already discussed, extensive experimental and theoretical studies of amides and ureas reveal that the trans form of the amide group is usually the thermodynamically more stable form.[1−6,15,18] The present DFT theoretical results confirm these findings. The estimated energy difference between the trans and cis forms in the series of acetanilides studied is between 2.62 and 4.15 kcal/mol with lower energy for the trans conformer in all cases. This energy difference corresponds to a ratio of 99.2−97.6% trans and 0.8−2.4% cis form at ambient temperature.

The main focus of the present study was to analyze the factors determining the barriers of rotation around the amide carbon−nitrogen bond and, especially, the effect of polar substituents in the para position in the aromatic ring of acetanilides. The available methods of contemporary computational quantum chemistry allow

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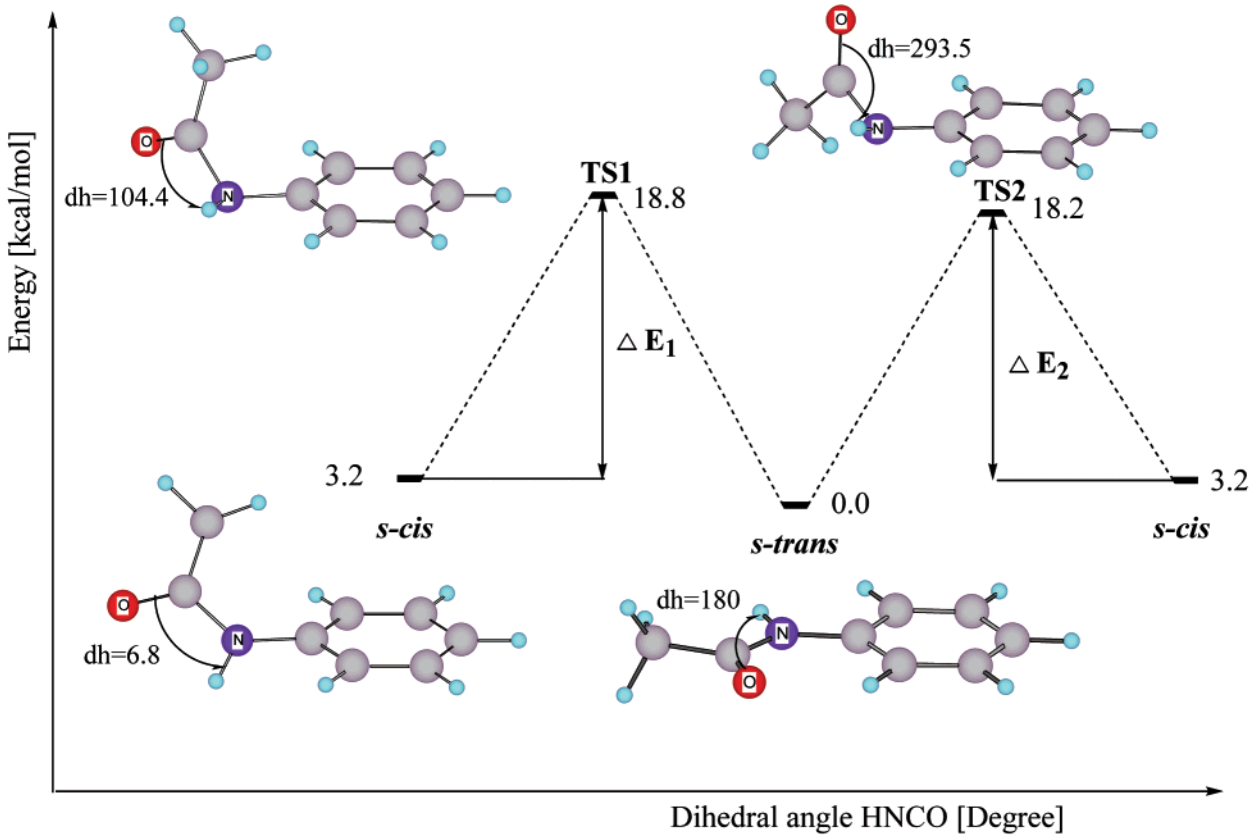


