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On the Origin of Higher Rotational Barriers in Thioamides than in Amides. Remote Substituent Effects on the Conformational Stability of the Thioamide Group in Thioacetanilides

Boris Galabov,* Sonia Ilieva, Boriana Hadjieva, and Eli Dinchova

Department of Chemistry, University of Sofia, Sofia 1164, Bulgaria

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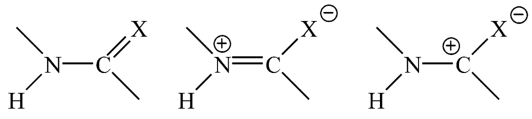
The variations of barrier heights for rotation around the amide C−N bond in para-substituted thioacetanilides was studied in a comparative context with data for a series of acetanilides by applying density functional theory at the B3LYP/6-31G(d,p) level. The shifts of the energy barriers induced by remote substituents in the para position of the aromatic ring are interpreted in terms of changes of the bond lengths and electric-charge parameters for the equilibrium configurations, as well as in terms of charge fluctuations that accompany the internal rotation. A satisfactory explanation for the distinctly greater shifts of rotational barriers in the thioacetanilide series upon substitution in the aromatic ring, as compared with data for the respective acetanilides, is obtained by analyzing the dependences of barriers heights on the charge shifts upon substitution in the aromatic ring and upon rotation. Several linear relationships are established linking the barrier heights with structural and electronic parameters that characterize the amide and thioamide groupings. A common linear equation quantifying the dependence of barrier heights on the shifts of natural bond orbital partial charges at the amide S and O atoms upon substitution in the aromatic ring in the two series is found. The relationship is confirmed by data from a Mulliken population analysis. The results obtained are consistent with the views for a classical amide resonance as being the origin of higher rotational barriers in thioamides than in amides.

1. Introduction

In a previous study,[1] we analyzed the electronic effects of remote substituents on the barrier of internal rotation around the amide C−N bond in a series of acetanilides by applying theoretical computations and experimental IR spectroscopy. The aim of the present work is to extend these studies to a series of *p*-substituted thioacetanilides and analyze the rotational stability of the thioamide group in a comparative context with the results for the respective oxygen analogues. Two relatively stable conformers can be found in amides and thioamides that are linked to the hindered rotation around the central C−N bond of the −CO−NH− and −CS−NH− groupings.[1−11] These are usually designated as cis and trans conformers. The relative stability of these forms has been usually attributed to the resonance interaction between the nitrogen lone pair and the carbonyl bond, although other intramolecular factors have been also considered. In the case of amides, experimental and theoretical results[1−8,10,11] have shown that the trans conformers are usually more stable. For many amides, this is the only form found by IR and NMR experiments at ambient temperature.[1,4,10,11] In the IR spectra, the clearest evidence for the existence of cis and trans conformers is offered by the position of the N−H stretching mode bands. The trans conformers have N−H stretching frequencies that are 20−30 cm^{-1} higher than those of the respective cis conformers.[4]

The origin of the rotational barrier in amides and thioamides has been the subject of a prolonged debate. Extensive and sometimes contradictive data about the nature of interactions between the atoms forming the −CO−NH− and −CS−NH− moieties have been produced from theoretical studies that considered several properties of selected model systems: the redistribution of atomic charges accompanying rotation,[7−9,12,13] changes of bond lengths,[12] variations of delocalization energies,[14] integrated Fermi correlations,[13] and changes in charge-density difference plots and in hybridization.[9] On the experimental side, NMR data on the ^{17}O, ^{13}C, and ^{15}N chemical shifts obtained by Yamada[15,16] in planar and twisted amides support the classical two-structure resonance model (Chart 1, structures 1 and 2). NMR data of Bennet et al.[17] are in accord with these data.

CHART 1



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Wiberg and Rablen,[8,12] by studying the variations in partial atomic charges, bond lengths, and charge-density difference plots, concluded that the classical model of amide resonance involving two structures (Chart 1, structures 1 and 2) does not describe satisfactorily the nature of the electronic interactions that determine the rotational barrier in amides and showed the necessity for inclusion of a third structure as well (Chart 1, structure 3). In the case of thioamides, however, the authors showed that a two-structure model (structures 1 and 2) is more adequate. The theoretical data[8,12] confirmed that the thioamides have larger rotational barriers than amides. The difference is determined mostly by larger charge transfer from nitrogen to

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* Author to whom correspondence should be addressed. E-mail: galabov@chem.uni-sofia.bg.

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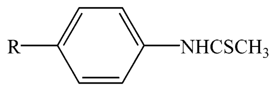
CHART 2



R = H, CH$_3$, OCH$_3$, OC$_2$H$_5$, Cl, COOH, OH, NH$_2$, NO$_2$

sulfur in thioamides than to oxygen in amides. Later studies of Laidig and Cameron[13] challenged the validity of the resonance model in formamide and thioformamide, on the basis of data obtained from Fermi resonance correlations and AIM population analysis.[18] Lauvergnat and Hiberty[14] performed model theoretical computations on formamide and thioformamide by examining the energies of delocalization of the nitrogen lone pair. Their results agree with the traditional view of strong resonance in both amide and thioamide groups. The authors concluded also that the rotational barriers are not solely due to conjugation but arise, in part, from the preferred spatial orientation of the nitrogen lone pair. They attributed the larger rotational barrier in thioformamide to a greater role of resonance effects, relative to formamide. The discussion also continued in recent years.[18] Glendening and Hrabal[18a] analyzed the origin of rotational barriers in formamide and its chalcogen replacement analogues by applying the Weinhold's natural bond orbital (NBO) population analysis method.[19] The results of these authors are consistent with the conventional resonance representation of the electronic interactions in all amide analogues. Wiberg and Rush[18g] analyzed the effect of solvents on the thioamide rotational barrier, using NMR experiments and theoretical G2 (MP2) computations. The authors provided also a summary of the principal experimental findings and theoretical results related to the origin of the rotational barrier in amides and thioamides.

The IR and NMR spectra of thioanilides have been the subject of several studies.[20−23] The conformational state of the thioamide group is one of the principal themes in these works. Suzuki et al.[20] determined the energy difference between the cis and trans conformers of thioformanilide and thioacetanilide from the temperature dependence of the intensities of the respective N−H stretching mode bands. The effect of remote aromatic substituents on the thioamide group has been examined by Waisser et al.[24] in the case of thiobenzamides via experimental determination of dissociation constants.

We hoped that the comparative study of *p*-substituted thioacetanilides and acetanilides may provide further evidence on the origin of rotational barriers in amides and thioamides, because the remote effect of polar substituents in the para position of the aromatic ring are expected to be exerted predominantly through resonance interactions, whereas the influence of the direct through space and steric effects will be low. The most interesting result from our previous study on acetanilides[1] was the established, almost-perfect linear dependence between the magnitude of the rotational barrier for the transition between the cis and trans conformers and the variation of the carbonyl stretching mode frequency. It was concluded that the C═O stretching frequency can be employed in characterizing the conformation stability of the amide group in the studied compounds quantitatively. A similar relationship for other type of amides has been discussed earlier by Eberhardt et al.[25] In the present study, we apply density functional theory (DFT) at the B3LYP/6-31G(d,p) level to determine the geometries, vibrational frequencies, and rotational barriers in a series of nine *p*-substituted thioacetanilides (Chart 2). The theoretical results are supplemented by experimental measurements of the IR spectra of several compounds from the series whose solution spectra in CHCl$_3$ could be obtained.

2. Computations and Experiments

Becke-style three-parameter DFT with the Lee−Yang−Parr correlation functional (B3LYP)[26,27] and 6-31G(d,p)[28] basis set was applied to determine the energies of the stable rotameric forms and barrier heights for the transition between cis and trans conformers of the studied compounds. Full geometry optimization was conducted for the cis and trans rotameric forms. The transition states associated with rotation around the amide C−N bond were fully optimized at the B3LYP/6-31G(d,p) level by traditional transition-state optimization, using the Berny's algorithm,[29] and all structures were further characterized by analytic computations of harmonic frequencies at the same level/basis set. (See Supporting Information.) For the parent molecule of thioacetanilide, computations employing several types of larger basis sets, including Dunning's cc-pvdz and cc-pvtz[30] sets, were performed to determine the correct results for the ratio of cis and trans conformers at ambient temperature. Population analysis employing NBO[19] and Mulliken partial atomic charges[31] was applied in interpreting the variations of rotational barriers. All computations were performed with the Gaussian 98 program package.[32]

The *p*-substituted thioacetanilides were prepared by treatment of the respective anilides with phosphorus pentasulfide in boiling solvents (pyridine, toluene).[33,34] The IR spectra of the compounds were obtained in chloroform solutions on a Perkin−Elmer model 983G spectrometer. The N−H stretching mode frequencies were measured with an accuracy of ±1 cm^{-1}.

3. Results and Discussion

3.1. Molecular Geometry. Full geometry optimization of the cis and trans rotameric forms of the studied series of nine *p*-substituted thioacetanilides was performed. The theoretical results for the structural parameters related to the −CS−NH− group are given in Table 1. The most important structural parameter that can be linked to the rotational barriers between the cis and trans conformers is the amide C−N bond length, $r_{\mathrm{C-N}}$. This parameter can be considered as a quantity characterizing the strength of the bond and could, therefore, be related to the barrier of rotation. For comparison, geometrical parameters for para-substituted acetanilides[1] are also given in Table 1. As can be seen, the bond length $r_{\mathrm{C-N}}$ in the thioacetanilides is distinctly shorter than that in the acetanilide series, which suggests a stronger bond that would involve higher barriers of rotation for the transition between the cis and trans structures.

The trans thioacetanilides have a planar structure of the main skeleton of the molecule, with the thioamide group lying in the plane of the aromatic ring. The deviations from planarity are $<3°$. The cis form, as in the case of acetanilides, is nonplanar. The dihedral angle between the −CS−NH− group and the aromatic ring is in the range of 33°−57°. Similar structural features are also found in the substituted acetanilides.

3.2. Rotational Barriers. The theoretically determined barriers of rotation around the amide C−N bond for the studied series of thioacetanilides, as obtained from DFT computations, are presented in Table 2. The results show a very small difference between the energies of the cis and trans forms in the range of 0.03−0.63 kcal/mol. The data indicate that both rotameric forms will be populated at ambient temperature. The theoretical results for the respective *p*-substituted acetanilides[1] showed that the trans form is distinctly more stable than the cis rotamer. Both theory and experiment revealed a dominant presence of the trans form at room temperature. The stability of cis and trans isomers of some thioacetanilides has been studied by IR and NMR spectroscopies.[21−24] The experimental

TABLE 1: Geometrical Parameters, Calculated at the B3LYP/6-31G Level of Theory, for the Series of Para-Substituted Thioacetanilides and Acetanilides**