**FIGURE 1.** Energy diagram for the rotation around the C−N bond in acetanilide.

**TABLE 1. Energy Barriers for Rotation around the C−N Bond in *p*-Substituted Acetanilides from B3LYP/6-31G(d,p) Calculations**

| *p*-substituent | $E_{TS1}^{rel}$ [a] [kcal/mol] | $E_{TS2}^{rel}$ [a] [kcal/mol] | $\Delta E_1 = E_{TS1} - E_{cis}$ [b] [kcal/mol] | $\Delta E_2 = E_{TS2} - E_{cis}$ [b] [kcal/mol] | Hammett constants[c] |
|---|---|---|---|---|---|
| −H | 18.8 | 18.2 | 15.5 | 15.0 | 0 |
| $-CH_3$ | 18.9 | 18.4 | 15.8 | 15.3 | −0.170 |
| $-OCH_3$ | 19.3 | 18.8 | 16.5 | 16.1 | −0.268 |
| $-OCH_2CH_3$ | 19.4 | 19.1 | 16.4 | 16.1 | −0.240 |
| −Cl | 18.9 | 18.3 | 15.2 | 14.6 | 0.227 |
| −COOH | 18.0 | 17.3 | 14.4 | 13.8 | 0.450 |
| −OH | 19.3 | 18.8 | 16.5 | 16.0 | −0.370 |
| $-NH_2$ | 19.6 | 19.2 | 17.0 | 16.5 | −0.660 |
| $-NO_2$ | 17.8 | 17.1 | 13.7 | 12.9 | 0.778 |
| $-SO_2NH_2$ | 18.3 | 17.5 | 14.4 | 13.6 | 0.620 |

[a] $E_{TS1}^{rel}$ and $E_{TS2}^{rel}$ are the energies of the first and second transition state, respectively, relative to the energy of the trans conformer. [b] $\Delta E_1$ and $\Delta E_2$ are the energy barriers for the cis → trans rotations through TS1 and TS2 transition states, respectively (see Figure 1). [c] From ref 27.

reliable theoretical estimates of the relative energies of the conformers[26] as well as of the transition states linked to conformational changes to be obtained.

The overall energy profile of the conformational transitions between cis and trans forms in the studied series of acetanilides is illustrated in Figure 1, where the theoretical estimates for the respective quantities in the case of acetanilide are presented. Two different transition states are obtained because of the asymmetry of rotation around the C−N bond (Figure 1). In the subsequent discussion, we will present results only for the lower barrier transition. Further asymmetry is introduced when considering the possible different conformations of some substituents. These effects are, however, very small, and the results presented refer to the lowest energy species for the cis and trans forms.

When the effect of substituents on the properties of a reference functional group is discussed, in our case, the secondary amide grouping, it is of interest to first examine possible correlations with the Hammett sigma constant.[27] The variations in the barriers of rotation induced by the substituents are shown in Table 1. The values refer to the transition from cis to trans conformers of the acetanilides studied, in particular, the difference in energy between the transition state 2 (TS2) and the cis form (Figure 1). The thermodynamically most probable pathway from cis to trans conformation is through

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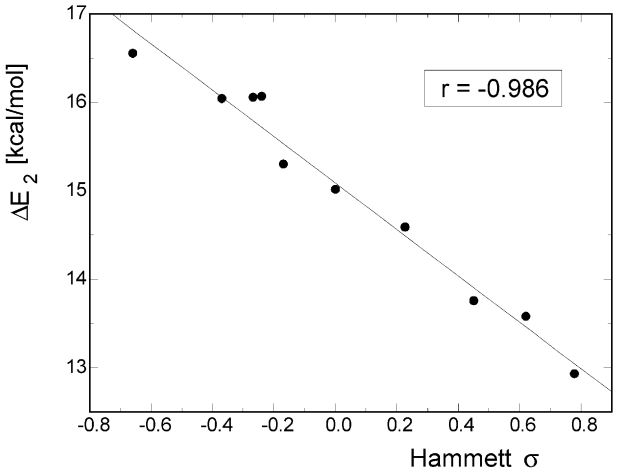



**FIGURE 2.** Dependence between the B3LYP/6-31G(d,p) computed rotational energy barrier $\Delta E_2 = E_{TS2} - E_{cis}$ and Hammett sigma constants ($\sigma$) for *p*-substituted acetanilides.