	Thioacetanilides						Acetanilides[a]					
	trans			cis			trans			cis		
R	r_{C-N} amide (Å)	$r_{C=S}$ (Å)	∠CCNC[b] (degrees)	r_{C-N} amide (Å)	$r_{C=S}$ (Å)	∠CCNC[b] (degrees)	r_{C-N} amide (Å)	$r_{C=O}$ (Å)	∠CCNC[b] (degrees)	r_{C-N} amide (Å)	$r_{C=O}$ (Å)	∠CCNC[b] (degrees)
H	1.358	1.665	180.6	1.360	1.669	43.1	1.378	1.222	180.0	1.386	1.223	43.4
CH_3	1.357	1.666	178.7	1.359	1.669	44.0	1.377	1.223	180.3	1.385	1.223	44.8
OCH_3	1.355	1.669	180.6	1.357	1.670	49.7	1.375	1.224	180.6	1.382	1.223	51.6
OC_2H_5	1.355	1.669	180.0	1.357	1.670	50.2	1.375	1.224	180.0	1.382	1.223	52.6
Cl	1.360	1.664	180.0	1.362	1.667	42.7	1.380	1.222	180.0	1.388	1.222	42.8
COOH	1.364	1.661	180.7	1.365	1.666	35.1	1.384	1.220	179.5	1.391	1.221	33.6
OH	1.355	1.668	180.6	1.357	1.669	50.8	1.375	1.224	180.0	1.383	1.223	52.9
NH_2	1.354	1.670	182.8	1.356	1.671	52.8	1.374	1.224	178.9	1.380	1.224	57.3
NO_2	1.367	1.659	179.5	1.368	1.663	31.8	1.387	1.219	179.5	1.395	1.220	30.0
SO_2NH_2							1.384	1.220	180.0	1.392	1.221	34.6

[a] From ref 1. [b] Dihedral angle between the aromatic ring and the amide C−N bond.

TABLE 2: B3LYP/6-31G(d,p) Calculated Rotational Barriers in Para-Substituted Thioacetanilides and Acetanilides

	$\Delta E = E_{TS2} - E_{trans}$[a] (kcal/mol)	
para substituent	thioacetanilides	acetanilides
H	19.29	18.25
CH_3	19.70	18.42
OCH_3	20.66	18.85
OC_2H_5	20.67	19.06
Cl	19.08	18.26
COOH	17.74	17.31
OH	20.30	18.85
NH_2	21.05	19.17
NO_2	17.06	17.08
SO_2NH_2		17.49

[a] The rotational barriers are calculated as a difference between the energy of the TS2 transition state (E_{TS2}) and the energy of the trans conformer (E_{trans}).

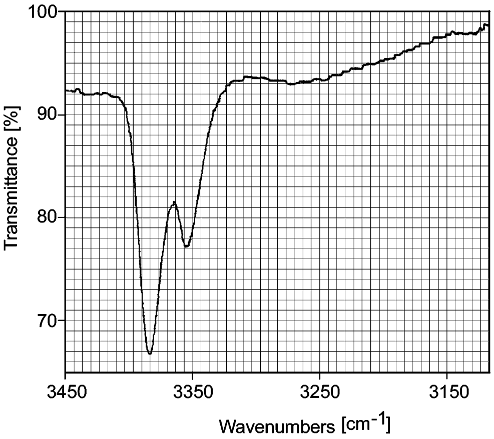


Figure 1. IR spectrum of thioacetanilide in $CHCl_3$ solution.

data clearly show that both rotameric forms are found. The IR spectroscopic data obtained in the present work are in accordance with these results. The IR spectrum of the parent compound of thioacetanilide in the N−H stretching mode region is shown in Figure 1.

For this compound, a higher-intensity trans N−H band is observed at 3383 cm^{-1} and a lower-intensity cis N−H band is observed at 3355 cm^{-1}. Assuming similar absorption coefficients for the N−H bands in the two forms, it can be concluded that the trans conformer has a higher population and is, therefore, the more stable form. The calculated energies at the B3LYP/6-31G(d,p) level of theory for the two conformers of the studied thioacetanilides indicate that the trans rotameric form is more stable in the case of the *p*-nitro, *p*-carboxy, and *p*-chloro derivatives. In all other cases, the cis form seems to be the thermodynamically favored form. There is, therefore, an apparent disaccord between experiment and theory for some of the molecules studied. To elucidate the cause of the observed discrepancy, we performed further computations of the relative energies of the two conformers in the case of thioacetanilide by applying DFT computations that employed larger basis sets in the evaluation of the hybrid functional. The results are presented in Table 3.

TABLE 3: Calculated Energies of Cis and Trans Conformers of Thioacetanilide Obtained at the B3LYP Level with Different Basis Sets

basis set	E_{trans} (hartree)	E_{cis} (hartree)	$\Delta E = E_{cis} - E_{trans}$ (kcal/mol)
6-31G**	−763.231244	−763.231678	−0.27
6-311G**	−763.335811	−763.336410	−0.36
6-311+G**	−763.340683	−763.340940	−0.16
6-311++G**	−763.340887	−763.341143	−0.16
cc-pvdz	−763.256177	−763.255976	0.13
aug-cc-pvdz	−763.280351	−763.280372	−0.01
cc-pvtz	−763.3812454	−763.381139	0.07
experiment[a]			0.225 ± 0.02

[a] From ref 20; CCl_4 solution.

It is seen that increasing the size of the basis set leads to a decreased energy separation between the cis and trans forms. At the B3LYP/cc-pvdz and B3LYP/cc-pvtz levels of theory, the trans conformer is the thermodynamically more stable form, in accord with the experimental findings. Deficiencies of lower levels of electronic structure theory in correctly predicting small energy differences between conformers was the subject of a recent study that involved 3-fluoropropane.[35] It was shown that highly correlated wave functions and large basis sets are needed to arrive at the correct relative energies.

As already underlined, the principal aims of the present work were to study the factors determining the rotational barriers for the transition between the cis and trans forms in the studied series of *p*-substituted thioacetanilides, as well as the origin of differences in conformational stabilities of the thioamide and amide groupings in thioanilides and anilides. Two transition states are found for the conversion between the two rotameric forms, reflecting two possible orientations of the nitrogen lone pair, with respect to the C═S bond. These are illustrated in Figure 2 in the case of *p*-chloro-thioacetanilide. In Table 2, the theoretically estimated energy barriers for the transition from cis to trans conformations are given. The conformational change between the two forms is more likely to occur via the lower-

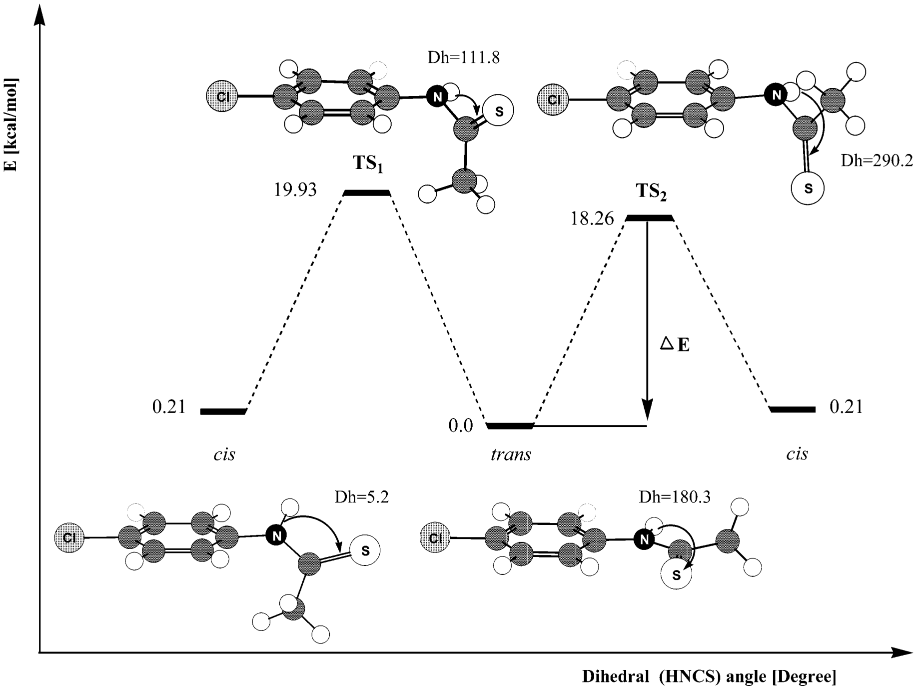


Figure 2. Energy diagram for the rotation around the C−N bond in *p*-chlorothioacetanilide, as calculated at the B3LYP/6-31G** level of theory.

energy TS2 state. Throughout the further discussion, we use the difference between the energy of the TS2 transition state and the energy of the more stable trans rotamer as the barrier height for these systems. It is simply denoted by ΔE:

$$\Delta E = E_{\mathrm{TS2}} - E_{\mathrm{trans}} \qquad (1)$$

In the last column of Table 2, the rotational barriers that were calculated in our previous study[1] for a series of *p*-substituted acetanilides are given.

The comparison of ΔE values between the two series of compounds reveals two important characteristics: (i) the rotational barriers in the thioacetanilides are higher than those in the respective acetanilides, and (ii) the influence of the remote substituents in the aromatic ring over the rotational barriers is almost twice as high in the thioanilides. A satisfactory theoretical explanation of both of these findings is needed to characterize the origin of the differences in conformational stability of the amide and thioamide groupings in these systems. As we have seen, earlier computational studies[8,9,12,14,18a] discussed electronic interactions within the $-$CX$-$NH$-$ (X $=$ O, S) group as being the major factor that determines the larger rotational barrier in thioamides than in amides. Suzuki et al.[20] and Walter[23] considered the possibility that the higher rotational barrier in thioanilides, compared with that of the respective anilides, might be due to a steric hindrance between the bulkier S atom and the H atom in the ortho position in the aromatic ring. If this hypothesis is accepted, we should expect that this type of steric effect would be strongest in the case of the trans planar conformations of both thioacetanilides and acetanilides. However, as Table 1 shows, the theory predicts almost perfectly planar structure for the trans conformers for all compounds of the two series. The result indicates that there are no significant steric hindrance effects tha result from the size of the S atom in the thioacetanilide series. For the cis conformers, the equilibrium structure is nonplanar, evidently because of the steric interaction between the methyl group and the ortho H atom. The latter will be similar for both series of anilides. Therefore, in analyzing the origin of the differences in barrier heights in the studied amides and thioamides, it is necessary to concentrate on the electronic structure of the compounds at equilibrium and also on its dynamics with the internal rotation around the C−N bond. The selected series of thioacetanilides is suitable in analyzing the intramolecular electronic interactions, because the substituents are quite distant from the $-$CX$-$NH$-$ grouping and are expected to exert their influence mostly through conjugation. Thus, the possible influence of close-range effects is eliminated. A suitable basis for comparison between the thio and oxy analogues are the results from our previous study on *p*-substituted acetanilides.[1]

Table 2 reveals that, in the case of strong electron-donating substituents (OCH_3, NH_2), the differences in barrier heights between the respective thioanilides and anilides is increased. In the case of strong electron-withdrawing substituents (COOH, NO_2), the difference diminishes. For the para nitro compounds of both series, the barrier heights are practically equal. An explanation of these findings can be made in terms of resonance interactions in the systems. The electron-donating substituents facilitate the resonance between the nitrogen lone pair and the carbonyl oxygen, resulting in an increased barrier of rotation. Inversely, the COOH and NO_2 substituents hamper the amide resonance by attracting the nitrogen lone pair in strong conjugation across the aromatic ring. These results support the classical views on the amide resonance involving structures 1 and 2 in Chart 1.

The variations in barrier heights in the studied series of anilides is analyzed in the subsequent sections in terms of changes of the bond lengths and the electric-charge parameters for the equilibrium structures, as well as in terms of charge fluctuations that accompany the internal rotation.