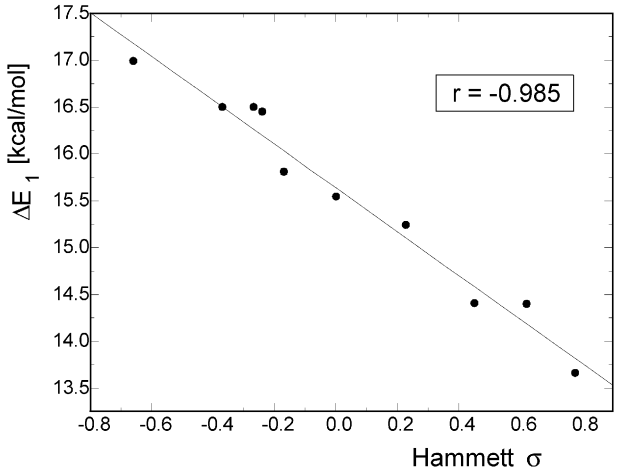



**FIGURE 3.** Dependence between the B3LYP/6-31G(d,p) computed rotational energy barrier $\Delta E_1 = E_{TS1} - E_{cis}$ and Hammett sigma constants ($\sigma$) for *p*-substituted acetanilides.

the lower energy transition state TS2. The linear regression analysis shows quite good linear dependences between $\Delta E_{TS2/cis}$ and the standard Hammett sigma constants (number of compounds $n = 10$, correlation coefficient $r = 0.986$). The dependence is illustrated in Figure 2. Similarly, good linear correlation is also found for the dependence between $\Delta E_{TS1/cis}$ and the $\sigma$-constants (Figure 3).

The relations found indicate that the barriers of rotation around the amide C−N bond are governed by the general substituent effects that influence chemical reactivity and other properties. The data obtained underline once again the usefulness of the Hammett constants in the description of properties of organic molecules.

**Molecular Geometry.** Full geometry optimization of the cis and trans conformers of the studied acetanilides was carried out. Geometry details are provided in Supporting Information. The bond lengths of the amide C−N, C═O, and N−H bonds change as expected. The most significant difference between the cis and trans conformers is in the dihedral angle between the aromatic ring

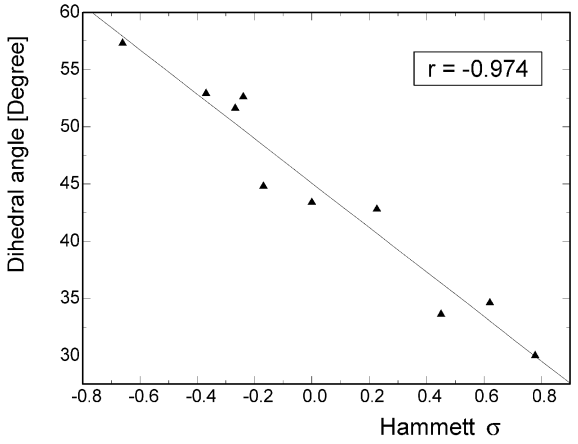


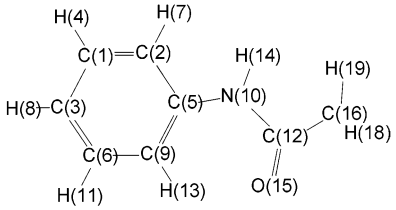

**FIGURE 4.** Relationship between Hammett sigma constants of *p*-substituents and dihedral angle between the aromatic ring and the amide −NH−CO− grouping in *p*-substituted acetanilides.