3.2.1. Consideration of Bond-Length Variations. The trends of variation in the theoretically evaluated barriers of rotation in the studied thioacetanilides can be rationalized in terms of changes of the intrinsic structural and electronic parameters of the thioamide grouping. It is natural to expect that the barrier for the transition from the more-stable trans conformers to the cis structures will be dependent on the strength of the C−N bond. A reasonable estimate of the variations of the C−N bond

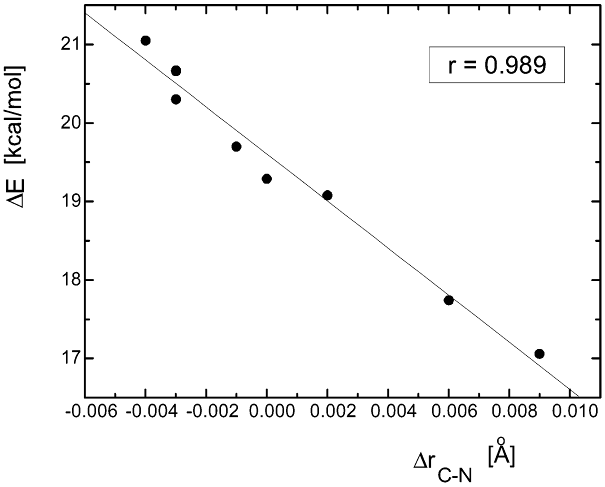


Figure 3. Dependence of rotational barriers (ΔE) on the change in the amide C−N bond length (Δr_{C-N}) upon substitution in the aromatic ring for the trans conformers of thioacetanilides.

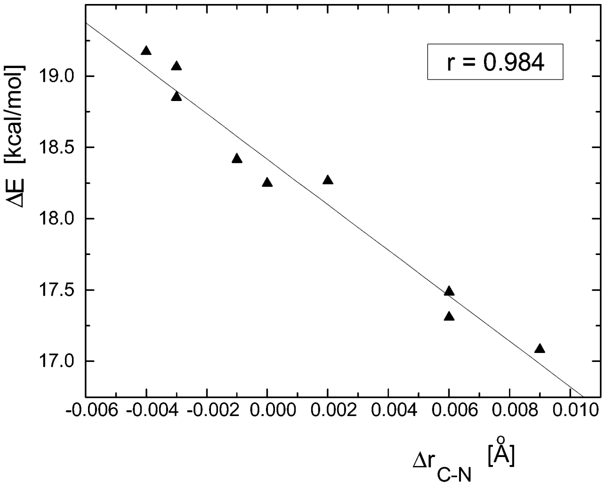


Figure 4. Dependence of rotational barriers (ΔE) on the change in the amide C−N bond length (Δr_{C-N}) upon substitution in the aromatic ring for trans conformers of acetanilides.

strengths in the more-stable trans forms of the compounds is offered by the changes of the amide C−N bond length (Table 1). The plot between the energy barriers ΔE against the change in the C−N bond length (Δr_{C-N}) upon substitution in the aromatic ring is shown in Figure 3. A good linear relationship is observed. The analogous dependence for acetanilides is shown in Figure 4.

It is important to note that the maximal variations in C−N bond lengths induced by the para substitients are identical for the two series of compounds. The range of variation of r_{C-N} in both series of anilides is 0.013 Å (Table 1). The result is somewhat unexpected, because we have seen (Table 2) that the same substituent induces distinctly greater change in the rotational barrier, in the case of the thio analogues. It can be concluded that the variations of the C−N bond lengths do not provide a sufficiently sensitive basis for rationalizing the differences in rotational barriers that are induced by the substituents in the two series of compounds.

3.2.2. Effects of Charge Shifts upon Substitution in the Aromatic Ring. The variation of barrier heights can also be linked to the charge rearrangements in the −CX−NH− (X = S, O) moiety. We will first concentrate on the shifts of partial charges on the heavy atoms of the amide group that are induced by the para substituents. The shifts of NBO charges for the trans conformers of thioacetanilides and acetanilides are presented in Table 4. Table 5 contains the respective shifts of the Mulliken charges.

As can be seen, both NBO and Mulliken methods reveal substantial charge fluctuations at the thiocarbonyl S atom and the carbonyl O atom upon substitution in the aromatic ring. The dependences between rotational barriers, ΔE, and the NBO charge shifts at the S and O atoms induced by the aromatic substituent R, Δq_X(R), are illustrated in Figures 5 and 6. The Δq_X(R) values refer to the equilibrium structure of the trans conformers. Similar linear relationships are obtained from an analysis that is based on Mulliken atomic charges. The respective correlation coefficients are $r = 0.994$ for thioacetanilides and $r = 0.991$ for acetanilides. The dependences shown in Figures 5 and 6 indicate that the variations in barrier heights for the two series of molecules can be linked to the fluctuations of the atomic charges in the amide grouping. These charge shifts are most logically explained in terms of a typical resonance interaction between the para substituents and the amide group. The effect is much stronger in the thioanilides. Tables 4 and 5 show that the same substituents induce much greater charge shifts in the thioacetanilide series than in the respective acetanilides.

It was of interest to plot the charge shifts at the carbonyl S and O atoms against ΔE for the two series of compounds simultaneously. To avoid the segments, the differences in rotational barriers between a given compound and the parent unsubstituted molecule in both series, $\Delta\Delta E$, were considered. The following relationship between $\Delta\Delta E$ and the shifts of NBO charges, Δq_X, was obtained:

$$\Delta\Delta E = -56.58\Delta q_X + 0.14 \qquad (\text{for } n = 19,\ r = 0.984) \quad (1)$$

The relationship is confirmed by analyzing the data from the Mulliken population analysis. The respective dependence, on the basis of Mulliken charges, has a correlation coefficient $r =$ 0.986. The dependence between the $\Delta\Delta E$ values and Δq_X(NBO) is illustrated in Figure 7. Equation 1 explains the differences in rotational barriers in acetanilides and thioacetanilides quite well. Greater electronic interactions in the thioamides lead to a stronger C−N bond and a higher rotational barrier. The electronic effect of para aromatic substituents is exerted primarily through resonance. Therefore, it may be concluded that eq 1 supports the usual amide resonance as being the determining factor for the difference in rotational barriers in the studied amides and thioamides. Equation 1 also quantitatively describes the variations of barrier heights upon substitution in the aromatic ring. It provides, therefore, a theoretical basis for understanding the origin of the higher rotational barrier in the thioanilides series, as well as the variation of barrier heights upon substitution in the aromatic ring.

3.2.3. Effect of Charge Shifts Accompanying the Rotation from the Ground State to the Transition State. So far, we have analyzed the dependences between rotational barriers and static structural and electronic parameters for the two studied series of molecules. We have seen that considerations of C−N bond-length changes alone do not provide a satisfactory explanation of the much larger variations in the barriers of rotation in the thioacetanilides, compared to those of the acetanilides. The shifts of the electric charges at the carbonyl S and O atoms at the ground-state geometries upon substitution in the aromatic ring offer, however, a consistent and logical basis for understanding the origin of variations in barriers heights. In view of these results, it was of interest to analyze the role of the dynamic electronic effects accompanying rotation. The calculated shifts

TABLE 4: Shifts of NBO Atomic Charges[a] in the Amide Group for Trans Conformers of Para-Substituted Thioacetanilides and Acetanilides upon Substitution in the Aromatic Ring

	Thioacetanilides			Acetanilides		
substituent	Δq_N (e)	Δq_C (e)	Δq_S (e)	Δq_N (e)	Δq_C (e)	Δq_O (e)
H	0	0	0	0	0	0
CH_3	0.00156	0.00013	−0.00657	0.00050	−0.00094	−0.00229
OCH_3	0.00486	0.00077	−0.02034	0.00091	−0.00308	−0.00574
OC_2H_5	0.00538	0.00081	−0.02188	0.00131	−0.00311	−0.00708
Cl	−0.00173	−0.00171	0.01069	0.00006	0.00137	0.00275
COOH	−0.00374	−0.00456	0.02946	−0.00100	0.00352	0.01306
OH	0.00434	−0.00031	−0.01721	0.00066	−0.00306	−0.00547
NH_2	0.00688	0.00007	−0.02964	0.00196	−0.00496	−0.00948
NO_2	−0.00553	−0.00665	0.04674	−0.00063	0.00638	0.01837
SO_2NH_2				−0.00201	0.00467	0.01242

[a] The Δq_X values are calculated as the differences between the NBO charges for a given substituted compound and the respective values for the parent compounds of thioacetanilide and acetanilide.

TABLE 5: Shifts of Amide Group Partial Atomic Charges in the Trans Conformers of Para-Substituted Thioacetanilides and Acetanilides upon Substitution in the Aromatic Ring

	Thioacetanilides			Acetanilides		
substituent	Δq_N (e)	Δq_C (e)	Δq_S (e)	Δq_N (e)	Δq_C (e)	Δq_O (e)
H	0	0	0	0	0	0
CH_3	−0.00041	0.00040	−0.00574	−0.00062	−0.00070	−0.00195
OCH_3	−0.00187	0.00307	−0.01682	−0.00174	−0.00155	−0.00526
OC_2H_5	−0.00203	0.00400	−0.01828	−0.00156	−0.00119	−0.00678
Cl	−0.00221	−0.00309	0.01068	−0.00255	0.00128	0.00255
COOH	−0.00340	−0.00659	0.02576	−0.00130	−0.00037	0.01192
OH	−0.00272	0.00336	−0.01383	−0.00193	−0.00138	−0.00506
NH_2	−0.00057	0.00295	−0.02528	−0.00049	−0.00281	−0.00898
NO_2	−0.00682	−0.00857	0.04124	−0.00355	0.00066	0.01716
SO_2NH_2				0.00008	0.00025	0.01181

TABLE 6: Shifts of NBO Charges Accompanying the Transition from Trans Conformers to the TS2 Transition State in Para-Substituted Thioacetanilides and Acetanilides

	Thioacetanilides			Acetanilides		
substituent	Δq_N (e)	Δq_C (e)	Δq_S (e)	Δq_N (e)	Δq_C (e)	Δq_O (e)
H	−0.13532	−0.01523	0.20001	−0.1037	0.03512	0.10028
CH_3	−0.13860	−0.01397	0.20303	−0.10586	0.03637	0.10122
OCH_3	−0.14549	−0.01381	0.21209	−0.10965	0.03784	0.10293
OC_2H_5	−0.14619	−0.01347	0.21305	−0.11045	0.03827	0.10339
Cl	−0.13052	−0.01829	0.19804	−0.10120	0.03236	0.10092
COOH	−0.11815	−0.01807	0.18985	−0.09004	0.03068	0.09559
OH	−0.14544	−0.01362	0.20977	−0.10957	0.03786	0.10276
NH_2	−0.14983	−0.01047	0.21427	−0.11243	0.04056	0.10377
NO_2	−0.10858	−0.02217	0.18576	−0.08327	0.02649	0.09563
SO_2NH_2				−0.08957	0.02890	0.09632

TABLE 7: Charge Shifts Accompanying the Transition from Trans Conformers to the TS2 Transition State in Para-Substituted Thioacetanilides and Acetanilides