and the amide C−N bond (CCNC dihedral angle). In the trans conformers of all studied acetanilides, the amide group is essentially in the plane of the aromatic ring. The respective dihedral angle is close to 180°. In the cis conformers, the dihedral angle varies from 30.01 to 57.28°. The deviation from planarity is due, most probably, to steric hindrance between the methyl group of the NH−CO−$CH_3$ moiety and the hydrogen at the ortho position in the aromatic ring. Surprisingly, there is substantial variation in the values of the CCNC dihedral angle in the *p*-substituted acetanilides studied. The effect cannot be attributed to local steric interactions because the substituents are quite distant from the NH−CO−$CH_3$ moiety. Moreover, a very good linear dependence was found between the Hammett sigma constants of the substituents and the value of the CCNC dihedral angle in cis acetanilides. The relationship is illustrated in Figure 4. It should be accepted that the resonance interaction between the substituents and the amide grouping affects quite directly the magnitude of the dihedral angle between the aromatic ring and the amide grouping. The electron-withdrawing substituents increase the double-bond character of the $N-C^{aromatic}$ bond, thus hampering the rotation around the bond. The balance between these resonance effects and the steric hindrance between the methyl group of the $NHCOCH_3$ fragment and the *o*-hydrogen atom in the aromatic ring of cis conformers determines the final value of the CCNC dihedral angle.

The theoretical geometry data for acetanilide compare very well with experimental crystal structure data[16] as can be seen from Table 2. The only notable difference between theoretical geometry and experiment is for the CCNH dihedral angle. In the crystal structure, the amide group deviates by an angle of 17.6° from the plane of the aromatic ring.

**Vibrational Frequencies.** We have extended our study with a search for possible dependences of the energy barriers between the different rotameric forms of the acetanilides and physical quantities that also depend on the rearrangements in the electronic structure of the CO−NH grouping. A most suitable quantity that is expected to reflect well the electronic effects of substit-

**TABLE 2. B3LYP/6-31G(d,p)-Optimized and Experimental Geometry of Acetanilide**




| | trans | | cis |
|---|---|---|---|
| | calcd | experimental[a] | calcd |
| | Bond Lengths[b] | | |
| $C_5N_{10}$ | 1.412 | 1.413 | 1.413 |
| $N_{10}H_{14}$ | 1.009 | 1.080 | 1.013 |
| $N_{10}C_{12}$ | 1.378 | 1.354 | 1.386 |
| $C_{12}O_{15}$ | 1.222 | 1.219 | 1.223 |
| $C_{12}C_{16}$ | 1.523 | 1.495 | 1.517 |
| | Bond Angles[b] | | |
| $C_5N_{10}C_{12}$ | 129.1 | 127.6 | 131.9 |
| $C_{12}N_{10}H_{14}$ | 116.1 | 117.0 | 111.1 |
| $C_5N_{10}H_{14}$ | 114.8 | 115.0 | 116.5 |
| $N_{10}C_{12}O_{15}$ | 124.3 | 123.1 | 119.3 |
| $N_{10}C_{12}C_{16}$ | 114.4 | 115.4 | 118.8 |
| $O_{15}C_{12}C_{16}$ | 121.3 | 121.3 | 121.9 |
| | Dihedral Angles[b] | | |
| $C_2C_5N_{10}H_{14}$ | 0.0 | 0.0 | 43.4 |
| $C_5N_{10}C_{12}C_{16}$ | 180.0 | 176.6 | 0.9 |

[a] From ref 16. [b] Bond lengths in Å, angles in degrees.

**TABLE 3. Experimental and Calculated N−H and C═O Stretching Frequencies for *p*-Substituted Acetanilides**

| | experimental[a] | | calcd[b] | | | |
|---|---|---|---|---|---|---|
| | | | trans | | cis | |
| *p*-substituent | $\nu_{N-H}$ | $\nu_{C=O}$ | $\nu_{N-H}$ | $\nu_{C=O}$ | $\nu_{N-H}$ | $\nu_{C=O}$ |
| −H | 3432.5 | 1685.5 | 3635.5 | 1788.4 | 3595.9 | 1789.4 |
| $-CH_3$ | 3433.0 | 1681.5 | 3636.1 | 1786.4 | 3595.9 | 1788.8 |
| $-OCH_3$ | 3436.5 | 1678.0 | 3637.0 | 1783.6 | 3595.0 | 1788.7 |
| $-OCH_2CH_3$ | 3434.5 | 1678.0 | 3637.2 | 1782.0 | 3594.9 | 1788.6 |
| −Cl | 3433.0 | 1689.0 | 3637.3 | 1789.7 | 3595.6 | 1793.1 |
| −COOH | 3426.5 | 1702.0 | 3629.1 | 1797.3 | 3592.2 | 1793.7 |
| −OH | 3435.0 | 1683.5 | 3638.5 | 1783.4 | 3595.8 | 1789.4 |
| $-NH_2$ | 3435.0 | 1677.0 | 3638.3 | 1779.9 | 3593.5 | 1788.0 |
| $-NO_2$ | 3426.5 | 1707.5 | 3627.5 | 1801.5 | 3589.7 | 1798.7 |
| $-SO_2NH_2$[c] | | | 3630.2 | 1797.5 | 3592.3 | 1795.6 |