	Thioacetanilides			Acetanilides		
substituent	Δq_N (e)	Δq_C (e)	Δq_S (e)	Δq_N (e)	Δq_C (e)	Δq_O (e)
H	−0.01390	−0.08547	0.14465	0.01176	−0.10420	0.10793
CH_3	−0.01371	−0.08532	0.14676	0.01228	−0.10407	0.10874
OCH_3	−0.01163	−0.08859	0.15272	0.01655	−0.10764	0.11133
OC_2H_5	−0.01172	−0.08920	0.15365	0.01066	−0.10345	0.11072
Cl	−0.01226	−0.08664	0.14329	0.01283	−0.10610	0.10852
COOH	−0.01418	−0.08103	0.13870	0.00867	−0.09944	0.10329
OH	−0.00870	−0.09033	0.15033	0.01635	−0.10771	0.11131
NH_2	−0.01027	−0.08755	0.15358	0.01550	−0.10638	0.11224
NO_2	−0.01225	−0.08264	0.13672	0.00840	−0.09934	0.10293
SO_2NH_2				−0.00886	−0.10144	0.10369

of NBO charges that accompany the transition between the trans conformers and the TS2 transition state (Figure 2) are given in Table 6. The respective shifts of the Mulliken charges are presented in Table 7. A survey of the tables shows that a much greater portion of negative charge is withdrawn from the S atom in thioacetanilides upon rotation, compared with the respective charge shifts at the carbonyl O atom in acetanilides. Analysis of the NBO charge fluctuations reveal that most of the charge transfer is between the carbonyl S (or O) and the N atoms. The shifts of carbon charges are small in both series. The results are in accordance with the classical picture of amide resonance. The conjugative effects are strong in the trans planar structures while being essentially eliminated in the transition states. A somewhat different picture emerges from an analysis based on

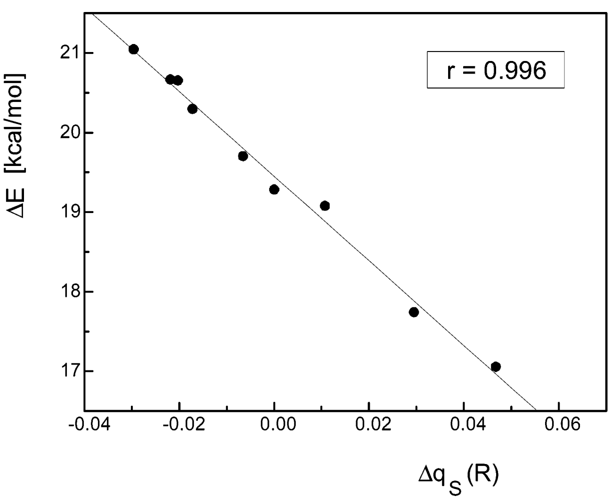


Figure 5. Dependence of rotational barriers (ΔE) on shifts of NBO charges at the S atom (Δq_S) induced by aromatic substituents in thioacetanilides.

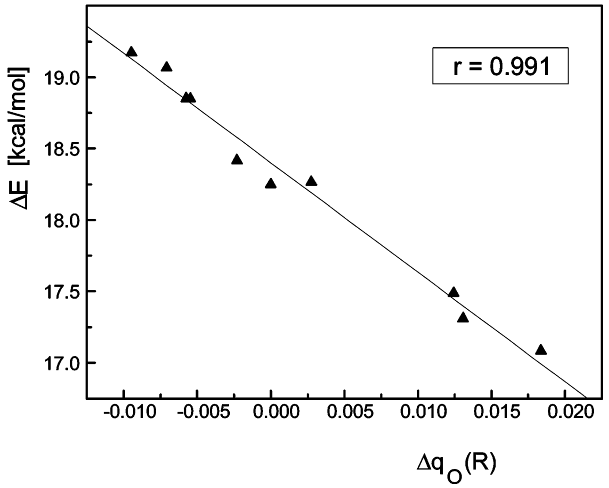


Figure 6. Dependence of rotational barriers (ΔE) on shifts of NBO charges at the O atom (Δq_O) induced by aromatic substituents in acetanilides.

the Mulliken charges. The data (Table 7) reveal a greater participation of the C atoms in the charge shifts for both thioanilides and anilides.

In view of the formal equipartitioning of overlap charges between atoms[37] inherent in the Mulliken population analysis, however, the respective data for the charge distribution in the amide grouping cannot be viewed as a sufficiently reliable basis for interpretations. Both NBO and Mulliken charges reveal much greater charge fluxes upon rotation in the thioanilide series.

The relationships between ΔE and shifts of the NBO charges (Δq_S and Δq_O) are shown in Figures 8 and 9. Similar linear plots are found from an analysis based on the Mulliken partial charges. The respective linear regression correlation coefficients for the dependences between the shifts of Mulliken charges and ΔE are $r = 0.987$ for thioacetanilides and $r = 0.988$ for acetanilides.

The dependences are consistent with the interpretation of rotational barriers, in terms of amide resonance. The disruption of resonance interactions upon rotation is accompanied by greater charge shifts within the amide grouping in the thioacetanilides. The results indicate that these interactions are significantly greater in the thioamides. As we have seen, similar conclusions are reached by analyzing the atomic charges at equilibrium. These results are in accord with previous theoretical findings that underline a key role for the resonance interactions and charge shifts that accompany the internal rotation in amides and thioamides.[1,8,9,12,14,18a]

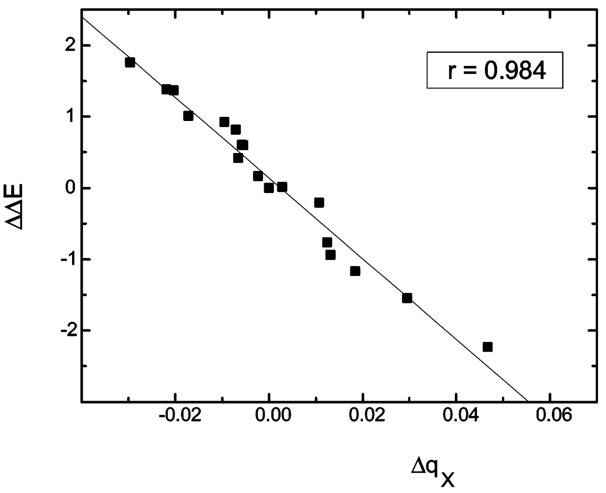


Figure 7. Plot of shifts of rotational barriers ($\Delta\Delta E$) against NBO charge shifts (Δq_X, where X = O, S) induced by substitution in the aromatic ring.