[a] Experimental frequencies ($cm^{-1}$) are measured in $CHCl_3$ solution. [b] Calculated frequencies ($cm^{-1}$) from B3LYP/6-31G(d,p) computations. [c] Experimental frequencies for *p*-sulfonamidoacetanilide have not been obtained because of the very low solubility of the compound in $CHCl_3$.

uents transferred through the aromatic ring are the characteristic stretching mode frequencies of the amide CO and NH bonds. The theoretically estimated positions of the C═O and N−H stretching mode vibrations for the two rotameric forms are presented in Table 3. It is clearly seen that the N−H stretching frequency of the trans conformers is 30−50 $cm^{-1}$ higher than that of the cis forms, in accordance with literature assignments.[15,25]

As mentioned, the theoretically determined energy differences between the cis and trans conformations suggest that at ambient temperature, the trans conformers strongly predominate. Thus, our attention was focused mostly on the variations of CO and NH stretching frequencies for the trans rotameric form. Following the focus of the present, study it was of interest to analyze

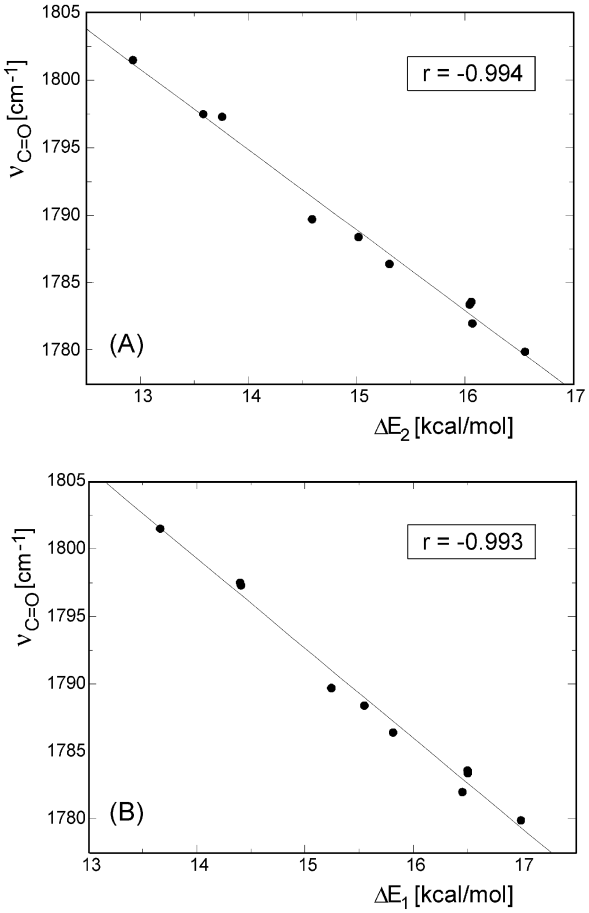



**FIGURE 5.** Relation between the B3LYP/6-31G(d,p) computed C═O stretching frequencies in trans *p*-substituted acetanilides and (A) the rotational energy barrier $\Delta E_2 = E_{TS2} - E_{cis}$ and (B) the rotational energy barrier $\Delta E_1 = E_{TS1} - E_{cis}$.

the interdependence in the variation of CO and NH characteristic vibrational frequencies and the barriers of rotation. Excellent linear relation between the theoretically estimated C═O stretching frequencies and energy barriers was found with a correlation coefficient $r = 0.994$ ($n = 10$). The dependence is illustrated in Figure 5. In many ways, the linear link between $\nu_{C=O}$ and $\Delta E_{rotation}$ is expected since both quantities depend on the changes in the electronic structure of the amide group induced by the substituents. What is surprising is the perfectness of the linear relationship found. It illustrates the great strength of computational chemistry methods in describing in a quantitative way the intramolecular phenomena in chemical systems. The conclusion that comes out of these results is that the variation of the C═O stretching mode frequency can be used to quantitatively characterize the rotational flexibility of the studied acetanilides.