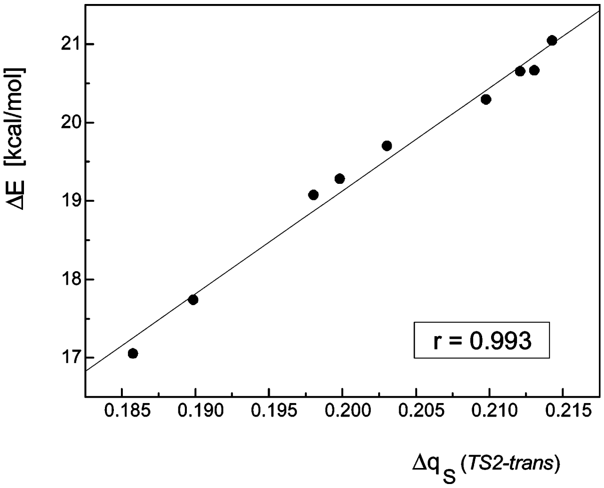


Figure 8. Dependence of rotational barriers (ΔE) on shifts of NBO charges (Δq_S) upon rotation in thioacetanilides.

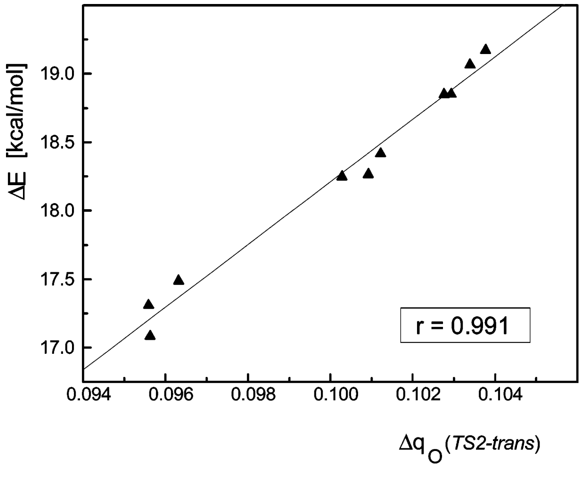


Figure 9. Dependence of rotational barriers (ΔE) on shifts of NBO charges (Δq_O) upon rotation in acetanilides.

3.3. Supporting Experiment. IR spectra in $CHCl_3$ solution of five compounds from the series studied were obtained. The data are presented in Table 8. The most interesting feature of

TABLE 8: Experimental and B3LYP/6-31G Calculated Vibrational N−H Stretching Frequencies for Cis and Trans Para-Substituted Thioacetanilides**

	Vibrational N−H Stretching Frequency (cm^{-1})			
	Experimental		Theoretical[a]	
substituent	trans	cis	trans	cis
H	3383	3355	3448	3427
CH_3	3382	3354	3445	3427
OCH_3	3381	3354	3447	3425
CL	3382	3350	3445	3426
NO_2	3383		3442	3423

[a] Scaling factor = 0.96 (from ref 36).

the experimental spectra is the appearance of two N−H stretching mode bands for all the studied compounds (Figure 1) except *p*-nitrothioacetanilide. These bands correspond to trans and cis rotameric forms. The presence of two N−H bands at ambient temperature suggests that the energy difference between the two conformers is small. The experimental N−H characteristic frequencies are compared with the theoretically estimated values. A good correlation is observed between the experimental and theoretical values (Table 8). The experiments show that the intensity of the trans N−H band is distinctly higher in all the studied cases, which suggests that the respective conformers are the thermodynamically favored forms.

An interesting finding in the previous study on rotational barriers in para-substituted acetanilides[1] was the established excellent linear relationship between the rotational barriers around the amide C−N bond and the shifts of the carbonyl stretching-mode frequency. In the case of thioacetanilides, the C═S stretching is strongly mixed with other distortions and the respective band in the experimental spectra is usually difficult to assign experimentally. Vibrations with relatively strong participation of C═S stretching were theoretically estimated in the range of 1154−1159 cm^{-1} for the trans conformers and 1189−1196 cm^{-1} for the cis conformers.

4. Conclusions

Density functional theory computations for selected series of para-substituted thioacetanilides and acetanilides reveal that structural and electronic parameters can be employed in rationalizing the variations of barrier heights for the rotation around the amide C−N bond. A satisfactory explanation for the distinctly greater shifts of rotational barriers in the thioacetanilide series upon substitution in the aromatic ring, as compared with data for the respective acetanilides, is obtained by analyzing the dependences between barriers heights and the charge shifts upon substitution in the aromatic ring and upon rotation. Several linear relationships are established that link the barrier heights with structural and electronic parameters characterizing the amide and thioamide groupings. A common linear equation quantifying the dependence between barrier heights and shifts of NBO partial charges at the amide S and O atoms upon substitution in the aromatic ring in the two series is found. The results obtained are consistent with the views for a classical amide resonance as being the origin of higher rotational barriers in thioamides than in amides.

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

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