The relationship between the cis/trans energy barrier and N−H stretching mode frequency is not so good. The electronic structure of the N−H bond is less influenced by the predominantly resonance mechanism of transmission of the effect of aromatic substituents on the amide grouping. Nevertheless, the dependence between $\nu_{N-H}$ and $\Delta E_{rotation}$ has a linear regression coefficient $r = 0.927$, $n = 10$. The established excellent linear correlation between the theoretically estimated C═O stretching frequencies and the energy barriers of rotation around

the amide carbon−nitrogen bond is quite significant. Such dependence offers opportunities to determine trends of changes of conformer ratios of substituted amides from easily accessible experimental observables such as the carbonyl characteristic frequency.

**Supporting Experiment.** To support our theoretical findings, we synthesized the chosen model series of *p*-substituted acetanilides and determined the CO and NH stretching mode frequencies from the IR spectra in dilute chloroform solutions. The experiments carried out offer a chance to validate the correctness of the purely theoretical conclusions. The spectroscopic data obtained are presented in Table 3. The IR spectra of all compounds studied exhibit just one amide N−H stretching band in the range 3426−3437 $cm^{-1}$. Its position corresponds to the trans rotameric form of the CO−NH moiety. The result is in full accordance with the theoretical predictions showing that the compounds studied should be in the trans conformation at ambient temperature. The predicted percentage of the cis form is from 0.8 to 2.6%. Such amounts are difficult to detect in experimental spectra. It was also of interest to assess the correctness of the theoretically predicted trend of changes of the C=O stretching frequency. The dependence between the theoretical and experimental quantities is presented in Figure 6 ($n = 9$, $r = 0.980$). It is evident that density functional theory at the B3LYP/6-31G(d,p) level is capable of accurately predicting the variations of the C=O characteristic frequency in the studied acetanilides. In view of these results, the relationships between theoretical energy barriers and vibrational parameters can be extended to the experimental frequencies as well.

## Conclusions

Density functional theory computations at the B3LYP/6-31G(d,p) level provide a valuable approach to studying the factors determining the conformational stability of

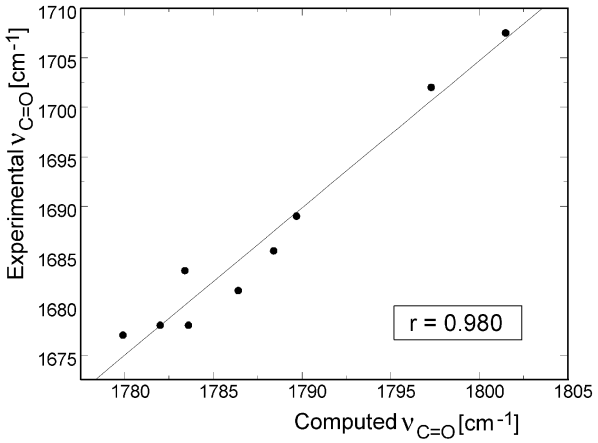



**FIGURE 6.** Relationship between experimental ($CHCl_3$) and B3LYP/6-31G(d,p) computed C=O stretching frequencies in trans *p*-substituted acetanilides.

*p*-substituted acetanilides. It is found that the variations in the barriers of rotation around the amide C−N bond can be rationalized in terms of the usual aromatic substituent constants and, more importantly, by the C=O stretching frequency shifts induced by the substituents. An excellent linear dependence between the barriers of rotation and frequencies exists. The variations of the amide C=O stretching mode frequency can be used for quantitative characterization of the amide group conformational flexibility in the studied series of acetanilides.

**Supporting Information Available:** Cartesian coordinates and energies in Hartree for B3LYP/6-31G(d,p) fully optimized geometries of cis and trans conformers and TS1 and TS2 transition states for *p*-substituted acetanilides. This material is available free of charge via the Internet at http://pubs.acs.org.

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